FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee

January 30, 2009

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

M E M O R A N D U M

DATE: January 15, 2009

FROM: Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Life Support Drugs Advisory Committee (ALSDAC)

RE: Overview of the January 30, 2009, ALSDAC Meeting to Discuss the Efficacy and Safety of Propoxyphene

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Propoxyphene is an opioid analgesic and is controlled under Schedule IV of the Controlled Substances Act. Propoxyphene is marketed in single-entity products and in the more commonly prescribed acetaminophen-containing combination products. The safety and efficacy of propoxyphene-containing products has come under review as the result of a Citizen's Petition dated February 28, 2006, asserting that the overall risk to benefit balance for these products is unfavorable. This petition was written by Dr. Sidney Wolfe representing Public Citizen's Health Research Group and asserts the following:

- There is insufficient evidence to establish that propoxyphene alone is an effective analgesic and, in products which combine propoxyphene with acetaminophen, it appears to contribute little if at all to the efficacy.

- The Committee on Safety of Medicines, a committee under the Medicines and Healthcare Products Regulatory Agency of the United Kingdom, determined that the there was inadequate evidence to support the efficacy of propoxyphene and that the risk of toxicity associated with both deliberate and accidental overdose was unacceptably high and, therefore, the product should be withdrawn from the U.K. market.

- Propoxyphene and its major metabolite are potent cardiotoxic agents with a narrow therapeutic index.

- Propoxyphene is widely prescribed, particularly in the elderly, and has been associated with a large number of deaths, mainly in these elderly patients who are at greater risk for drug toxicity.

Propoxyphene-containing products are widely prescribed in the U.S. with more than 20,000,000 prescriptions written in 2007. At this meeting of the ALSDAC, you will hear a presentation by Dr. Wolfe regarding his perspective on the risk-benefit ratio for propoxyphene, and you will hear a presentation from representatives of two of the companies that manufacture propoxyphene drug products. In addition, FDA and SAMHSA representatives will present the data supporting the efficacy and safety of propoxyphene documented in the NDAs for these products and in the medical literature, as well as adverse event data from FDA's Adverse Event Reporting System (AERS) and from SAMHSA's Drug Abuse Warning Network (DAWN). In addition we will be presenting outpatient prescription usage data from SDI Vector One® National (VONA) and SDI Total Patient Tracker (TPT). The overriding question that we will be asking you to consider is whether this data support the continued marketing of propoxyphene-containing products based on an overall risk-benefit analysis.

We ask that you carefully consider all of the data that will be presented to you as the recommendations you make could have a significant impact on the use of these widely prescribed analgesic drug products. We appreciate your taking your valuable time to participate in this important process and look forward to seeing you on the 30th.

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Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

February 28, 2006

Andrew Von Eschenbach, M.D., Acting Commissioner
U.S. Food and Drug Administration
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Von Eschenbach:

Public Citizen, representing 160,000 consumers nationwide, hereby petitions the Food and Drug Administration (FDA) pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30 to immediately begin the phased removal from the market of propoxyphene (Darvon) and all propoxyphene-containing products such as Darvocet (propoxyphene and acetaminophen). Propoxyphene (now sold mainly as a generic drug), which has a cardiotoxic metabolite, has been associated with 2110 reported accidental deaths in the U.S. from 1981 through 1999. It is a narcotic that induces the classic triad of psychological dependence, physical dependence, and tolerance, and has repeatedly been shown in controlled clinical trials to be a relatively weak painkiller. The phased withdrawal in the U.K of these products was announced one year ago when the British government stated that the efficacy of this product "is poorly established and the risk of toxicity in overdose, both accidental and deliberate, is unacceptable." They further said that "It has not been possible to identify any patient group in whom the risk-benefit [ratio] may be positive." (http://www.mhra.gov.uk/home/groups/pl-a/documents/drugsafetymessage/ con019461.pdf) A phased withdrawal, instead of an immediate one, is necessary because of the addicting properties of the drug and the need to switch patients to other painkillers.

Overview

Explaining the background for removing propoxyphene products from the market, the British Committee on the Safety of Medicines pointed out, in January 2005, that "Each year there are 300-400 fatalities following deliberate or accidental drug overdose involving co-proxamol [propoxyphene/acetaminophen] in England and Wales alone. Approximately one-fifth of these deaths [60-80] are considered to be accidental." Thus in those two countries alone, with a population of 53 million people---approximately 18% of the size of the U.S.-- there were an estimated 60 to 80 accidental deaths a year from co-proxamol or propoxyphene/ acetaminophen.

Because it continues to be so widely prescribed in the U.S. (the 12th highest-selling generic drug in 2004 with 23 million prescriptions filled and sales that year of $291 million[1]) and

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because toxicity develops at only slightly above the recommended daily dose – especially in combination with alcohol and other central nervous system depressants – propoxyphene is consistently mentioned as one of the top 10 drugs found in the subject's system during autopsies.[2] Medical examiners note its presence in more deaths each year than most other prescription drugs. Data from the Drug Abuse Warning Network (DAWN), which provides autopsy information from medical examiners nationwide, has implicated propoxyphene in 5.6% of all drug-related deaths (including prescription, over-the-counter, and illicit drugs) in just over 19 years (1981-1999). This amounts to 7,109 total reported U.S. deaths since 1981 merely for the counties covered by DAWN, which account for only approximately one-third of the population of the country.

Propoxyphene is implicated in a high proportion of accidental deaths each year, because the majority of the drug is converted into a metabolite that is even more toxic and has a longer half-life than its parent compound. From 1981 to 1999, DAWN reported 2,110 accidental propoxyphene-related deaths, or 38.6% of the total number of propoxyphene-related deaths. (DAWN no longer details manner of death but the total number of propoxyphene-related deaths has remained relatively the same since data collection on manner of death stopped in 1999—see Figure 1 for total death data through 2002). Because DAWN reports data only from medical examiners in counties whose total population makes up one-third of the country, it is reasonable to conclude that the true number of accidental propoxyphene-related deaths since from 1981 through 1999 may be three times greater than the 2,110 deaths actually reported.

Beers et al. put propoxyphene among the drugs that are inappropriate for use in the elderly due to its lack of significant efficacy and high incidence of adverse effects.[3] Nevertheless, propoxyphene is the most prevalent of all drugs considered inappropriate by Beers that are used by the elderly.[4] Further, the elderly account for a large proportion of propoxyphene use. As Li Wan Po, et al. conclude in a systematic review of the efficacy of propoxyphene as an analgesic: "on the basis of data on analgesic efficacy and acute safety...there is little objective evidence to support prescribing a combination of paracetamol [acetaminophen as in Tylenol] and dextropropoxyphene in preference to paracetamol alone in moderate pain such as that after surgery."[5]

Among community-dwelling elderly patients, 6.6 percent were using propoxyphene in 1999, translating into more than two million community-dwelling Medicare beneficiaries.[6] In a study involving 157,000 elderly HMO members, the rate of use of propoxyphene was seven percent, making it the most commonly used of the list of 33 medicines deemed inappropriate for the elderly.[7] In a nationwide study of emergency departments, propoxyphene, was the third most commonly prescribed drug on the inappropriate list, being prescribed 3.3 million times to the elderly during emergency room visits from 1992-2000.[8] In nursing homes, the inappropriate use of propoxyphene was even higher than in the community, with use by 15.5 percent of institutionalized elderly Medicare beneficiaries.[9] In a recent study in nursing homes, the first study to measure the adverse health impact of inappropriate prescribing, the authors calculated the increased risk of serious adverse health outcomes (hospitalizations, emergency department visits or death) for various inappropriately prescribed drugs. Those using propoxyphene were almost 2.4 times more likely to require hospitalization or emergency department visits or to die.[10]

History of Propoxyphene Restriction Efforts

In November 1978, the Health Research Group (HRG) of Public Citzen proposed significantly altering propoxyphene's regulatory status in either of two ways: HRG petitioned the

Department of Health, Education and Welfare (HEW) to ban the drug as an "imminent hazard." As an alternative, HRG asked HEW to tighten restrictions on the drug's use by placing it in Schedule II of the Controlled Substances Act. A key factor in the HEW decision to reject the HRG proposals was Eli Lilly's commitment to an "educational program" intended to sensitize prescribers and patients to the hazards of propoxyphene products. In a 1978 HEW appraisal of Lilly's efforts, the following was reported: "Lilly has not conducted its campaign to prescribers as FDA had expected. Detail persons visiting physicians failed to emphasize the user warnings in the majority of visits, left samples of Darvon in 50-75 percent of visits, and on the average spent less than half of the time on Darvon during the visits."[11] It appears that Eli Lilly converted its education program into a marketing initiative.

According to a DEA compliance survey regarding propoxyphene: "abuse of propoxyphene appears to be directly related to the relative ease with which this drug is obtained from physicians."[12] Yet as FDA's Dr. Louis Morris wrote "the Darvon educational campaign has not been shown to have had an important impact into physician decision-making."[13]

In fact, even though Lilly no longer manufactures these drugs, having sold the rights to Darvon/Darvocet to aaiPharma several years ago, propoxyphene-containing compounds, mostly generic versions, remain among the top-selling drugs on the market.[14] This high level of prescribing persists despite propoxyphene's eventual placement in Schedule IV of the Controlled Substances Act (which includes drugs with limited potential for dependence such as diazepam [Valium] as opposed to Schedule II, which includes drugs with a high potential for dependence such as codeine). Lilly's half-hearted attempts to comply with the weak restrictions enacted the last time the government considered the dangers of propoxyphene have clearly allowed this drug to remain as a viable analgesic in the minds of doctors throughout the nation, despite its inappropriateness for treating pain and the serious dangers it presents to patients.

Weak Analgesic Properties

Many studies have shown the relative ineffectiveness of propoxyphene as a painkiller. In a recent comprehensive review of randomized clinical trials, Collins, et al., found that for most kinds of pain (e.g., post-operative pain), ibuprofen is more effective than propoxyphene/acetaminophen (the latter, the ingredient in Tylenol). Further, codeine/acetaminophen was found to be more effective than propoxyphene/acetaminophen, although that difference was not statistically significant. Ibuprofen, however, was a significantly stronger analgesic than the propoxyphene compound, requiring that fewer patients be treated at the standard dose for at least one of those patients to achieve 50% pain relief.[15]

The similarity of the efficacy of the acetaminophen-containing preparations of propoxyphene and codeine appears to be deceptive, as evidence suggests that much of the analgesic properties of propoxyphene /acetaminophen are due to the acetaminophen alone. Hopkinson, et al., for example, compared the analgesic effect of two combinations of drugs: 1) 1000 mg. acetaminophen alone and 2) 650 mg. acetaminophen plus 100 mg. propoxyphene. They found that the acetaminophen only treatment was significantly more effective than the propoxyphene/acetaminophen combination in the relief of pain (63% vs. 42% achieving effective pain relief), indicating that propoxyphene adds no analgesic properties to acetaminophen.[16]

Propoxyphene alone has been shown to be no more effective than two aspirin for relief of most kinds of pain, such as post-operative pain.[17] Further, in a comprehensive survey of the published literature up to 1970, Miller, et al., examined 243 articles on propoxyphene and found few hard data on its therapeutic value compared with other analgesics. Seven of the 16

reviewed studies comparing propoxyphene with placebo — 4 of which used the manufacturer's suggested dose of 65 mg. — showed that propoxyphene was not superior to placebo. The authors concluded that "propoxyphene is no more effective than aspirin or codeine, and may even be inferior to these analgesics."[18] A more recent systematic review by Li Wan Po et al. of 26 randomized trials comprising 2231 patients with post-operative pain (including some of the data mentioned earlier) found that in head to head and indirect comparisons of acetaminophen with the combination of propoxyphene and acetaminophen, the combination was no better than acetaminophen on its own. The authors conclude that "on the basis of data on analgesic efficacy and acute safety...there is little objective evidence to support prescribing a combination of acetaminophen and dextropropoxyphene in preference to acetaminophen alone in moderate pain such as that after surgery." The authors further "concur with Miller et al that the popularity of the acetaminophen combination does not lie in improved efficacy" over other analgesics.[19]

Although some have claimed that propoxyphene may be effective in chronic pain such as that from cancer,[20] there exist no randomized controlled trials that indicate any such effect. Dr. Charles Moertel, a well-known former cancer specialist at the Mayo Clinic, noted that "for the treatment of severe pain, the use of Darvon either alone or in combination is grossly inadequate treatment and is really inhumane to the patient." Dr. Moertel also stated that "it is possible to maintain good medical practice without the use of Darvon."[21] Further, even were propoxyphene shown to be effective for this kind of pain, chronic usage increases the likelihood of adverse events due to buildup of the cardiotoxic propoxyphene metabolite, norpropoxyphene.

Beyond the questionable wisdom of prescribing a drug with severe adverse effects that provides little benefit, the relative ineffectiveness of propoxyphene translates into an additional kind of increased danger to patients. When the recommended dose fails to alleviate their pain, patients may choose to take additional pills, exceeding the recommended daily dose. It does not require much additional drug beyond the daily dose to generate either dependency or toxicity, as the following section demonstrates.

Toxicity: Extremely Low Margin of Safety

Propoxyphene, a potent cardiotoxic agent, can cause severe cardiovascular effects with overdose or even when used as directed. Upon metabolism, the majority of propoxyphene is converted into norpropoxyphene (NPX), which is particularly dangerous as it is 2.5 times more potent than its parent compound in producing cardiac depression and has a half-life (time before ½ of the substance is cleared from the body) of approximately 36 hours, three times longer than that of propoxyphene. Adverse cardiovascular events are marked by prolongation of the QRS complex on an electrocardiogram (which can increase the risk for an abnormal cardiac rhythm) and include bundle branch block (interruption of cardiac conduction), bradycardia (slowed heartbeat), asystole (absence of contractions), diminished myocardial contractility (ability of the heart to contract), and hypotension. These events are not reversed by opiate antagonists such as naloxone and up to 76% of deaths from propoxyphene overdose are a result of cardiac toxicity.[22] This high toxicity accounts for the finding that only 30-40% of propoxyphene-related deaths are attributed to suicidal overdoses; over 40% have been found to be accidental.[23]

The fact that norpropoxyphene is cleared from the body more slowly than its parent compound and thus reaches considerably higher blood levels and is more cardiotoxic, explains the high risk of accidental overdose.[24] According to Dr. Randall Baselt, FDA expert toxicology witness at the April 6, 1979 hearings on Darvon: "This accumulation of drug sets the stage for accidental overdosage; one or two additional depressant drugs, such as alcohol or diazepam,

may be sufficient even in normally used amounts [of alcohol or diazepam] to cause death in susceptible persons."[25]

Henry, et al., report that the cardiac toxicity of propoxyphene may derive from membrane stabilization, the depression of excitability in nerve and heart tissue.[26] Whitcomb et al. similarly found that propoxyphene acts as a potent sodium channel blocker, which depresses the action potential of myocytes.[27] There is a significant relationship between the dose of propoxyphene and prolongation of the QRS complex, representing an increase in the time required for the ventricles to depolarize. This relationship is not seen with other opioids.[28] The prolongation of the QRS complex associated with sodium channel blockade can be a precursor to ventricular arrhythmia, which is often fatal.

Table 1 below, constructed from published and unpublished data on blood levels of propoxyphene and norpropoxyphene in individual users illustrates the propensity of norpropoxyphene to accumulate over time to amounts far in excess of propoxyphene even when the recommended doses are being used. For example, in the four people using propoxyphene chronically at levels up to 6 pills per day, the recommended daily dose, blood levels of propoxyphene of 0.24-0.85 µg/g and blood levels of norpropoxyphene of 0.6-3.0 µg/g were noted. In the six people using between one and two times the recommended dose (7-12 pills) blood levels of propoxyphene of 0.42-0.87 µg/g but norpropoxyphene levels of 1.8-5.1 µg/g were noted. In these six subjects, the average blood level of propoxyphene was 0.61 µg/g, but the average level of norpropoxyphene was 3.7 µg/g – more than six times higher than the propoxyphene level.[29,30,31]

Pills/day[a]	Type of Subject[b]	Duration of Drug Use	Maximum Blood Concentration (µg/g)[c]		Reference
			DXP	NPX	
3 (HCl)	Cancer patient	60 days	0.746 (2)	3.01 (2)	29
3 (HCl)	Cancer patient	14 days	0.275 (2)	0.75 (2)	29
3 (HCl)	Normal vol.	4 days	0.241 (2)	0.6 (4)	29
6 (HCl)	Normal vol.	4 days	0.849 (2)	1.24 (6)	29
9 (N)	Addict	28 days	0.519 (3)	3.83 (6)	30
11 (N)	Addict	42 days	0.567 (3)	4.94 (9)	30
11 (N)	Addict	84 days	0.513 (6)	5.07 (6)	30
12 (N)	Addict	84 days	0.424 (6)	1.83 (6)	30
12 (HCl)	Cancer patient	365 days	0.866 (2)	3.23 (4)	31

Table 1: Blood propoxyphene and norpropoxyphene levels in individual regular users of propoxyphene products

a: The recommended daily dose is 1 pill every 4 hours or 6 pills per day
HCl = propoxyphene hydrochloride N = norpropoxyphene napsylate
b: The subjects included normal volunteers, cancer patients using propoxyphene products for pain relief, and former addicts involved in addiction maintenance experiments.
c: The number in parentheses represents the hours after the last dose when the maximum blood levels of propoxyphene and norpropoxyphene were attained.

The fact that people using propoxyphene products at or slightly above the recommended dose can get norpropoxyphene blood levels above 1 µg/g is particularly alarming in view of the findings that in many cases of accidental death due to propoxyphene products, the blood

norpropoxyphene levels are in the same range as those found in chronic users of the drug, such as those listed in Table 1.[32] This suggests that chronic users of propoxyphene are at high risk for accidental overdose. Furthermore, comparable blood levels (above 1 µg/g) of norpropoxyphene in animals can cause significant blockage of conduction through the heart – a toxicity which can lead to arrhythmias and death.[33]

The margin of safety of propoxyphene, the ratio between the dose that contains 99% of the effectiveness of the drug and that which kills 1% of those who use it,[34] is extremely low, especially given its relative inefficacy as an analgesic. The dose of propoxyphene necessary for cardiac toxicity to occur overlaps significantly with the increased dose which a user, dissatisfied with the analgesic effects and still in pain, may ingest. The margin of safety is even worse when other drugs are involved, especially alcohol. The recommended dose for both chronic and acute pain is one pill every four hours, or six pills per day. Young, et al., found that death can occur with 20 pills while Whittington found that as few as 6-15 pills can cause death.[35,36] The lower number reflects the ability of alcohol to potentiate the toxicity of propoxyphene. Similarly, Obafunwa, et al., found that as little as 0.168% blood alcohol content (BAC) can potentiate lethality within the propoxyphene limit of toxicity of 0.75 µg/g.[37] A study analyzing over 1000 fatal intoxications (both intentional and accidental) due to alcohol, a single drug, or both, found that the median post-mortem blood alcohol concentrations -sufficient to cause death - were much lower when propoxyphene was found in combination with alcohol (3.3 parts per thousand BAC without propoxyphene, 1.7 parts per thousand with propoxyphene).[38] Thus, propoxyphene is particularly dangerous when combined with alcohol.

A Swedish study further highlights the dangers and prevalence of propoxyphene and alcohol consumption. Jonasson, et al., identified 766 propoxyphene-related suicides in Sweden from 1992-1996 and an additional 1,016 non-suicide deaths. Alcohol was present in 425 of those non-suicides and of those, 220 were classified as having been caused directly by propoxyphene. Among the fatally intoxicated, the mean blood propoxyphene concentration was only 2 µg/g – less than three times the blood level typically found after the recommended, therapeutic dose. Further, the authors concluded that the majority of those who died from an accidental poisoning were not part of the "drug addict population."[39] The same team of authors concluded in a separate study that suicides were generally over-reported in propoxyphene-related deaths and that accidents were under-reported.[40] The authors concluded that "probably more than 40 individuals die from accidental poisonings due to a combination of propoxyphene and alcohol each year" in Sweden alone[41] – and since accidents are under-reported, this may not even reflect the true dangers of accidental poisoning from propoxyphene.

The high numbers of some of these deaths are due to the lethality of a propoxyphene overdose. Propoxyphene is rapidly absorbed from the gastrointestinal tract, leading to early cardiac risk following an overdose and death within an hour. In a study of 222 patients treated for propoxyphene overdose, both accidental and suicidal, the mortality rate was 7.7%, over three times that of tricyclic antidepressants in the same medical center.[42] A recent study by Hawton, et al., looking at suicide found that an overdose of propoxyphene /acetaminophen is more fatal than an overdose of either tricyclic antidepressents or acetaminophen. Of 4162 drug-related suicides in England from 1997-1999, 18% involved only propoxyphene /acetaminophen, while tricyclic antidepressants accounted for 22% and 9% involved acetaminophen alone. This yields 766 deaths in England over three years due only to one mode of propoxyphene-related death: suicide via poisoning with / propoxyphene acetaminophen alone. There were an additional 171 deaths in which propoxyphene /acetaminophen was used with another drug.[43]

Propoxyphene's deadly nature is revealed by the fact that among those who attempted suicide via overdose, as described in the Hawton study, an overdose with propoxyphene was 2.3 times more likely to be fatal than one with tricyclic antidepressants and 28.1 times more likely to be fatal than one with acetaminophen alone. The study's authors conclude that "Given earlier concerns about deaths from poisoning with co-proxamol (propoxyphene/acetaminophen), the absence of specific initiatives to try to reduce them is surprising and should now be addressed...availability of co-proxamol should be restricted".[44]

Data from Sweden, where propoxyphene was not required to be prescribed on a special prescription form like other narcotic drugs in the country until 2001, suggest that the drug is one of the deadliest of all those heavily prescribed. Jonsson et al. determined the number of deaths from fatal intoxications found during autopsy from 1992-2002 at the Department of Forensic Chemistry in Lingkoping, which has complete national coverage of Sweden's population of 8.9 million. Out of 6998 fatal intoxications, propoxyphene was found in 1863 – 27% - of cases, second only to ethanol. Toxic levels of propoxyphene (defined by the authors based on Druid, et al.,[45] as 0.8 μg/g) were found in 1370– 74% of the 1863–more than any other prescription drug.

The study also measured the fatality ratio, which relates the number of fatal intoxications with toxic concentrations of the substance to the number of defined daily doses per 1000 inhabitants of the country per day. Thus, a drug with a fatality ratio of 1 would cause one fatal intoxication per dose per 1000 inhabitants per day. Using this measure of the lethality of a drug, the authors determined a fatality ratio of 10.8 for propoxyphene, almost five times as high as that for acetaminophen (2.3), the drug with the next highest number of absolute deaths. In other words, for a given number of prescriptions, propoxyphene was involved in almost five times as many deaths as acetaminophen.[46] This study highlights the deadliness of the combination of high lethality and massive prescribing that characterizes propoxyphene.

The Rising U.S. Death Toll

Propoxyphene and combinations including it constitute one of the most prescribed prescription drugs in the country. In 2004, propoxyphene was the 12th most prescribed generic drug with over 23 million prescriptions sold.[47] Over the past 47 years, it has also been one of the deadliest drugs on the market, being associated with well over 10,000 confirmed deaths in the United States alone.

In the United States, DAWN collects data from medical examiners and emergency rooms in approximately 40 metropolitan areas. As of 2002, 94 million people lived in counties that reported to DAWN. Given a 2000 US population of 293 million, this means that the network represents approximately 1/3 of the total population. Although data from DAWN cannot be directly extrapolated, multiplying its results by three gives a general idea of the enormity of the damage this relatively ineffective yet dangerous drug has wrought.

Data regarding propoxyphene-related deaths for the past 20 years of DAWN are presented in figure 1.[48] While these numbers do not necessarily implicate propoxyphene as the direct or sole cause of death, since other drugs were found with it in 93.3% of the 459 cases in 1999, its toxicity makes causation likely. Furthermore, a large proportion of deaths involving propoxyphene involved alcohol and/or acetaminophen as having been used in combination. Alcohol was one of the drugs involved in 33.8% of propoxyphene deaths involving two or more drugs and acetaminophen was in 19.6%. Alcohol is not particularly lethally toxic on its own, but has been shown to potentiate propoxyphene lethality. When we originally petitioned the FDA to

ban propoxyphene in 1978, the Chief Coroner of San Francisco, Dr. Boyd Stevens, told Public Citizen that, based on autopsy findings, "if you double the Darvon dosage and take just one or two [bar] drinks, you can get into the toxic or lethal range." In some cases, acetaminophen was likely found in autopsies due to its presence in propoxyphene/acetaminophen preparations. Since propoxyphene has been shown to have a fatality ratio almost five times as great as that for acetaminophen[49], it can be concluded that propoxyphene represents the cause of death in a significant proportion of these cases.

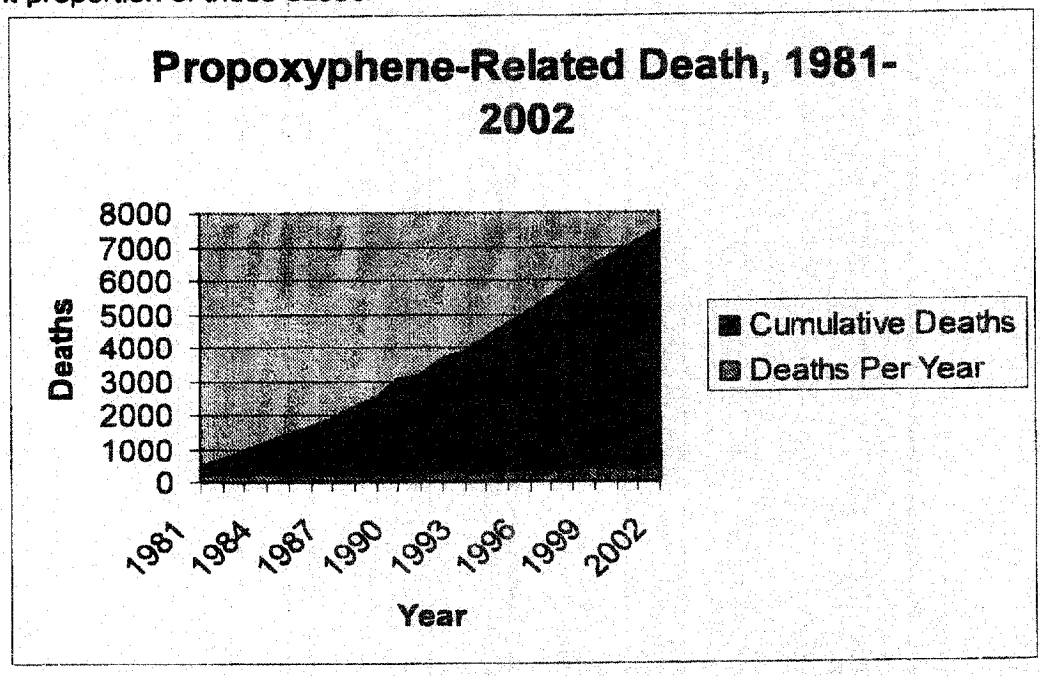

Figure 1: The DAWN system has tabulated 7,109 deaths involving propoxyphene in the period from 1981-2002.

The number of deaths involving propoxyphene in the US alone is striking. Although in 1981, propoxyphene was implicated in over 8% of drug deaths mentioned in DAWN, that number has declined to around 4% as of 1999. Nevertheless, the actual number of propoxyphene-associated deaths in absolute terms has been creeping steadily upwards since 1981. Whereas 227 deaths were reported in 1981, a high of 459 was reported in 1999. The cumulative deaths since 1981 have, at last count, reached 7,109 through 2002. As propoxyphene has been on the market since 1957, there are many more deaths, occurring before 1981 and after 2002 that have not even been calculated. Further, these numbers represent only those cases in which an autopsy was performed.

Accidental Propoxyphene-related Deaths

From 1981 to 1999, the Drug Abuse Warning Network reported 2,110 propoxyphene-related accidental deaths, 38.6% of the total number of 5,462 deaths involving propoxyphene. There has been a slight trend towards an increasing number of accidental deaths reported, such that in the five years from 1995-1999, an average of 40.3% of the deaths were accidental. Although DAWN did not release the breakdown for manner of death in 2000-2002, assuming 199 accidental deaths (as there were in 1999) yearly during this time period yields 2,707

propoxyphene-related accidental deaths for the period from 1981-2002 out of a total of 7,109 propoxyphene-related deaths.

There are several reasons why the actual number of deaths involving propoxyphene in which that person did not intend to die (accidental deaths) is certainly much higher. First, because of the nature of Federal reporting, there are no data categorized by accidental deaths either for the first two decades of propoxyphene use prior to 1981 or for the years since 1999. Second, DAWN reports data only from medical examiners in counties whose total population makes up only about 1/3 of the country. Thus, the true number of accidental propoxyphene-related deaths may be three times greater than 2,110 cases actually reported. Third, Jonasson et al. concluded, based on a review of the criteria used to assign manner of death in fatal propoxyphene poisonings in Sweden, that propoxyphene-related accidental deaths were under-reported and suicides over-reported. This suggests that a greater proportion of the 7,109 confirmed U.S. propoxyphene-related deaths since 1981 may be accidental than has been reported as such.

Lastly, these data represent only deaths in which the index of suspicion was high enough that the case was sent to a medical examiner. Cases in which an autopsy was performed in a hospital are not reported. Further, the autopsy rate in the US has been declining steadily since the 1950s from around 50% to between 5-10% today.[50,51] Since autopsies are now much less likely to be routinely performed, the true number of accidental propoxyphene poisonings is almost certainly much higher than the 2,110 confirmed cases from medical examiners' offices in the past twenty years alone.

Related to the above issue of autopsies, under-reporting of accidental deaths may be an especially significant problem in the elderly. Autopsies are performed at particularly low rates in nursing homes – Katz, et al., found an autopsy rate of only 0.8% from 1980-1984.[52] Propoxyphene is widely prescribed in the elderly, making up over 18% of prescribed analgesics in nursing homes[53], and the highly cardiotoxic and long-lasting propoxyphene metabolite norpropoxyphene is extremely prone to building up to high levels in the elderly. Since high levels of norpropoxyphene can occur at low doses of propoxyphene (as mentioned earlier, Inturrisi reports a case where a norpropoxyphene level of 5.07 µg/g was found where the propoxyphene level was only 0.513 µg/g – significantly under the level considered lethally toxic[54]), such a death from a ventricular arrhythmia in an infirm elderly decedent is unlikely to raise an index of suspicion sufficient to perform an autopsy. All this evidence points to a significantly higher number of accidental deaths related to propoxyphene than that reported by DAWN.

Propoxyphene-related Suicides

Although a large proportion of propoxyphene-related deaths have been accidental, due to the narrow margin of safety of the drug, especially when co-consumed with alcohol, for many years propoxyphene has been an important method of suicide. Since 1981, there appears to be a trend towards a somewhat lower proportion of propoxyphene-related deaths being determined to be suicides by the medical examiners included in DAWN (figure 2). Furthermore, Jonasson et al. conclude that suicides involving propoxyphene are generally over-reported and accidents under-reported.

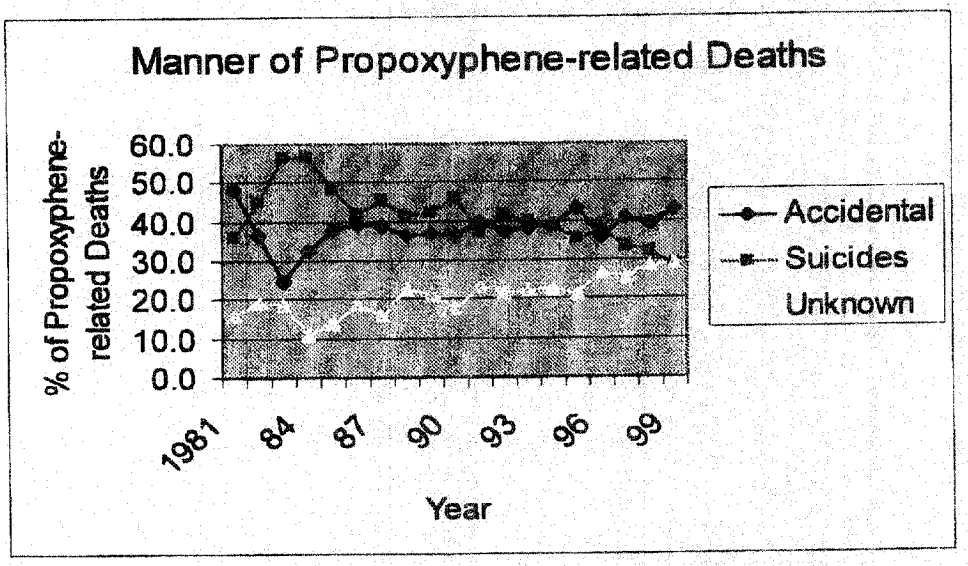

Figure 2: Proportion of deaths involving propoxyphene classified by DAWN as accidental, suicide, or unknown, on a yearly basis.

Nevertheless, in the most recent five years with such information, DAWN has reported that approximately one-third of deaths involving propoxyphene have been suicides (see figure 2 above). It could be argued that banning propoxyphene would have no effect on these deaths -- those intent on suicide will choose another route and no net benefit will be produced. Indeed, a Lilly representative stated in 1980 that transferring propoxyphene to Schedule II, a less stringent restriction than our proposed complete banning of the drug, would have "negligible impact on the suicide rate" since abusers would merely "move to another drug."[55] However, the restriction of several drugs typically involved in suicides demonstrates this not to be the case. For example, figure 3 shows that restricting the availability of barbiturates by imposing Schedule II controls had a marked positive effect on reducing the number of barbiturate suicides.[56] Although the number of total drug suicides did not drop as steeply as the number of barbiturate suicides, indicating that there was some substitution of other drugs for barbiturates, this substitution was clearly not 100%. Note that the steep drop in prescriptions and suicides began in 1970 when Congressional hearings regarding barbiturates began and dropped again in 1975, when the drugs were controlled in Schedule II. The graph shows that people intending to commit suicides did not completely turn to other drugs for suicides, as the total number of drug suicides decreased along with the number of barbiturate suicides. Given that we propose removing propoxyphene from the market rather than merely restricting its use by placing it in Schedule II, the resulting drop in total suicides would be predicted to be even more significant.

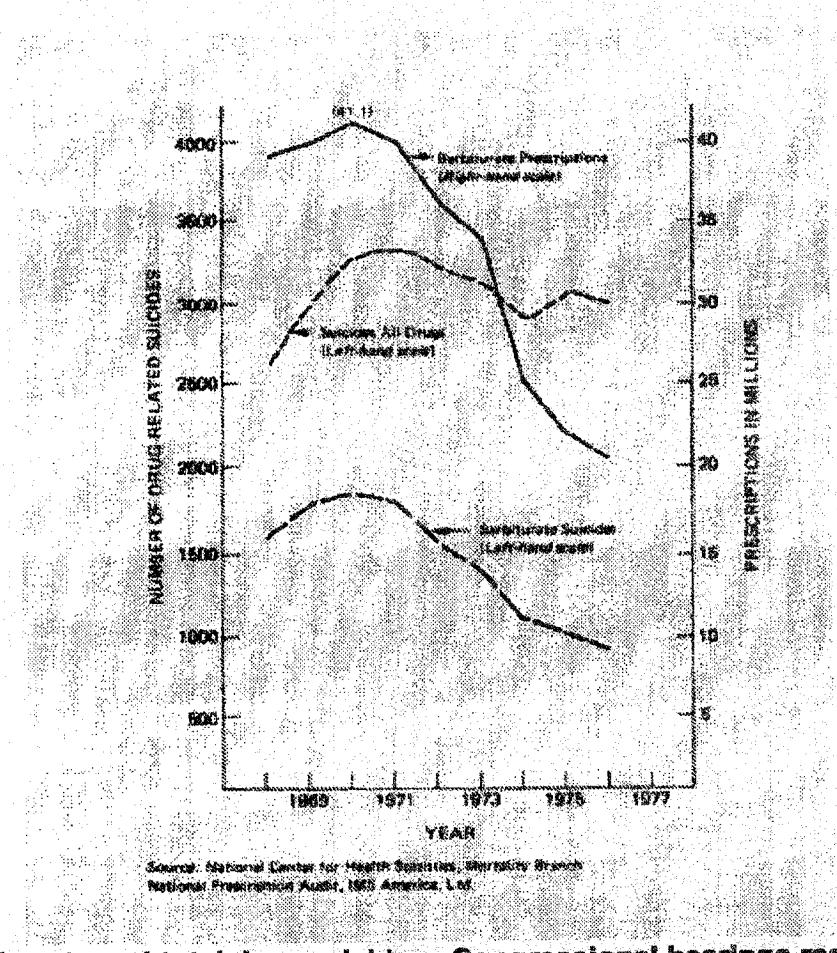

Figure 3: Barbiturate and total drug suicides. Congressional hearings regarding the restriction of barbiturates began in 1970 and barbiturates were controlled in Schedule II in 1975. Note the reductions in both barbiturate and total drug suicides at these points.

Further, many suicides are cries for help, not truly wishes for death. However, with the low margins of safety of propoxyphene due to its high toxicity, these attention-seeking attempts—often called suicidal gestures—are more likely to be "successful" when this drug is used. Thus, as a drug implicated in a large number of suicides yearly and one with few redeeming benefits, the ban of propoxyphene will likely result in a significant reduction in the total number of drug-related suicides.

Propoxyphene and the Elderly

The misuse of propoxyphene of greatest magnitude is caused by its over-prescription in the elderly. The elimination half-lives of both propoxyphene and its even more potent metabolite, norpropoxyphene, are prolonged in healthy elderly subjects relative to young controls due to decreased renal and hepatic function. In young people, propoxyphene had a 13.2 day half-life, as compared to a 23.7 day half-life in the elderly group; norpropoxyphene pharmacokinetics showed a similar trend. With repeated dosing, at the recommended doses, the elderly subjects were thus exposed to a much higher dose of the drug for longer periods of time, increasing their risk of adverse reactions.[57]

In addition to the toxic effects on the heart, the central nervous system-related adverse effects of propoxyphene use may increase the likelihood of falls and hence fall-related fractures in the elderly. Propoxyphene is thus a drug inappropriate for prescription to the elderly as defined by the criteria described by Beers et al.[58] Kamal-Bahl, et al., showed that propoxyphene use is widespread in the institutionalized population, the population of elderly that is most vulnerable and in which propoxyphene use is most inappropriate. The rate of propoxyphene use, at 15.5%, was more than twice as high in this population as in community-dwelling elderly. Further, propoxyphene use was 1.48 and 1.45 times more likely in those elderly with a history of osteoporosis and hip fracture respectively, conditions that, according to Beers, et al., should explicitly contraindicate propoxyphene.[59] Won, et al., found a similar rate of propoxyphene prescribing in nursing homes at 18.2% of prescriptions, the 2nd most prescribed analgesic behind only acetaminophen.[60]

Addiction

Evidence of dependence on propoxyphene is well-documented in the literature. Clinical trials and published case histories illustrate that propoxyphene can produce physical addiction, as manifested by withdrawal symptoms, strong psychological dependence, and tolerance. Reports on propoxyphene dosage suggest addiction can occur at less than the maximum recommended daily dose of 390 mg. and unequivocally confirm addiction at just twice the recommended daily dose. Particularly for the elderly, the long-term use consequent to addiction can have devastating consequences because of the greater build-up of the cardio-toxic metabolite, norpropoxyphene in older people.

In a well-controlled, double-blind study performed at Harvard Medical School, patients with pain were given 65 mg. of Darvon 4 times daily. (The maximum recommended daily dose is one 65 mg. pill taken 6 times daily.) Three out of 19 patients taking this dose for 3 months developed withdrawal symptoms "suggesting addiction" compared to 4 out of 16 developing withdrawal symptoms after discontinuation of 32 mg. codeine per day. None of the 14 patients using a non-narcotic analgesic ethoheptazine (Zactane) instead of propoxyphene had symptoms of addiction.[61]

In Lilly's own case reports, which they submitted to the Justice Department in 1970, is a description of a patient who took 8 Darvon tablets daily (1 1/3 the recommended dose) and was said to have "psychic dependence." Another case report describes physical addiction in a man using 10 capsules per day (1 2/3 the recommended dose) for one year.[62]

Additionally, Fraser et al. reported that propoxyphene has addiction liability, demonstrating several hallmarks of addiction caused by the drug. These include propoxyphene's abilty to partially suppress the symptoms of morphine abstinence after 800 mg. (twice the recommended daily dose) is administered within one 24-hour period. It can also induce patients to experience effects similar to those from marijuana, heroin, morphine, and cocaine after oral administration in single doses of 355-650 mg. or 6-10 pills.[63] (The maximum recommended daily dose is one 65 mg. pill six times daily.)

Given its euphoria and addiction causing properties, propoxyphene is a drug with high potential for abuse. Between September 1976 and March 1977, the National Youth Polydrug Study surveyed 2,750 teenagers, 18 or younger. 488 subjects (17.7%) indicated that they had used Darvon or Darvon-N in their lifetimes, making propoxyphene the most frequently mentioned opiate drug. When ranked in terms of prevalence of "regular use" (i.e. at least once a week), Darvon/Darvon-N was second only to heroin.[64] In a 1976 study of a stratified

probability sample (by region, race, income, etc.) of 3,024 19-30 year old men, whose names were obtained from selective service records, it was found that 14.9% had used propoxyphene for non-medical purposes. Projected to the total US male population at that time, this suggests that 3 million American men in this age group (19-30) had used propoxyphene for non-therapeutic purposes.[65]

A more recent study by Ng, et al., reports that propoxyphene is a drug of primary abuse. Of the records of 73 propoxyphene abusers from a detoxification unit, 67% revealed that propoxyphene was the first opiate ever abused. The authors concluded that propoxyphene abuse is not secondary to heroin dependence.[66] Thus, propoxyphene poses a serious addiction risk.

Emergency Room Visits

Propoxyphene is still a major drug of abuse, as can be seen by the yearly number of emergency room visits reported by the Drug Abuse Warning Network (DAWN). Data from 1994-2002 indicate approximately 5,000 emergency room visits related to propoxyphene each year. In 2002, 1680 out of 4676 or 36% of people with an emergency room visit related to propoxyphene indicated that either psychic effects or dependence on propoxyphene were the reason for the emergency room visit.[67] Thus, propoxyphene abuse remains a major problem.

Conclusion

The Health Research Group urges, by this petition, the immediate implementation of a phased withdrawal from the U.S. prescription drug market of all propoxyphene-containing products. This should be initiated immediately because this drug has considerable human toxicity, addiction potential, abuse liability, but very limited therapeutic usefulness. That this drug, which has been associated with at least 7109 reported deaths including 2110 in which the death was accidental and many times more emergency room visits since September 1972, is a serious public health problem is not disputable. Only by banning propoxyphene can this danger be eliminated.

We agree with the January 2005 decision of the U.K. to phase out this dangerous drug because efficacy of this product "is poorly established and the risk of toxicity in overdose, both accidental and deliberate, is unacceptable" and find it inexcusable that the U.S. FDA is lagging so far behind in taking this important, life-saving public health regulatory action.

Sidney M. Wolfe, M.D.
Director

Dan Suzman,
Research Associate

Public Citizen's Health Research Group

Ulf Jonasson
Doctor of Public Health,
Nordic School of Public Health, Gothenburg, Sweden
ulf.jonasson@wtnord.se

Birgitta Jonasson PhD,
Department of Forensic Medicine,
University of Uppsala, Sweden

ENDNOTES

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HUNTON
WILLIAMS

HUNTON & WILLIAMS LLP
1900 K STREET, N.W.
WASHINGTON, D.C. 20006-1109

TEL 202 • 955 • 1500
FAX 202 • 778 • 2201

GARY C. MESSPLAY
DIRECT DIAL: 202-955-1933
EMAIL: gmessplay@hunton.com

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April 14, 2006

FILE NO: 67037.000003

HAND-DELIVERED

Dockets Management Branch
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

COMMENTS ON CITIZEN PETITION
Docket No. 2006P-0090

The undersigned, on behalf of Xanodyne Pharmaceuticals, Inc. ("Xanodyne"), which markets Darvocet A500® (propoxyphene napsylate and acetaminophen), Darvocet-N® 50 (propoxyphene napsylate and acetaminophen), Darvocet-N® 100 (propoxyphene napsylate and acetaminophen), Darvon® (propoxyphene hydrochloride), and Darvon-N® (propoxyphene napsylate), submits these Comments to the February 28, 2006, Citizen Petition filed by Public Citizen.

For the reasons discussed below, the Petition should be denied.

I. OVERVIEW

Public Citizen's February 28, 2006, Citizen Petition requests that the United States Food and Drug Administration (FDA) immediately begin the phased removal of propoxyphene-containing drug products from the marketplace. Drug product approval may be removed only under specific circumstances as set forth in the Federal Food, Drug, and Cosmetic Act and its implementing regulations. The Secretary of the Department of Health and Human Services may withdraw approval of an application or abbreviated application for a new drug if he or she finds it presents an "imminent hazard" to the public health. In the alternative, FDA may remove approval after it determines that clinical or scientific data demonstrate the drug is unsafe under the conditions of use for which the product is approved and labeled or that there is a lack of substantial evidence from adequate and well-controlled studies that the drug will have the effect it purports to have under the conditions of use prescribed in its labeling.

In this case, Petitioner does not contend that propoxyphene represents an "imminent hazard." Therefore, these products may be removed by FDA only upon a determination that they are

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unsafe or ineffective. Public Citizen's Petition fails to present credible scientific evidence that propoxyphene drugs are unsafe or ineffective when used according to approved labeling.[1]

More than 25 years ago, Public Citizen similarly petitioned FDA to remove propoxyphene drugs from the market. The group has now repeated its removal request, supported with little more than the data it presented in its 1978 Citizen Petition, which was denied in 1979 by the Department of Health, Education, and Welfare (HEW) (the predecessor of the Department of Health and Human Services). Public Citizen's Petition does not raise any new safety or efficacy issues that have not already been considered by FDA. For nearly 50 years, FDA, along with other national governmental bodies tasked with regulating pharmaceutical products, have carefully watched over the use of propoxyphene drugs and have considered propoxyphene safe and effective when taken as directed. While all prescription and over-the-counter pharmaceutical products carry some risks, propoxyphene has a long history of safe use in the United States and is an essential option in the treatment of mild to moderate pain.

Pain, a condition that stems from many diverse disease processes and conditions, is highly subjective and varies based on its source and duration. Acute pain generally results from injury, surgery, or sudden illness, and typically resolves as the body heals, while chronic pain is often tied to disease or injury. Whether chronic or acute, pain can significantly affect functioning and reduce a patient's quality of life. The diversity and subjectivity of pain make it difficult to treat, thereby necessitating a wide variety of therapeutic options.

Propoxyphene has been one of the most widely prescribed treatments for mild to moderate pain since FDA first approved Darvon nearly 50 years ago. Propoxyphene was first approved in the 1950s based on its safety. Subsequently, pursuant to the Kefauver-Harris Drug Amendments of 1962, propoxyphene underwent a second, independent evaluation of the product's efficacy. This second evaluation found the drug efficacious in the treatment of mild to moderate pain. The product's safety and efficacy was reaffirmed each time a new propoxyphene drug product was reviewed and approved by FDA, including where sponsors requested new formulations, new strengths, and new combinations of the product with other active ingredients. As recently as 2003, FDA approved a Darvocet line extension, Darvocet A500 (propoxyphene napsylate and acetaminophen), and subsequently approved a generic version of that same product in 2006.

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[1] In addition, Petitioner fails to acknowledge that other requirements must be satisfied before a product may be withdrawn from the market, including notice to all applicants and opportunity for a hearing. *See* 21 U.S.C. § 355(e); *see also* 21 C.F.R. § 314.150.

As with all drugs, there are risks associated with propoxyphene use, including deaths associated with overdose and concomitant use with drugs and/or alcohol, and drug addiction. However, these risks have not prevented the safe use of propoxyphene in accordance with the approved prescribing information. The safe and appropriate use of propoxyphene is further safeguarded by its classification as a Schedule IV drug under the Controlled Substances Act. As a Schedule IV controlled substance, propoxyphene drugs are subject to specific registration, security, labeling and packaging, inventory and recordkeeping, import/export, and prescription requirements.[2]

Public Citizen's 1978 Petition requested a propoxyphene ban based on an alleged "imminent threat" the drug presented to the public health. After considering the 1978 Petition, HEW found there to be no imminent threat, declined to remove the drug from the market, and denied the Petition. As with the denied 1978 Petition, Public Citizen's 2006 Petition provides no credible scientific evidence to support an FDA withdrawal of the products.

Instead, Public Citizen approaches its 2006 Citizen Petition with inaccurate and misleading data and information to summarily suggest that propoxyphene drug products should be removed because the products are unsafe and not effective. Public Citizen provides no legitimate scientific or clinical evidence that propoxyphene products are not safe or effective when used according to the approved labeling. Rather, Public Citizen relies upon strained interpretations of the public literature and unpublished "personal communications," unsubstantiated claims regarding the effect of a propoxyphene metabolite, conclusory summaries of compilation data without true causal analyses, and largely irrelevant data from non-U.S. populations and dissimilar drug usage, bearing little correlation to the propoxyphene products utilized in the United States. Additionally, Public Citizen's reliance on the United Kingdom's (U.K.'s) experience with co-proxamol is misplaced and not relevant in the United States; as discussed below, in the U.K., the composition, use, and availability of propoxyphene-containing products is not compatible with the propoxyphene products in United States, where the drugs are regulated as controlled substances.

In failing to meet the necessary scientific and statutory evidentiary standard, Public Citizen's Petition should be denied.

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[2] *See* 21 U.S.C. Chapter 13, 21 C.F.R. Part 1300 *et seq.*

II. PROPOXYPHENE-CONTAINING PRODUCTS ARE SAFE AND EFFECTIVE

A. The Petition does not raise new safety or efficacy concerns.

For nearly 50 years, propoxyphene drugs have been considered safe and effective when taken as directed. Physicians have long found propoxyphene products to be safe and useful drugs in the treatment of mild to moderate pain. As a result, propoxyphene has been, and continues to be, widely prescribed. Since its first approval nearly 50 years ago, it is estimated that more than 600 million prescriptions for propoxyphene drugs have been dispensed. In 2005, over 26 million prescriptions were filled, making it one of the twenty-five most commonly prescribed drugs. Propoxyphene drugs are also used throughout the world, including in South America, Europe, Africa, Australia, and Asia. In addition to the fact that propoxyphene has been used for nearly 50 years to safely and effectively treat many millions of patients with pain, the extensive regulatory history of these drugs offers further support for their continued availability.

1. FDA has approved propoxyphene as safe and effective.

The Petition does not present information or data that FDA has not already evaluated and considered. FDA first reviewed the safety of propoxyphene-containing drugs when Eli Lilly and Company (Lilly) submitted new drug applications (NDAs) for its Darvon products in the 1950s. Following FDA approval of the Darvon products, Lilly began marketing the drug as a single agent, containing a dose of either 32 mg or 65 mg propoxyphene hydrochloride, and in combination with aspirin, phenacetin, and caffeine.

After the Kefauver-Harris Drug Amendments of 1962, which in part required the effectiveness of a drug to be established prior to marketing, FDA commenced a Drug Efficacy Study to review drug products approved before 1962 on the basis of safety alone. The National Academy of Sciences/National Research Council (NAS/NRC) Drug Efficacy Study Group specifically evaluated studies related to the efficacy of propoxyphene drugs, and concluded they are effective for the relief of pain. Based on the panel's recommendations, FDA issued a Drug Efficacy Study Implementation ("DESI") notice, confirming the efficacy of Darvon products for the treatment of mild to moderate pain, and approving the continued marketing of 65-mg formulations.[3] The

[3] 34 Fed. Reg. 6264 (April 8, 1969).

DESI notice permitted the 32-mg formulation to remain on the market for the purpose of treating patients for whom that dosage was shown to be effective.[4]

Subsequent to the DESI review, FDA periodically reviewed the safety and efficacy of modified propoxyphene formulations when Lilly submitted NDAs for drugs containing the napsylate salt of propoxyphene, either alone or in combination with acetaminophen. In 1972, after considering the differences between the dosing of the hydrochloride and napsylate salts of propoxyphene, FDA approved these products based on standards of safety and efficacy.[5]

2. FDA has re-examined the safety and efficacy of propoxyphene.

In addition to FDA's specific approval of a number of propoxyphene drugs, such as propoxyphene hydrochloride, propoxyphene napsylate, and propoxyphene/acetaminophen in combination, as both safe and effective, FDA and HEW have re-evaluated the safety and efficacy of propoxyphene-containing products. In November 1978, the Health Research Group of Public Citizen petitioned HEW to either: (1) immediately ban marketing of propoxyphene as an "imminent hazard" under 21 U.S.C. § 355(e) and make it available only as an investigational drug for treating narcotics addicts, or (2) reschedule it as a Schedule II narcotic under the Controlled Substances Act.[6] In response to the 1978 Petition, FDA Commissioner Donald Kennedy and FDA's Bureau of Drugs evaluated the scientific and medical issues related to

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[4] 37 Fed. Reg. 26538 (Dec. 13, 1972).

[5] For a discussion of the differences between the propoxyphene HCl and napsylate salts, see *infra* section IV.

[6] Citizen Petition from Sidney M. Wolfe, M.D. and Public Citizen Health Research Group, to Joseph Califano, Secretary, Dept. of HEW (Nov. 21, 1978) (on file with FDA).

propoxyphene.[7] After reviewing FDA's evaluation, HEW Secretary Joseph Califano denied the Petition, finding that propoxyphene did not present an "imminent hazard" to public health.[8]

Before reaching their ultimate conclusion on the 1978 position, FDA and HEW evaluated many of the identical safety and efficacy concerns raised in the current Petition. The current Petition's safety and efficacy concerns previously addressed by FDA include the following:

- The 1978 Petition and the current Petition both argue that many of the deaths reported as attributed to propoxyphene are due to a so-called "cardiotoxic" effect of its major metabolite, norpropoxyphene.[9] For example, the current Petition states, "Propoxyphene is implicated in a high proportion of accidental deaths each year, because the majority of the drug is converted into a metabolite [(norpropoxyphene)] that is even more toxic and has a longer half-life than its parent compound."[10] However, in response to the 1978 Petition making similar allegations, HEW concluded there was little evidence that norpropoxyphene's effects were a "common factor in the deaths associated with propoxyphene."[11] The current Petition, in fact, provides no new data for this argument. Public Citizen merely restates the same unsubstantiated speculation that FDA considered and rejected more than 25 years ago.

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[7] *See* letter to the HEW Secretary, from Donald Kennedy, FDA Commissioner (Jan. 17, 1979) (on file with FDA), Memorandum from Director, Division of Neuropharmacological Drug Products, to Director, Bureau of Drugs (Jan. 15, 1979) (on file with FDA) [hereinafter 1979 FDA Recommendation].

[8] Order of the Secretary Denying Petition, HEW (Feb. 15, 1979) [hereinafter Order Denying Petition].

[9] Citizen Petition from Sidney M. Wolfe, M.D., Director, Public Citizen's Health Research Group, to Andrew von Eschenbach, M.D., Acting Commissioner, FDA 1 (Feb. 28, 2006) [hereinafter Petition].

[10] *Id.* at 2.

[11] Order Denying Petition, *supra* note 8, at 13.

- Petitioner repeatedly claims, in both the 1978 Petition and the current Petition, that even when taken as directed, propoxyphene drugs can cause accidental death. The current Petition states, for example, "Propoxyphene . . . can cause severe cardiovascular effects with overdose or *even when used as directed*" (emphasis added).[12] The Petition also repeatedly suggests that many of the reported propoxyphene-related deaths are accidental.[13] However, in 1979, FDA's Bureau of Drugs concluded: "there are *no well documented examples of deaths when the drug is taken under the approved conditions of labeling*" (emphasis added).[14] Furthermore, in the Order denying Petitioner's 1978 request, Secretary Califano stated: "there is no clear evidence to date demonstrating that the use of propoxyphene, *in the absence of tranquilizers or alcohol*, has caused accidental death" (emphasis added).[15] The Secretary further remarked that "most identified propoxyphene-associated deaths appear to be the result of misuses of the drug" and referenced a report showing that some of the cases classified as "accidental" involved "such large quantities of propoxyphene that it is very likely that the drug was not being used for therapeutic purposes at the recommended dosage level."[16] The current Petition provides no examples of, or direct support for, the contention that propoxyphene causes accidental, unintended death when used as directed. Thus, just as in 1978, propoxyphene remains safe when used according to the approved conditions of labeling.

- Both Petitions argue that other analgesics, including acetaminophen or aspirin, are better alternatives to propoxyphene.[17] However, in its 1979 analysis of propoxyphene, FDA appropriately noted that acetaminophen and aspirin are also toxic at high doses and may

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[12] Petition, *supra* note 9, at 4.

[13] *E.g.*, *id.* at 4.

[14] 1979 FDA Recommendation, *supra* note 7, at 2.

[15] Order Denying Petition, *supra* note 8, at 13.

[16] *See id.*, (citing Wright Baselt *et al.*, *Propoxyphene and Norpropoxyphene Tissue Concentrations in Fatalities Associated with Propoxyphene HCl and Propoxyphene Napsylate*, 34 ARCH. TOXICOL. 145-152. (1975)).

[17] *See, e.g.*, Petition, *supra* note 9, at 3.

> not be safe options for some patients.[18] Specifically, FDA stated: "they [acetaminophen and aspirin] are toxic at high doses and can produce adverse reactions in certain individuals including severe allergic reactions and, in the case of aspirin, gastrointestinal bleeding and peptic ulcer."[19]

Just as FDA and HEW rejected Public Citizen's 1978 Petition, the same result is warranted in response to the 2006 Petition, which does little more than restate the same arguments based on almost entirely the same information.

Although FDA's and HEW's conclusions regarding the 1978 Petition resulted in HEW's denial of that Petition, due to concern over the use of propoxyphene in suicides and deaths resulting from the interaction of alcohol and/or other drugs with propoxyphene, HEW directed FDA to hold a public hearing on the continued marketing of propoxyphene. HEW also advised that it would forward any recommendations regarding the possible rescheduling of propoxyphene to the Department of Justice.[20]

Following the public hearings, FDA again determined that propoxyphene drugs were safe and effective, and propoxyphene drugs remained on the market. Importantly, the public hearing brought into specific focus certain safety issues that could be adequately addressed through additional education of practitioners. In response, Lilly agreed to revise the labeling of its propoxyphene products to emphasize further the warnings applicable to the improper use of the products.[21] Additionally, Lilly undertook an educational effort with doctors, pharmacists, and patients to provide and enhance warnings regarding the improper use of propoxyphene products.[22] Today, the approved labeling for propoxyphene products contains strong warnings

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[18] Indeed, virtually all drugs are toxic when misused and taken in high doses.

[19] 1979 FDA Recommendation, *supra* note 7, at 9.

[20] Order Denying Petition, *supra* note 8, at 20.

[21] KEY DOCUMENTS AND STATEMENTS RELATING TO HEARINGS CONDUCTED BY THE SENATE SELECT COMMITTEE ON SMALL BUSINESS AND THE FOOD AND DRUG ADMINISTRATION AND TO MEETINGS OF THE FDA DRUG ABUSE ADVISORY COMMITTEE, JANUARY-JUNE, 1979, ELI LILY AND COMPANY 7-9 (July 1979) (on file with Xanodyne).

[22] *Id.*

and precautions regarding appropriate use of the products. More specifically, the full prescribing information for propoxyphene products bears a boxed warning highlighting issues related to suicide, overdose, addiction, and concomitant alcohol or drug abuse.[23] Additionally, the package insert contains extensive information on how to manage a suspected drug overdosage.[24]

3. Propoxyphene's addictive properties are well-characterized, and appropriately managed.

The Petition argues that the addictive properties of propoxyphene warrant removal of all propoxyphene containing drug products from the market. However, many drug products have addictive properties and nevertheless may be safely and effectively utilized in patient therapy. In the United States, over 200 substances used for medical treatment are scheduled as controlled substances due to their addictive or abuse potential.[25] The proper management of this class of drugs is not product removal, but rather, adequate controls derived from scheduling. In the case of propoxyphene, it is successfully managed as a Schedule IV controlled substance. The Drug Enforcement Administration (DEA) has not taken steps or expressed any perceived need to further restrict the availability of propoxyphene by changing its scheduling.

As Petitioner notes, the addictive nature of propoxyphene drugs is well-documented. Investigations into the addictive properties of propoxyphene date back to the mid-1950s. At a meeting in 1957, before the enactment of the Controlled Substances Act of 1970, the Committee on Drug Addiction and Narcotics of the National Research Council reviewed studies on propoxyphene and found that it did not have the same addiction producing or sustaining properties as morphine, but that it would be in the public interest to apply to such substances some "modified form of control."[26] Ultimately, in 1977, the DEA issued an order placing

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[23] *See, e.g.*, Package Insert, Darvocet-N® 50 and Darvocet-N® 100 (propoxyphene napsylate and acetaminophen tablets).

[24] *See, e.g.*, *id.*

[25] U.S. DRUG ENFORCEMENT ADMINISTRATION, DRUG SCHEDULING, *available at* http://www.dea.gov/pubs/scheduling.html (last visited April 3, 2006).

[26] Letter from H.J. Anslinger, Commissioner of Narcotics, to Mr. T. P. Carney, Vice President, Eli Lilly and Company (Feb. 8, 1957) (on file with Xanodyne).

propoxyphene products in Schedule IV of the Controlled Substances Act.[27] The DEA based its decision on the following findings:

1. Propoxyphene has "a low potential for abuse relative to the drugs or other substances currently listed in Schedule III."
2. Propoxyphene has a "currently accepted medical use in treatment in the United States."
3. Abuse of propoxyphene "may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III."[28]

Schedule IV classification subjected propoxyphene drugs to registration, security, labeling and packaging, inventory and recordkeeping, import/export, and prescription requirements.[29]

Following the request of the 1978 Petition and another Petition filed by Dr. Edward Press, a public health officer for Oregon, to place propoxyphene into Schedule II, HEW conducted a scientific and medical evaluation of the drug. From that evaluation, HEW concluded there was insufficient evidence to justify reclassification.[30] In 1980, based on this assessment, the DEA announced in the Federal Register that propoxyphene would remain in Schedule IV.[31]

B. The Petition is Misleading in its Use of Data Regarding Propoxyphene-Related Deaths.

1. Petitioner's use of DAWN data is misleading.

The Petitioner's allegations rely heavily on its interpretation of data from the Drug Abuse Warning Network (DAWN). However, the Petition misrepresents the significance of data from

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[27] 42 Fed. Reg. 8636 (Feb. 11, 1977).

[28] *Id.*

[29] *See id.*; *see also* 21 C.F.R. Part 1300 *et seq.*

[30] 45 Fed. Reg. 3923 (Jan. 21, 1980).

[31] *Id.*

DAWN as it relates to deaths caused by propoxyphene. While FDA has used DAWN data to assess the abuse potential of prescription drugs,[32] DAWN data are not intended to scientifically assess a product's safety and are not a sufficient basis for substantive regulatory action.

DAWN data on drug abuse deaths do not provide an accurate reflection of actual deaths caused by a specific drug; rather, they only show whether a particular drug was reported or "mentioned" by a medical examiner (ME) in a drug abuse death report submitted to DAWN.[33] This means the DAWN statistics repeated throughout the Petition involve any death where a ME found propoxyphene in the blood of a decedent. While the statistics Public Citizen relies upon suggest a temporal association between propoxyphene and death, causation is not proven through the DAWN data.

In fact, close examination of DAWN's 1999 ME data reveal the misleading nature of Petitioner's representations, such as, "from 1981 to 1999, DAWN reported 2,110 accidental propoxyphene-related deaths, or 38.6% of the total number of propoxyphene-related deaths."[34] In 1999, there were 466 mentions of propoxyphene out of a total of 11,651 reported drug abuse deaths.[35] Of these 466 propoxyphene mentions, only 6.7% (or 31) were cases where no other drugs were found.[36] In fact, propoxyphene was not the direct cause of death in the majority of even these cases. Only five (or 1.1%) of the 466 deaths were reported as being caused directly by propoxyphene alone; 29.2% of these 466 deaths were actually reported as being caused by "drug

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[32] DRUG ABUSE WARNING NETWORK, WHO USES DAWN?--FEDERAL AGENCIES, *at* http://dawninfo.samhsa.gov/about/whousesdawn/federal.asp (last visited April 3, 2006).

[33] *See, e.g.*, Dept. of Health and Human Services, Substance Abuse and Mental Services Admin., Office of Applied Sciences, DRUG ABUSE WARNING NETWORK ANNUAL MEDICAL EXAMINER DATA 1999, 2-4 (Dec. 2000) [hereinafter 1999 DAWN ME DATA] (describing methodology used to collect data).

[34] Petition, *supra* note 9, at 2.

[35] 1999 DAWN ME DATA, *supra* note 33, at 39.

[36] *Id.* at 54.

and physiological condition," "drug and external physical event," "drug and medical disorder," or "unknown."[37]

Furthermore, Petitioner neglects to examine DAWN statistics in light of the amount of propoxyphene ingested. DAWN data does not show drug quantities found by MEs, only whether a specific drug was present. The 1999 ME report shows that out of the 466 propoxyphene mentions, 69.7% represented multiple drugs being reported as the direct cause of death.[38] Given the wide use of propoxyphene for the treatment of pain, it would be expected that many of the propoxyphene DAWN mentions reporting more than one drug as the direct cause of death were actually situations in which the decedent was taking propoxyphene as pain treatment appropriately, and not abusing it.

Petitioner admits other drugs were found along with propoxyphene in nearly all of the cases reported by DAWN. However, the admission is buried among suggestions that there was a causal relationship between propoxyphene and these deaths. In fact, immediately following this acknowledgment, the Petition states: "toxicity makes causation [between propoxyphene consumption and deaths where propoxyphene was mentioned] likely."[39] Petitioner's unscientific, self-determined "likely" standard is completely inadequate to meet the scientific, evidence-based standard required to justify market removal of an important and widely-used medication like propoxyphene.

The Petition's statements regarding "accidental" propoxyphene-related deaths are also misleading. For example, the Petition provides, "[propoxyphene's] toxicity accounts for the finding that only 30-40% of propoxyphene-related deaths are attributed to suicidal overdoses; over 40% have been found to be accidental."[40] Deaths reported by DAWN as "accidental/unexpected" are not necessarily directly attributable to an overdose or use of any specific drugs. Some of the cases reported included individuals who were taking propoxyphene as directed for therapeutic purposes, and abusing a different drug altogether. Other cases

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[37] *Id.* at 47 & 51.

[38] *Id.*

[39] Petition, *supra* note 9, at 7.

[40] *Id.* at 4

reported included drug abuse, but an incident or physical trauma (such as an injury) actually caused the death.[41] Therefore, Petitioner's correlation between propoxyphene's toxicity and the number of accidental deaths reported by DAWN is inaccurate and misleading.

Petitioner also improperly compares findings from different ME panels. DAWN draws comparisons between different years based on data from a "consistent panel" of MEs.[42] DAWN specifically advises that "[f]indings from [one] consistent panel must not be compared with findings from earlier consistent panels" because the consistent panel changes for each period reported.[43] DAWN does examine trends over time using findings from a consistent panel; for example, DAWN provides trend tables for 1996 to 1999.[44] Petitioner, however, compares DAWN data from non-consistent panels of ME's: Figure 1 depicts trends from 1981-2002 and Petitioner directly states, "Whereas 227 deaths were reported in 1981, a high of 459 was reported in 2002."[45] Based on DAWN's own stated limitations, such comparisons are inaccurate because the panel from 1996-1999 was not consistent with panels from the other years quoted by Petitioner.

Furthermore, Petitioner's Figure 1, a graph showing DAWN reported propoxyphene-related deaths from 1981 to 2002, is blatantly misleading. Instead of showing deaths per year over this period in order to determine if the number of deaths are trending in a particular direction, Petitioner depicts cumulative deaths.[46] Not surprisingly, given that the number of deaths reported to DAWN have remained fairly constant over this time period,[47] Figure 1 shows a predictable increase of cumulative deaths over the years (as would any drug's cumulative

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[41] *See* 1999 DAWN ME DATA, *supra* note 33, at 51.

[42] A "consistent panel" is composed of the subset of total ME facilities reporting data for at least 10 months of a contiguous number of years. *E.g.*, *id.* at ix.

[43] *See, e.g.*, *id.* at 5.

[44] *Id.* at 66-90.

[45] Petition, *supra* note 9, at 8.

[46] *Id.*

[47] *Id.*

deaths). However, if not examined carefully, this figure leads the casual observer to conclude that the number of deaths since 1981 has been sharply increasing. This is not the case.

Besides compiling medical examiner data, DAWN also reports on drug-related emergency department (ED) visits. In January 2003, DAWN published a report on Narcotic Analgesics, showing trends from 1994 to 2001. This report provides that during this time period, the estimated number of ED visits involving the entire class of narcotic analgesics increased 117% (41,687 in 1994 to 90,232 in 2001).[48] However, when examining data for the specific drugs involved, propoxyphene mentions actually decreased from 6,731 in 1994 to 5,361 in 2001.[49] Thus, ED mentions of propoxyphene are *steadily declining*, even though narcotic analgesic mentions are rising rapidly. Virtually every other narcotic analgesic drug increased during this time.[50]

The Petition fails to acknowledge that removal of propoxyphene drugs from the market will result in patients being prescribed other painkillers as an alternative. So, instead of patients using a prescription drug such as propoxyphene with well-characterized safety concerns, patients may be prescribed other drugs in the class whose overall safety profile is less well-known and, in some instances, associated with greater risks. Thus, from a public health perspective, removing propoxyphene from the market may have the unintended effect of exposing patients to greater risk.

2. Petitioner's statements that propoxyphene drugs are unsafe and ineffective are scientifically unsupported and misleading.

Several of the Petition's statements regarding safety lack scientific substantiation. For example:

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[48] Office of Applied Studies, Substance Abuse and Mental Health Service Admin., THE DAWN REPORT: NARCOTIC ANALGESICS, IN BRIEF 1 (Jan. 2003), *available at* http://www.oas.samhsa.gov/2k3/pain/DAWNpain.pdf (last visited March 31, 2006) [hereinafter NARCOTIC ANALGESICS].

[49] *Id.* at 3.

[50] *Id.*

- The study conducted by Verebely and Inturrisi relied upon in the Petition is cited to support the assertion that "[t]he fact that norpropoxyphene is cleared from the body more slowly than its parent compound and thus reaches considerably higher blood levels and is more cardiotoxic, explains the high risk of accidental overdose."[51] The study does not make this conclusion. Instead, the study merely measured plasma levels of propoxyphene and norpropoxyphene and found that "the plasma level of norpropoxyphene was more persistent" than that of propoxyphene.[52] Verebely and Inturrisi did not show or suggest that drug persistence caused a cardiotoxic effect that "explained" a "high risk" of accidental overdose. In fact, the Petition refers to no studies that find a correlation between the cardiotoxic effects of norpropoxyphene and a high risk of accidental overdose when propoxyphene is taken as indicated. This statement is thus unfounded and unsupported.

- The Petition's argument that "chronic users of propoxyphene are at high risk of accidental overdose"[53] also lacks support. The Petition relies mainly upon unpublished, "personal communications" from the 1970s to create Table 1 showing blood propoxyphene and norpropoxyphene levels in a handful of individual regular users of propoxyphene products.[54] This dated, unsubstantiated, anecdotal information is completely inadequate for causing a product to be withdrawn from the market.

- Petitioner provides no support for the statement "even where propoxyphene shown (sic) to be effective for this kind of pain [chronic, such as that from cancer], chronic usage increases the likelihood of adverse events due to the buildup of the cardiotoxic

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[51] *Id.*

[52] Karl Verebely and Charles E. Inturrisi, *The Simultaneous Determination of Propoxyphene and Norpropoxyphene in Human Biofluids Using Gas-Liquid Chromatography*, 75 J. OF CHROMATOGRAPHY 195 (1973) .

[53] Petition, *supra* note 9, at 6.

[54] *See id.* at 5 (citing "Inturrisi CE. Personal communication to Dr. Sidney M. Wolfe. January 29, 1979" and "Gorodetsky C. Personal communication. February 8, 1979.").

propoxyphene metabolite, norpropoxyphene."[55] This proposition, in fact, has not been proven with any credible scientific data.

- The statement, "The dose of propoxyphene necessary for cardiac toxicity to occur overlaps significantly with the increased dose which a user dissatisfied with the analgesic effects and still in pain, may ingest"[56] is speculative and lacks scientific support. Propoxyphene drugs are dispensed only via prescription and have specific indications for use. Furthermore, propoxyphene drugs have been considered safe when taken as directed for nearly 50 years.

Petitioner, therefore, has not come forward with sufficient credible scientific evidence to support its contention that propoxyphene drugs are unsafe or ineffective. Rather, the Petitioner relies on unsubstantiated "personal communications" and draws scientifically unsupported conclusions from bits and pieces of information in the literature.

3. The Petition's assertion that propoxyphene is inappropriate for the elderly lacks scientific support.

While the Petition correctly notes that the elderly account for a large proportion of propoxyphene use, the studies relied upon to support the argument that propoxyphene use is "inappropriate" in the elderly and that there is an increased "risk of adverse reactions" in this population[57] are both flawed and misrepresented.

The Petition claims that the publication by Beers *et al.*[58] "put propoxyphene among the drugs that are inappropriate for use in the elderly due to its lack of significant efficacy and high incidence of adverse effects."[59] The Beers publication, however, is not a scientific study and is

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[55] Petition, *supra* note 9, at 4.

[56] *Id.* at 6.

[57] Petition, *supra* note 9, at 11-12

[58] Mark H. Beers *et al.*, *Explicit Criteria for Determining Inappropriate Medication Use in Nursing Home Residents*, 151 ARCH, INTERN. MED. 1825 (Sept. 1991).

[59] Petition, *supra* note 9, at 2.

replete with methodological flaws and bias. Beers was nothing more than a survey of 13 "experts" to "reach consensus on explicit criteria defining the inappropriate use of medications in a nursing home population."[60] These "experts" were personally selected by the study authors, rather than by scientific survey of the appropriate medical community. The qualifications of the "experts" were also not provided. Interestingly, one of the "experts" was Dr. Sidney Wolfe of Public Citizen, who submitted both the 1978 and current Petitions.[61] In addition, the survey questions were phrased in an inconsistent, biased manner. For example, one statement was phrased: "Pentazocine (Talwin) is not the best narcotic to use when a narcotic is needed," while the propoxyphene statement was: "Propoxyphene (Darvon, and as in Darvocet, Darvon Compound, Wygesic) should be avoided."[62] While both medications are narcotics and indicated for pain relief, the statement for propoxyphene was phrased such that it had no possible benefit, whereas the one for pentazocine was not. The selection of products in the survey also was biased, as only two analgesics (propoxyphene and pentazocine) were included, even though numerous other analgesics of varying efficacy and safety were available. No scientific evidence in the form of clinical studies, meta-analyses, or structured reviews was presented to support the opinions or the conclusions reached in the study.

Beers *et al.* updated their publication in 1997.[63] The 1997 publication used a similar "methodology" to the 1991 publication, but draws "consensus" from a panel of 6, rather than 13. Unlike the 1991 criteria, which stated that propoxyphene should be avoided, the criteria established for propoxyphene use in the 1997 study was slightly less biased. Panelists were asked if they agreed with the statement "Propoxyphene should generally be avoided in the elderly. It offers few analgesic advantages over acetaminophen, yet has the side effects of other narcotic drugs."[64] In addition, if the panelist believed the statement to be true, he was asked to

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[60] Beers, *supra* note 58, at 1825.

[61] *Id.* at 1830.

[62] *Id.* at 1826.

[63] Mark H. Beers, *et al.*, *Explicit Criteria for Determining Inappropriate Medication by the Elderly*, 157 ARCH, INTERN. MED. 1531 (Sept. 1997).

[64] *Id.* at 1533. The statistics for this study used a 90% confidence interval based on n=6, causing the results to have virtually no statistical validity. *Id.*

rate the severity of any problems that might arise because of use of the medication as stated.[65] "Severity" was defined conceptually as a combination of the likelihood that an adverse outcome would occur and the clinical significance should that outcome occur.[66] The study respondents opined that propoxyphene use, as described, was not "severe" based on this conceptual definition.[67]

Beers *et al.*'s publication was updated once again in 2003, this time by Fick *et al.*[68] The 2003 publication used a similar "methodology" as the 1997 Beers publication and also assigned it a "low" severity rating.[69] The Petition, however, makes no reference to either the 1997 or 2003 follow-up studies.

Petitioner also cites R.J. Flanagan *et al.* for the statement: "With repeated dosing, at the recommended doses," the elderly are "exposed to a much higher dose of the drug for longer periods of time, increasing their risk of adverse reactions."[70] However, this study conducted by R.J. Flanagan does not state that repeated dosing increases the risk of adverse reactions in the elderly. While Flanagan reported that propoxyphene and norpropoxyphene "often have prolonged half-lives in the elderly" and found that the results of their study "clearly demonstrate accumulation of [norpropoxyphene] and, to a lesser extent, [propoxyphene] itself in both young and elderly subjects," it concluded that "*the implications of this finding for therapy remain unclear since no side effects were reported in this study*" (emphasis added).[71]

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[65] *Id.* at 1532.

[66] *Id.*

[67] *Id.*

[68] Donna M. Fick *et al.*, *Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults*, 163 ARCH. INTERN. MED. 2716 (Dec. 2003).

[69] *Id.*

[70] Petition, *supra* note 9, at 11.

[71] R.J. Flanagan *et al.*, *Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dextropropoxyphene dosage*, 28 BR. J. CLIN. PHARMAC. 463, 468 (1989).

The Petition also states that "the central nervous system-related adverse effects of propoxyphene use may increase the likelihood of falls and hence fall-related fractures in the elderly."[72] However, no correlative, much less causative, evidence regarding this alleged link between propoxyphene use and falls is provided by Petitioner.

More importantly, propoxyphene products are labeled with a precaution for usage in the elderly, noting that an increased dosing interval should be considered in patients where the rate of propoxyphene metabolism may be reduced.[73] This precaution recognizes and warns that there may be a longer half-life of propoxyphene in some elderly patients, but provides for the safe management of the drug's use in these patients. Thus, FDA has specifically considered the issue of propoxyphene safety in the elderly and correctly determined that the risks raised by Petitioner are appropriately addressed through a precautionary statement in the product's label.

III. PROPOXYPHENE IS IMPORTANT THERAPY IN PAIN MANAGEMENT

A. Pain is diverse, debilitating, and prevalent.

Public Citizen's Petition is devoid of any discussion or even any acknowledgement of the real effects of pain on patients' lives. Each year, 25 million Americans experience acute (short-term) pain caused by injury or surgery.[74] Approximately 24% of Americans, or approximately 48 million people, suffer from chronic pain.[75] Pain greatly impacts those who suffer from it: two in five pain sufferers cannot work and three in five are unable to engage in daily activities.[76]

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[72] Petition, *supra* note 9, at 12.

[73] Package Insert, Darvocet-N® 50 and Darvocet-N® 100 (propoxyphene napsylate and acetaminophen tablets).

[74] American Academy of Pain Management, PAIN ISSUES: PAIN IS AN EPIDEMIC, *available at* http://www.aapainmanage.org/literature/Articles/PainAnEpidemic.pdf (last visited April 3, 2006).

[75] 1999 NATIONAL PAIN SURVEY, *at* http://www.chiro.org/LINKS/FULL/1999_National_Pain_Survey.html (last visited March 14, 2006).

[76] *Id.*

Unfortunately, pain is often inadequately treated, resulting in needless suffering, lost productivity, and excessive health care expenditures. In the United States, the total annual cost of pain, including healthcare expenses, compensation for lost work, and litigation, is estimated to be $100 billion.[77]

Pain is derived from many diverse disease processes and conditions. Some common causes of pain include migraines, headaches, medical procedures, burns, labor and delivery, surgery, back injuries, sickle cell disease, arthritis, neuropathic conditions, and cancer. As a result of the diverse nature of pain, managing patients with pain poses a significant challenge for healthcare professionals.

B. Effective pain management requires the availability of numerous therapeutic options.

The diverse nature of pain and the difficulty in appropriately treating it underlies the need to have a wide variety of treatment options, including propoxyphene, available to physicians. Indeed, some drugs are not viable options for patients. For example, Petitioner, relying upon a review article, states that ibuprofen is more effective than propoxyphene/acetaminophen and than propoxyphene alone. However, non-steroidal anti-inflammatory drugs (NSAIDs), which include ibuprofen and naproxen, may cause stomach bleeding, especially for individuals over 60, people who have had stomach ulcers or bleeding problems, and those who take anticoagulants or steroids, blood thinning or steroid drugs, other drugs containing an NSAID, have three or more alcoholic drinks per day while using the NSAID, or who take the NSAID for a longer duration than directed.[78] Additionally, long term, continuous use of NSAIDs have been associated with heart attack and stroke.[79] In fact, FDA's concern over the potential adverse effects of NSAIDs

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[77] BA Coda and JJ Bonica, *General Considerations of Acute Pain*, BONICA'S MANAGEMENT OF PAIN, 2001, at 222-40, M. Glajchen, Chronic pain: treatment barriers and strategies for clinical practice, 14 J. AM. BOARD FAM. PRACT. 178-83 (2001).

[78] *See, e.g.*, Drug Facts for Advil® (ibuprofen) products.

[79] *Id.*

prompted the Agency to request sponsors of such drugs to make labeling changes to their products.[80]

Petitioner also states that "propoxyphene alone has been shown to be no more effective than two aspirin for relief of most kinds of pain."[81] However, aspirin also can cause gastrointestinal bleeding.[82] Allergies are also a concern with both NSAIDs and aspirin.[83]

Petitioner also compares propoxyphene with other narcotic drugs. Petitioner, for example, states that codeine/acetaminophen is more effective than propoxyphene/acetaminophen, "although the difference is not statistically significant."[84] Codeine, however, is not always well tolerated, and can cause nausea and constipation.[85] Furthermore, Petitioner highlights the addictive properties of propoxyphene,[86] but codeine is considered more addictive, as evidenced by it being listed under Schedule II (codeine alone) or Schedule III (codeine combination products) under the Controlled Substances Act.[87] In contrast to these alternatives, propoxyphene has been associated with few side effects when taken as directed, as noted in its labeling: "In a survey conducted in

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[80] *See* Food and Drug Admin., COX-2 SELECTIVE (INCLUDES BEXTRA, CELEBREX, AND VIOXX) AND NON-SELECTIVE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), *at* http://www.fda.gov/cder/drug/infopage/COX2/default.htm (last visited March 30, 2006).

[81] Petition, *supra* note 9, at 3.

[82] *See, e.g.*, Package Insert for Bayer® Aspirin products.

[83] *See, e.g.*, Package Inserts for Advil® ibuprofen products and Bayer® Aspirin products.

[84] Petition, *supra* note 9, at 3.

[85] *See, e.g.*, prescribing information for Tylenol® with Codeine (acetaminophen and codeine phosphate tablets).

[86] *See* Petition, *supra* note 9, at 12-13.

[87] 21 C.F.R. §§ 1308.12 & 1308.13.

hospitalized patients, less than 1% of patients taking propoxyphene hydrochloride at recommended doses experienced side effects."[88]

All drugs have risks, as demonstrated by the risks enumerated above for NSAIDs and aspirin. However, the degree of risks associated with a particular drug exposure will vary among patients being treated for mild to moderate pain. It is important to have all these analgesic products available to treat pain due to the individualized needs of patients. Prescribing pain medication is a decision best left to the prescribing physician based on a number of factors. The Petition offers no credible medical or scientific justification for removing propoxyphene from the doctor's arsenal of tools over any other analgesic products.

C. The risks of propoxyphene are well-characterized and should not prevent its proper use.

Like all prescription medications, propoxyphene has risks. However, as a result of propoxyphene's use for nearly 50 years, practitioners are well-aware of these risks. Propoxyphene remains a widely-prescribed treatment option for pain. Physicians need the option of prescribing propoxyphene products to the appropriate patients who may benefit from it. Pain sufferers should not be deprived of an alternative that may relieve their pain because some patients may be inclined to abuse it. The potential for propoxyphene abuse is why it is subject to certain controls under the Controlled Substances Act.[89] The risks associated with propoxyphene use are adequately disclosed and described in the FDA-approved labeling of propoxyphene drugs.[90]

While petitioner suggests that removing propoxyphene products from the market will eliminate or reduce suicides, this contention does not flow naturally simply from a product removal. What is more likely is that removal of propoxyphene products from the market would only displace suicide. Petitioner inaccurately implies that restricting drugs typically involved with suicide

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[88] Package Insert, Darvocet-N® 50 and Darvocet-N® 100 (propoxyphene napsylate and acetaminophen tablets).

[89] *See* 21 C.F.R. Part 1300 *et seq.*

[90] Package Insert, Darvocet-N® 50 and Darvocet-N® 100 (propoxyphene napsylate and acetaminophen tablets).

greatly reduces suicide and that individuals intent on suicide will not move to another drug to attempt the act. Petitioner does this by showing a decline in the number of barbiturate and total drug suicides from 1968 to 1976 and suggesting the decline is due to the imposition of scheduling restrictions on barbiturates.[91]

Providing the number of barbiturate and total drug suicides from the late 1960s to the mid-1970s to show how "restricting the availability of barbiturates by imposing Schedule II controls had a marked positive effect on reducing the number of barbiturate suicides," and then conjecturing that removing propoxyphene from the market rather than merely restricting its use would result in a decline total suicides,[92] is inaccurate and based on flawed logic. Petitioner neglects to consider the fact that suicides would occur even if no drugs were available and provides no information regarding total suicides. The majority of suicides, in fact, do not occur with drugs, but with firearms.[93] Removing propoxyphene drugs from the market will likely lead suicidal persons to move to another method of suicide, whether drug or some other means.

IV. THE U.K.'S EXPERIENCE WITH CO-PROXAMOL IS DISTINGUISHABLE FROM THE USE AND AVAILABILITY OF PROPOXYPHENE-CONTAINING PRODUCTS IN THE UNITED STATES

The Petition notes that the U.K. ordered the phased withdrawal of co-proxamol from the market in January 2005. Indeed, the British Medicines and Healthcare Products Regulatory Agency (MHRA) withdrew co-proxamol from the market because it did not believe the benefits outweighed the risks, reporting that there are around "300-400 self-poisoning deaths [in the U.K.] each year, of which around a fifth are accidental" involving the product.[94] The situation in the U.K., however, is very different from that in the United States.

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[91] Petition, *supra* note 9, at 10-11.

[92] *Id.* at 10.

[93] *See e.g.*, Centers for Disease Control and Prevention, *Deaths, Injuries, 2002*, NATIONAL VITAL STATISTICS REPORT, Jan. 31, 2006, at 10 (stating that in 2002, firearm suicide accounted for 54.1 percent of suicides).

[94] Medicines and Healthcare Products Regulatory Agency, QUESTION AND ANSWER DOCUMENT: CO-PROXAMOL: OUTCOME OF THE REVIEW OF RISKS AND BENEFITS (Jan. 31, 2005),

(continued...)

Co-proxamol cannot be compared to products on the market in the United States. Co-proxamol is a fixed combination product containing 32.5 mg propoxyphene hydrochloride and 325 mg acetaminophen.[95] In the United States, products such as Darvon contain 65 mg propoxyphene hydrochloride, twice the amount of propoxyphene as in co-proxamol.[96] The lower quantity of propoxyphene found in co-proxamol likely resulted in the U.K.'s conclusion that "[t]here is no robust evidence that efficacy of this combination product is superior to full strength paracetamol alone in either acute or chronic use."[97] FDA has recognized that propoxyphene may not be effective at nearly the same level as the amount contained in co-proxamol. As described above, in its DESI review of propoxyphene products, FDA found that the efficacy of the 32 mg dose of propoxyphene hydrochloride was limited.[98] Today, a 32 mg dose of propoxyphene is not even available in the United States. Thus, the risk-benefit ratio in the United States is entirely different than in the U.K.

Additionally, propoxyphene hydrochloride products constitute only a fraction, less than 4%, of total propoxyphene drug prescriptions in the United States.[99] Instead, the vast majority of propoxyphene prescriptions in the United States are for propoxyphene napsylate products.

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available at http://www.mhra.gov.uk/home/groups/pl-a/documents/drugsafetymessage/con019462.pdf (last visited March 31, 2006).

[95] *Id.*

[96] Package Insert, Darvocet-N® 50 and Darvocet-N® 100 (propoxyphene napsylate and acetaminophen tablets).

[97] Medicines and Healthcare Products Regulatory Agency, WITHDRAWAL OF CO-PROXAMOL PRODUCTS AND INTERIM UPDATED PRESCRIBING INFORMATION (Jan. 31, 2005), *available at* http://www.mhra.gov.uk/home/groups/pl-a/documents/drugsafetymessage/con019461.pdf (last visited March 23, 2006).

[98] 37 Fed. Reg. 26538 (Dec. 13, 1972).

[99] *See* IMS National Prescription Audit.

Propoxyphene napsylate is considerably less soluble than propoxyphene hydrochloride.[100] Due to this lower solubility, the absorption rate of the napsylate salt, including very large doses, is significantly slower than that of equimolar doses of the hydrochloride.[101] This faster absorption rate of the hydrochloride salt increases the toxic effects of the product when taken at higher doses than indicated.[102] This would explain the higher incidences of deaths related to co-proxamol in the U.K., which consisted of propoxyphene hydrochloride, while the United States population primarily uses the napsylate formulation.

Moreover, propoxyphene products are not subject to the same controls and warning requirements in the U.K. as they are in the United States. First, propoxyphene is not considered a "controlled substance" in the U.K. as it is in the United States.[103] Additionally, the labeling of co-proxamol in the U.K. is quite different from the FDA-required labeling of propoxyphene products in the United States. In sharp contrast to the extensive warnings required in the labeling of propoxyphene products in the United States, key information provided in co-proxamol labeling in the U.K. is not uniform: of the 18 products licensed in the U.K., 17 advised avoiding alcohol and the other mentioned that co-ingestion of alcohol with excessive doses of the product was a major cause of drug-related deaths; all warned of the risk of concomitant use of central nervous system depressants, but to varying degrees; and only 10 of the 18 licensed products contained a warning against use in patients who are suicidal or addiction prone, while five others gave precautions against use in patients with a psychological or personality disorder.[104]

Furthermore, Petitioner improperly attempts to extrapolate U.K. data related to drug overdose involving co-proxamol in England and Wales to the United States ("in those two countries alone, with a population of 53 million people, approximately 18% of the size of the United States, there

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[100] Package Insert, Darvocet-N® 50 and Darvocet-N® 100 (propoxyphene napsylate and acetaminophen tablets).

[101] *Id.*

[102] *Id.*

[103] *See* Committee on Safety of Medicines, Subcommittee on Pharmacovigilence, RISK: BENEFIT OF CO-PROXAMOL PRODUCTS (April 15, 2004) (on file with Xanodyne).

[104] *Id.*

were an estimated 60 to 80 accidental deaths a year from co-proxamol"[105]) and uses studies examining propoxyphene overdose deaths in the U.K. and Sweden to show the "dangers" of "poisoning from propoxyphene" and argue that it should be removed from the market in the United States.[106]

Among these different countries, these drug products differ in composition, as well as how they are controlled and labeled, and how physicians prescribe them. Additionally, a multitude of factors contribute to drug abuse and suicide rates, some of which are societal, making drug abuse and suicide data from foreign countries not particularly relevant in the United States. In fact, according to one of the studies cited by Petitioner, 18% of all drug-related deaths from 1977 to 1999 were due to poisoning alone and co-proxamol was the "second most common prescribed drug used for suicides," after tricyclic antidepressants.[107] Thus, co-proxamol appears to be one of the "suicide drugs of choice" in the U.K. That is not the case in the United States.

The differences among countries has been recognized by the U.K. In its report on the risks and benefits of co-proxamol products, the U.K.'s Committee on Safety of Medicines Subcommittee on Pharmacovigilence cited the same studies by Jonasson as Petitioner discusses, but subject to the following qualification:

> Swedish data cannot be extrapolated to other countries. National prescribing patterns for analgesics and CNS depressants, the prevalence of drug abuse and alcohol consumption and differing population structures will produce major international variations in patterns of DXP [propoxyphene]-related deaths. [Additionally,] . . . in Sweden DXP is used for detoxification of opiate addicts and is frequently a drug of abuse.[108]

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[105] Petition, *supra* note 9, at 1.

[106] *Id.* at 6-7.

[107] Keith Hawton *et al.*, *Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self-poisoning*, 326 BMJ 1006 (May 10, 2003).

[108] RISK: BENEFIT OF CO-PROXAMOL PRODUCTS, *supra* note 103.

V. CONCLUSION

Propoxyphene products have a long history of safe and effective use as labeled, having been approved nearly 50 years ago and continually used in multiple strengths, dosage forms, and combinations since then. The Petition does not present any credible scientific evidence that propoxyphene drugs present an imminent hazard to public health or that propoxyphene drugs are unsafe and ineffective when used according to approved labeling. Nor does the Petition raise any new safety or efficacy concerns that have not previously been considered and rejected by FDA.

For all the foregoing reasons, the Petition should be denied.

Respectfully submitted,

Gary C. Messplay

cc: Daniel L. O'Korn, Esquire
Vice President and General Counsel
Xanodyne Pharmaceuticals, Inc.

Regulatory History and Efficacy of Propoxyphene Products

Background package for

Joint meeting of

Anesthetic & Life Support Drugs Advisory Committee (ALSDAC)
and
Drug Safety & Risk Management Advisory Committee (DSaRM)

On January 30, 2009

Division of Anesthesia, Analgesia and Rheumatology Products
Center for Drug Evaluation and Research
US Food and Drug Administration

December 16, 2008

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REGULATORY BACKGROUND

Propoxyphene (PPX) products currently marketed in the United States include six single entity propoxyphene products and 22 propoxyphene and acetaminophen (APAP) combination products. Combination products with aspirin (ASA) and caffeine that were approved have been discontinued from marketing. The New Drug Applications (NDAs) for products identified as Reference Listed Drugs (RLDs) in the Orange Book are listed below:

Xanodyne Pharmaceuticals, Inc:

- NDA 10-997, Darvon (propoxyphene HCl)
- NDA 16-892, Darvon-N (propoxyphene napsylate)
- NDA 17-122, Darvocet (propoxyphene HCl and acetaminophen)

Watson Laboratories, Inc:

- ANDA 40-139, propoxyphene HCl and acetaminophen

Key points in the regulatory history of the PPX products:

1957: In 1938, the Food, Drug, and Cosmetic Act was passed and under the new authority, a demonstration of safety was required prior to marketing approval for a new drug. The first propoxyphene-containing products were approved in the US based on a demonstration of safety only. The innovator was Eli Lilly and Company (later transferred to Xanodyne Pharmaceuticals).

- NDA 10-997, for Darvon Capsules (Propoxyphene HCl 32 mg and 65 mg), was approved on Aug 16, 1957
- NDA 10-996, for Darvon Compound Capsules, was approved on Nov 12, 1957 and included the following formulations:
  - Darvon Compound: Combination of 32 mg propoxyphene HCl, 389 mg aspirin and 32.4 mg caffeine
  - Darvon Compound-65: Combination of 65 mg propoxyphene HCl, 389 mg aspirin and 32.4 mg caffeine
  - Darvon with ASA: Combination of 65 mg propoxyphene HCl and 325 mg aspirin

1962: Drug Efficacy Study Implementation (DESI) evaluations began. In 1962, the Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act were passed. These amendments required, in addition to a demonstration of safety, a demonstration of efficacy prior to marketing approval.

DESI was designed to evaluate the efficacy of those drugs previously approved on the basis of safety alone. Panels of experts from the National Research Council of the National Academy of Science (NAS-NRC), reviewed what data were

available at the time of the DESI determination and found drugs effective, probably effective, ineffective, or ineffective as a fixed combination.

1969: The DESI conclusions for propoxyphene and its aspirin-containing combination drugs were published in the Federal Register. Based on the recommendation of the NAS-NRC, PPX and its ASA combination products containing 65 mg of propoxyphene HCl were found to be effective analgesics for mild to moderate pain (Federal Register April 8, 1969 and amended on Dec 13, 1972).

1971: Darvon-N Tablets (NDA 16-862), Darvon-N oral suspension (NDA 16-861), Darvon-N/ASA tablets (NDA 16-863), and Darvon-N/ASA capsules (NDA 16-829) were approved on Sept 9, 1971 based on bioequivalence to Darvon. Innovator: Eli Lilly and Company. Darvon-N differs from Darvon in the salt forms: napsylate vs. HCl.

1972: Darvocet-N capsules (PPX/APAP 32.5/325 mg combination) were approved on Dec 19, 1972 (NDA 17-122) based upon one efficacy trial (full factorial design study) and one positive bioequivalence/PK trial. Innovator: Eli Lilly and Company.
Approved indication: For the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever; 1-2 capsules q4-hr prn

1974: An Advisory Committee meeting was convened to discuss scheduling of propoxyphene products.

1976: An Advisory Committee meeting was convened to discuss abuse, dependence and the risk of fatal overdose with propoxyphene products. Propoxyphene was subsequently classified under Schedule IV of the Controlled Substance Act and labeling changes were made to the package insert.

1978: A Citizen's Petition from Health Research Group, requesting the removal of propoxyphene from the US market or upscheduling these products to Schedule II, was received and reviewed by FDA.

1979: An Advisory Committee meeting was convened to assess the safety and efficacy of propoxyphene. The committee concluded that propoxyphene should remain on the market, and should remain Schedule IV.

2006: A Citizen's Petition requesting decreasing acetaminophen strengths in the PPX/APAP combination products was received.

2006: A Citizen's Petition (February 28, 2006) requesting the removal of propoxyphene-containing products from the US market due to unfavorable benefit/risk ratio was received and reviewed.

2006: Pursuant to posting of the February 28, 2006 Citizen's Petition, Xanodyne Pharmaceutical, Inc, the current holder of the NDAs for the propoxyphene products, submitted comments on the 2006 Citizen's Petition regarding efficacy and safety of propoxyphene-containing products.

EFFICACY OF PROPOXYPHENE SINGLE INGREDIENT PRODUCTS

Efficacy assessment under DESI regulation

As noted, the efficacy of propoxyphene-containing products, Darvon, (NDA 10-997) and Darvon-Compound (NDA 10-996), was assessed under the FDA's DESI regulation according to the 1962 Kefauver-Harris Drug Amendments to the FD&C Act. FDA published the DESI results on April 8, 1969 with a follow-up notice and amendment on December 13, 1972 in the *Federal Register.* FDA concluded that, for NDA 10-997 and NDA 10-996, propoxyphene was effective for the relief of mild to moderate pain (as a general analgesic). The efficacy evidence in the NAS-NRC's report (see Attachment-1) primarily relied upon two published review articles: Beaver in 1966[1] (see Attachment-2) and Lasagna in 1964[2] (see Attachment-3).

In the review by Beaver, 18 clinical studies of propoxyphene (32, 65 and 130 mg) in acute pain (n=15) and chronic pain (n=4; duration of treatment ≤ 7 days) were evaluated. The studies were published between 1957 and 1965. The author drew the following conclusions:

- Propoxyphene is a mild oral analgesic which had proven superior to placebo in doses of 65 mg or greater but is of questionable efficacy in doses lower than 65 mg.
- Propoxyphene is definitely less potent than codeine (about 1/2 to 2/3 as potent as codeine)
- Propoxyphene 32-65 mg is certainly no more, and possibly less, effective than the usual dose of aspirin.

In the review by Lasagna, 13 clinical studies of propoxyphene in acute and chronic pain, published between 1955 and 1962 were included. Most of the publications evaluated data also considered in the review by Beaver. Lasagna drew a similar conclusion to Beaver, that propoxyphene is a mild analgesic, probably less effective than codeine and aspirin.

Based on the two literature review articles, NAR-NRC concluded that Darvon (65 mg and 100 mg) and Darvon-compound were usually superior to placebo in reasonably sensitive human analgesic assays, but additional methodology for the study of pain, particular for chronic pain indication, was needed.

Efficacy data from NDA submissions

Under the 1962 Kefauver-Harris Drug Amendments to the FD&C Act, evidence of both efficacy and safety was required for FDA approval of a new drug submitted after 1962. Applications for a variety of different formulations (dosage or salt forms or combination) of propoxyphene products were submitted to FDA for approval in late 1960s. These included:

- NDA 16-827: Darvon-N capsules (propoxyphene napsylate 50 mg and 100 mg)
- NDA 16-829: Darvon-N/ASA capsules (propoxyphene napsylate and ASA 100/325 mg)
- NDA 16-861: Darvon-N tablets (propoxyphene napsylate 50 mg and 100 mg)
- NDA 16-863: Suspension Darvon-N (propoxyphene napsylate 50mg/5ml) and Darvon-N/ASA tablets (propoxyphene napsylate and aspirin 100/325 mg)
- NDA 17-122: Darvocet-N tablets (propoxyphene napsylate and acetaminophen 50/325 mg or 100 mg/650 mg).

All of these NDAs were sponsored by Eli Lilly and Company. Except for Darvocet-N (NDA 17-122), all of these NDAs were approved on September 9, 1971. Efficacy was based on the bioequivalence of propoxyphene in Darvon (propoxyphene HCl 65 mg), previously found to be effective under the FDA's DESI evaluation.

EFFICACY OF PROPOXYPHENE/ACETAMINOPHEN COMBINATION PRODUCTS

Efficacy evidence from NDA submissions

Darvocet (propoxyphene HCl 32.5 mg and acetaminophen 325 mg), NDA 16-844, was approved on October 19, 1971 and Darvocet-N (propoxyphene napsylate 50 mg and acetaminophen 325 mg), NDA 17-122, was approved on December 19, 1971. The products only differ in the salt form. The data supporting approval were seven efficacy trials and bioequivalence PK trials using the propoxyphene-only products Darvon or Darvon-N as the comparator.

All seven efficacy trials had the same study design, treatment regimen and analgesic assessment, as summarized below:

<u>Study design:</u> Randomized, double-blind, placebo-controlled, single-dose, parallel-group of full-factorial design

<u>Study subjects:</u> Patients (n=30-48 per arm) with postpartum pain due to either uterine cramping or episiotomy.

<u>Treatment groups:</u>
A single oral dose of the following agents was administered:

- Propoxyphene HCl 65 mg or propoxyphene napsylate 100 mg (molar equivalent to propoxyphene HCl 65 mg)
- APAP 650 mg

- Propoxyphene HCl/APAP 65 mg/650 mg or propoxyphene napsylate/APAP 100 mg/650 mg
- Placebo

Analgesic assessment:
Patients were assessed over 6 hours following dosing for:
- Pain intensity (PI) score on a 5-point scale
- Pain relief (PR) score on a 5-point scale

Data analysis:
- Pain intensity difference (PID) and summed PID (SPID) over 6 hours
- Pain relief (PR) and total PR (TOTPAR) over 6 hours
- Analgesic score (PID+PR)

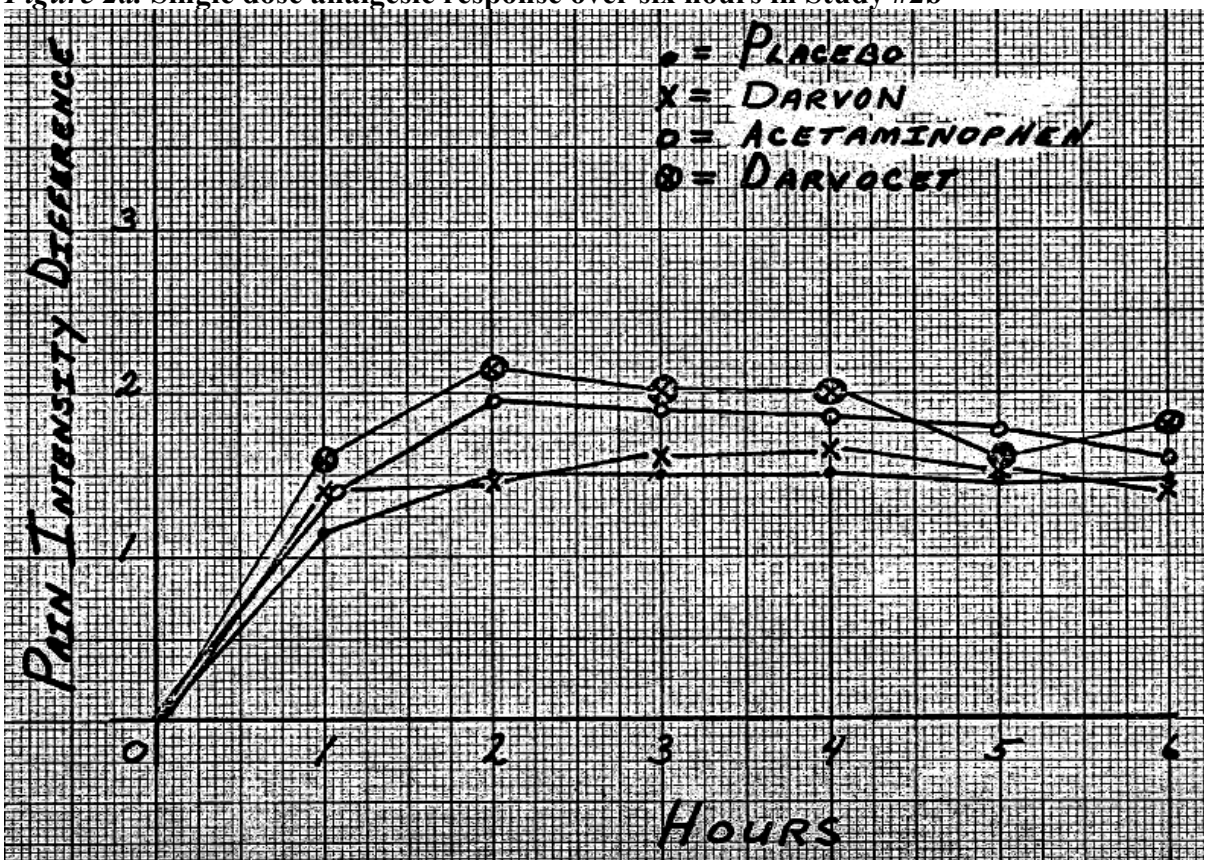
Results: The results of the pain intensity difference (PID), paint relief score and analgesic score (PID+PR) from each of seven trials are shown in Appendix 2 (Figures 1-7). The SPID and TOTPAR are summarized in Table 2. Except for one trial, Study #3a, all trials showed similar results summarized below:

Comparison of SPID and TOTPAR:
- The propoxyphene/acetaminophen combination was superior to placebo
- The propoxyphene/acetaminophen combination was slightly better than or similar to single ingredient acetaminophen.
- Single ingredient propoxyphene was either not different or slightly numerically better than placebo
- Single ingredient acetaminophen was superior to placebo and, in most of trials, was superior to single ingredient propoxyphene.

Comparison of PID, PR and analgesic scores (Figures 1-7 in Appendix 2; one representative PID curve over 6 hours is shown below in Figure 2b)**:**
- The propoxyphene/acetaminophen combination was superior to placebo and single ingredient propoxyphene
- The propoxyphene/acetaminophen combination overlapped with or was slightly better than the single ingredient acetaminophen
- The single ingredient propoxyphene mostly overlapped with, or was slightly better than placebo.
- The single ingredient acetaminophen was superior to placebo and, in most of trials, superior to single-ingredient propoxyphene.

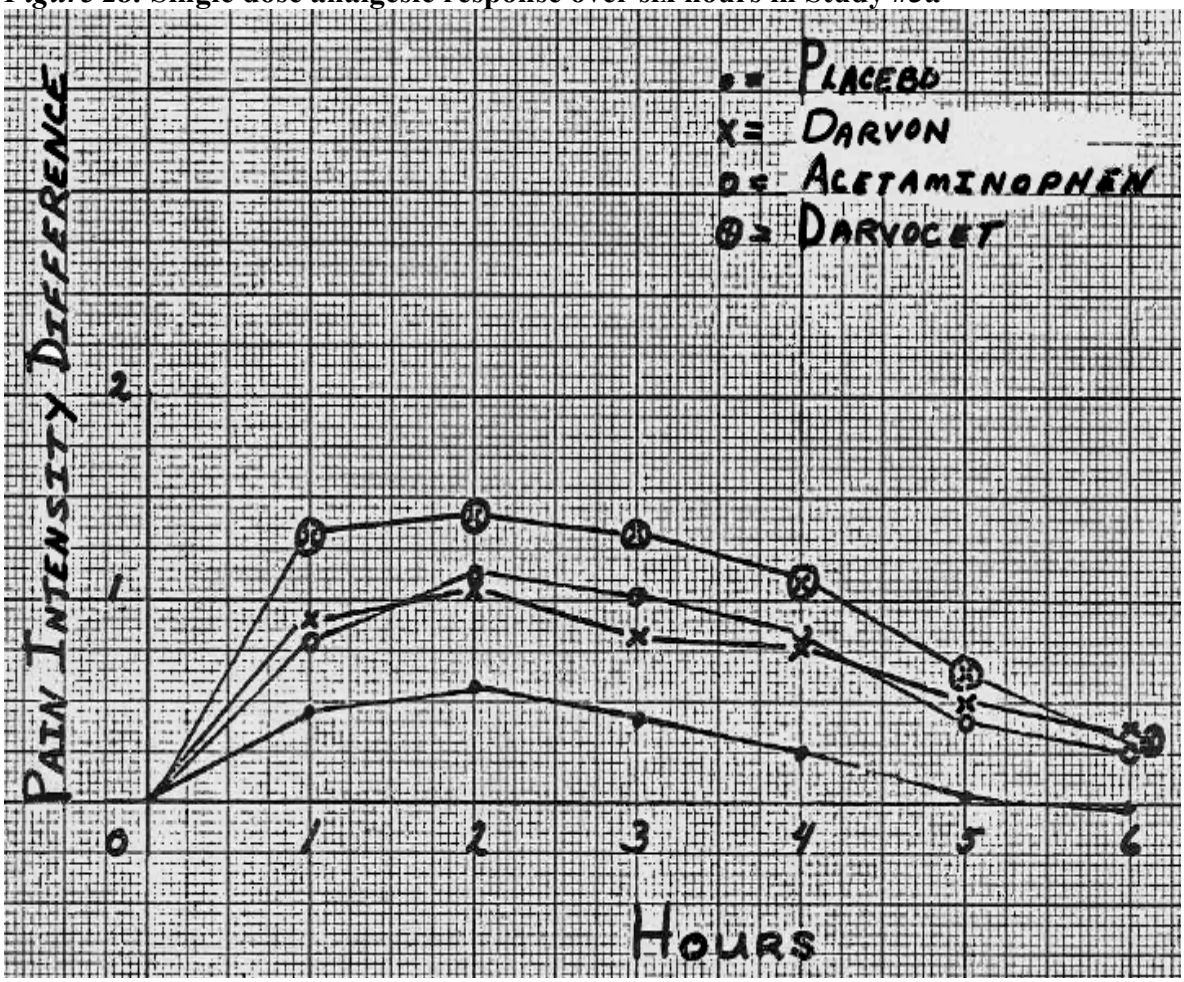
The sponsor concluded that the propoxyphene/acetaminophen combination had an additive analgesic effect at 1 and 2 hours after dosing.

Figure 2a. **Single dose analgesic response over six hours in Study #2b**



Study #3a was identical in design to the other six studies, but had a different set of results (see Figure 4 in Appendix 2). The PID over six hours is shown in Figure 2b. The propoxyphene/acetaminophen combination was superior to the single-ingredient acetaminophen and propoxyphene, and the single-ingredient acetaminophen and propoxyphene that were superior to placebo. The single-ingredient arms were similar in analgesic efficacy.

Figure 2b. **Single dose analgesic response over six hours in Study #3a**



Tables 1 and 2 provide a summary of all of the studies and results from NDA 16-844, Darvocet and NDA 17-122, Darvocet-N.

Table 1. **Summary of acute pain efficacy trials on propoxyphene/acetaminophen combination, NDA 16-844 (Darvocet) and NDA 17-122 (Darvocet-N)**

Protocol & Investigator	Subject (postpartum pain)	Efficacy Outcome
Study #1 Lash	N=192 (48/arm)	**SPID and TOTPAR:** PPX/APAP≈APAP > PPX ≈Placebo. Additive effects of PPX/APAP at 1 and 2 hours
Study #2a Lash	N=192 (48/arm)	**SPID and TOTPAR:** PPX/APAP≈APAP > PPX ≈Placebo. Additive effects of PPX/APAP at 1 and 2 hours
Study #2b Lash	N=192 (48/arm)	**SPID and TOTPAR:** PPX/APAP≈APAP > PPX ≈Placebo. Additive effects of PPX/APAP at 1 and 2 hours
Study #3a Bauer	N=122 (30-32/arm);	**SPID and TOTPAR:** PPX/APAP > PPX≈APAP > Placebo. Additive effects of PPX/APAP
Study #3b Bauer	N=53 (12-14/arm);	**SPID and TOTPAR:** PPX/APAP > Placebo; APAP>placebo. Additive effects of PPX/APAP at 1 not 2 hours
Study #4a Bauer	N=141 (34-36/arm);	**SPID and TOTPAR:** PPX/APAP≈APAP > PPX ≈Placebo
Study #4b Bauer	N=99 (24-25/arm)	**SPID and TOTPAR:** PPX/APAP≈APAP > PPX ≈Placebo;

Table 2. **Efficacy results across treatment groups, NDA 16-844 (Darvocet) and NDA 17-122 (Darvocet-N)**

Protocol	Subject (n/arm)	Summed Pain Intensity Difference (SPID)				Total Pain Relief (TOTPAR)			
		Placebo	PPX	APAP	PPX/APAP	Placebo	PPX	APAP	PPX/APAP
Study 1	48	6.1	6.4	8.0	8.5	11.8	12.3	14.7	15.0
Study 2a	48	6.1	6.2	6.8	8.2	9.9	10.5	11.8	13.2
Study 2b	48	8.6	9.1	10.5	11.2	12.3	13.0	15.9	16.1
Study 3a	**30-32**	**1.7**	**4.5**	**4.4**	**6.1**	**6.6**	**10.7**	**10.7**	**14.2**
Study 3b	12-14	3.9	5.4	6.5	8.4	11.1	12.9	14.1	17.8
Study 4a	34-36	4.3	3.4	5.8	4.9	10.3	11.9	14.1	13.7
Study 4b	24-25	7.4	7.4	9.0	9.8	14.5	14.9	17.2	18.0

The data in Table 2 represent the mean values from each treatment group. The standard deviation was not provided in the report. The statistical analysis was performed using Dunnett's test. PPX: propoxyphene HCl 65 mg or propoxyphene napsylate 100 mg; APAP: acetaminophen 650 mg and PPX/APAP: propoxyphene/APAP 65 mg/650 mg.

Supportive bioequivalence study: The sponsor conducted and submitted a number of bioequivalence/PK trials to support both NDAs. The FDA medical and statistical reviews note that one trial demonstrated that the propoxyphene in Darvocet-N was bioequivalent to the propoxyphene in Darvon-N capsules.

Efficacy data from the literature – Review Articles

As of December 1, 2008, based on a search of PubMed (1966-) and EMBASE (<1950-) using "propoxyphene" OR "dextropropoxyphene" as the MeSH term for PubMed or keyword for EMBASE and citations in the most relevant articles, we identified approximately 170 records under the category "randomized controlled trial" and approximately 90 records under "systematic review" or "meta-analysis."

All randomized controlled clinical trials for propoxyphene products (mostly single ingredient formulations), were published between 1950 and 1990. The majority of the trials were conducted in acute pain and studied a single oral dose. Reports of the relevant individual trials are summarized in Tables 1-3 in Appendix 1.

All systematic reviews, including meta-analyses, relied upon similar published data regarding randomized controlled trials in acute pain. The citations in those review articles were consistent with our results from our PubMed and EMBASE searches. The authors of these reviews reached similar conclusions: propoxyphene in doses of 65 mg or higher as a single-ingredient product, was a weak analgesic and generally less effective than other analgesics such as codeine, aspirin and acetaminophen. When not in

combination with another analgesic such as acetaminophen, propoxyphene was felt to have limited efficacy for the treatment of acute pain and probably chronic pain.

In this background package, we focus on two of the more comprehensive meta-analyses published. The clinical trials covered in these meta-analyses appear to represent the spectrum of efficacy of propoxyphene alone and in combination with acetaminophen in the literature. We also selected individual trials representing the most adequate study designs for detailed review following the discussion of the meta-analyses.

Moore et. al. 2008 (Attachment-4): This meta-analysis was first published in the Cochrane Database of Systematic Review in 1999 by Collin *et. al.*[4], and covered publications from 1954 through 1996. That paper was followed by two updates that extended the literature search first through January 2002, and then through December 2007. The following summary is based on the most recent version of the meta-analysis updated on February 18, 2008 by Moore *et. al.*[3].

A total of 132 randomized controlled trials (RCTs) were identified in a literature search from 1954 through 2007 using four electronic databases: Medline, EMBASE, Oxford Pain Relief database and Cochrane Central. All of these RCTs were published before 1987; there were no new eligible RCTs on any propoxyphene products published between 1988 and 2007.

Trials Analyzed:
Eleven of 132 trials met the inclusion criteria of randomized, double-blind, and placebo-controlled and were included in the meta-analysis.

Subjects:
Adult patients with postoperative pain:

- There were 440 patients from six trials that compared single-ingredient propoxyphene with placebo
- There were 325 patients from four trials and 638 additional patients from a meta-analysis[7] that compared propoxyphene and acetaminophen in combination with placebo

Treatment:
Patients in these trials received a single oral dose of one following:

- propoxyphene HCl 65 mg
- propoxyphene napsylate 100 mg (equivalent to 65 mg propoxyphene HCl)
- propoxyphene/acetaminophen (65 mg/650 mg) combination
- placebo

Efficacy measures:
Pain intensity and/or pain relief scores were measured for 4-6 hours after dosing.

Meta-analysis method:

The mean total pain relief score (TOTPAR) and/or mean summed pain intensity difference (SPID) from baseline over 4-6 hours were derived or calculated, and then converted to the percentage of maximum TOTPAR (maxTOTPAR) or SPID (maxSPID). This was used to calculate the relative benefit (RB) and number-needed-to-treat-to-benefit (NNTB) for one patient to achieve at least 50% pain relief (50% maxTOTPAR or maxSPID). The RB was defined as the ratio of patients achieving 50% or greater 50% pain relief for active treatment over placebo.

Meta-analysis results:

- Efficacy for a single dose of single-ingredient propoxyphene 65 mg (6 trials):
  - RB=1.5 (95% CI: 1.2-1.9) propoxyphene vs. placebo (Figure 1a)
  - NNTB=7.7 (95% CI: 4.6-22) vs. placebo over 4-6 hours
  - Remedication within 4-8 hours: 35% patients with propoxyphene and 43% with placebo; relative risk for remedication was 0.8 (95% CI: 0.7-1.03) without statistical significance.

Figure 1a. **Analgesic effects of propoxyphene 65 mg** vs. **placebo after a single oral dose for treatment of postoperative pain.** The effect was expressed as patients (n) experiencing >50% pain relief (>50% maxTOTPAR) over the total dosed patients (N). (From Moore *et. al.*, 2008[3]).

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 01 Dextropropoxyphene HCl 65mg Vs Placebo

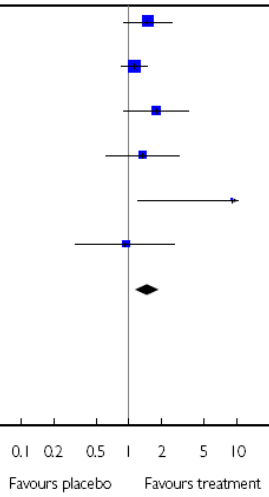
Outcome: 01 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Berry 1975	26/73	18/76		30.0	1.50 [0.90, 2.50]
Bloomfield 1980	21/25	19/25		32.3	1.11 [0.84, 1.46]
Cooper 1986	16/50	10/56		16.1	1.79 [0.90, 3.58]
Coutinho 1976	8/15	6/15		10.2	1.33 [0.61, 2.91]
Trop 1979	9/25	1/25		1.7	9.00 [1.23, 65.85]
Van Staden 1971	5/26	6/29		9.7	0.93 [0.32, 2.69]
Total (95% CI)	**214**	**226**		**100.0**	**1.48 [1.15, 1.90]**

Total events: 85 (Treatment), 60 (Placebo)

Test for heterogeneity chi-square=8.40 df=5 p=0.14 I^2 =40.5%

Test for overall effect z=3.01 p=0.003



Efficacy for a single dose of propoxyphene/acetaminophen 65 mg/650 mg (4 trials):

- RB = 2.5 (95% CI: 2.0-3.2) combination vs. placebo (Figure 1b)
- NNTB =4.4 (95% CI: 3.5-5.6) vs. placebo.
- Remedication within 4-8 hours: 34% with combination and 57% with placebo; relative risk 0.7 (0.5 to 0.8) with statistical significance.

Figure 1b. **Analgesic effects of propoxyphene/acetaminophen (65 mg/650 mg) combination** vs. **placebo after a single oral dose for treatment of postoperative pain.** The effect was expressed as patients (n) experiencing >50% pain relief (>50% maxTOTPAR) over the total dosed patients (N). (From Moore *et. al.*, 2008[3]).

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo

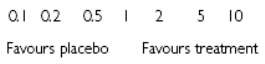
Outcome: 01 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cooper 1980	14/40	11/48		13.7	1.53 [0.78, 2.98]
Cooper 1981	24/42	6/37		8.7	3.52 [1.62, 7.67]
Evans 1982	15/30	8/30		10.9	1.88 [0.94, 3.75]
Honig 1981	17/50	9/48		12.5	1.81 [0.90, 3.67]
Moore 1997	114/316	40/322		54.1	2.90 [2.10, 4.02]
Total (95% CI)	**478**	**485**		**100.0**	**2.52 [1.99, 3.20]**

Total events: 184 (Treatment), 74 (Placebo)

Test for heterogeneity chi-square=5.14 df=4 p=0.27 I^2 =22.1%

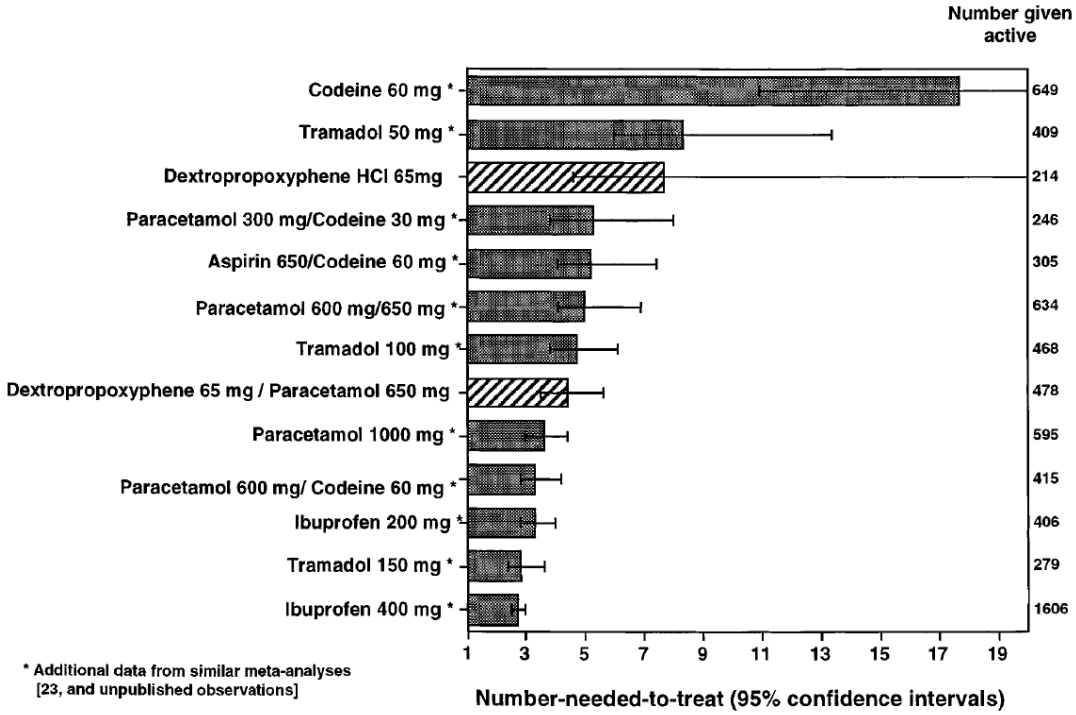
Test for overall effect z=7.59 p<0.00001



Collins *et. al.* 1998[5] (see Attachment-5): This meta-analysis compared the efficacy of propoxyphene with other analgesics. This results that follow are based on rank and the overlap of the 95% confidence interval:

- The efficacy of propoxyphene 65 mg was similar to codeine 60 mg and tramadol 50 mg (Figure 1c)
- Propoxyphene/acetaminophen 65 mg/650 mg combination was less efficacious than ibuprofen 400 mg and similar to acetaminophen 600 mg or 650 mg, acetaminophen/codeine 300 mg/30 mg, and tramadol 100 mg

Figure 1c. **Number-needed-to-treat (NNT) for single doses of analgesics in moderate-to-severe postoperative pain compared with placebo for at least 50% pain relief.** (From Collins *et. al.*, 1998[5]).



There are several other systematic reviews published in the last 40 years, including Miller *et. al.* 1970[8] and 1977[9], Beaver 1984[10], Moore and McQuay 1997[7], and Goldstein and Turk 2005[11]. There is considerable overlap in the clinical trials analyzed in these reviews.

The review by Miller et. al.[8] included 20 clinical trials published through May 1969 and was cited in the Citizen's Petition of February 28, 2006. The authors concluded that propoxyphene is not superior to codeine or aspirin with regard to analgesic effects and pointed out deficiencies in the study design and conduct of those trials. The review was updated in 1977[9], and included an additional 13 double-blind clinical trials published since the earlier version of the review. The trials were mostly conducted in acute pain patients with single-dose treatment. The authors concluded that propoxyphene HCl 65 mg had less analgesic effect than aspirin 650 mg and there was no conclusive evidence for the efficacy of propoxyphene when in combination with other analgesics such as acetaminophen or aspirin.

In 2005, Goldstein and Turk[11] reviewed nine published clinical trials to assess the efficacy and safety of propoxyphene products in older patients. Since no clinical studies directly addressed the efficacy and safety of propoxyphene in the elderly, the authors selected nine clinical trials in which more than 50% of patients were greater than 55 years old. The trials were published between 1960 and 1998. One study was a single-dose, placebo-controlled study[22] and the remainder were multiple-dose, active-controlled studies[12-18] (Table 3 in Appendix 1). The patients in the trials had chronic pain due to

osteoarthritis (OA), rheumatoid arthritis (RA), musculoskeletal pain, or cancer and received treatment for up to 24 weeks. The treat groups included propoxyphene 65 mg, propoxyphene in combination with APAP, placebo, or active comparators such as codeine, morphine, meptazinol, dihydrocodeine, aspirin, diclofenac, suprofen, or diflunisal. The authors concluded that propoxyphene appears to provide analgesic effects equivalent to most active comparators, but did not comment on differences between single or combination propoxyphene products.

In a meta-analysis published in 1997 by Po and Zhang[6] (see Attachment-6), a total of 26 clinical trials published between 1966 and 1997 were identified from Medline and BIDS (EMBASE and the Institute of Scientific Information database) that met the inclusion criteria of randomized, placebo- and/or active-controlled, and double-blind. Most of the patients had acute pain. This meta-analysis is summarized below:

Subjects:
Patients (n=2231) with postsurgical pain, arthritis and musculoskeletal pain

Treatment:
The patients received a single oral dose of the following:

- Acetaminophen 650 mg or 1000 mg
- Propoxyphene/acetaminophen (65 mg/650 mg) combination
- Placebo

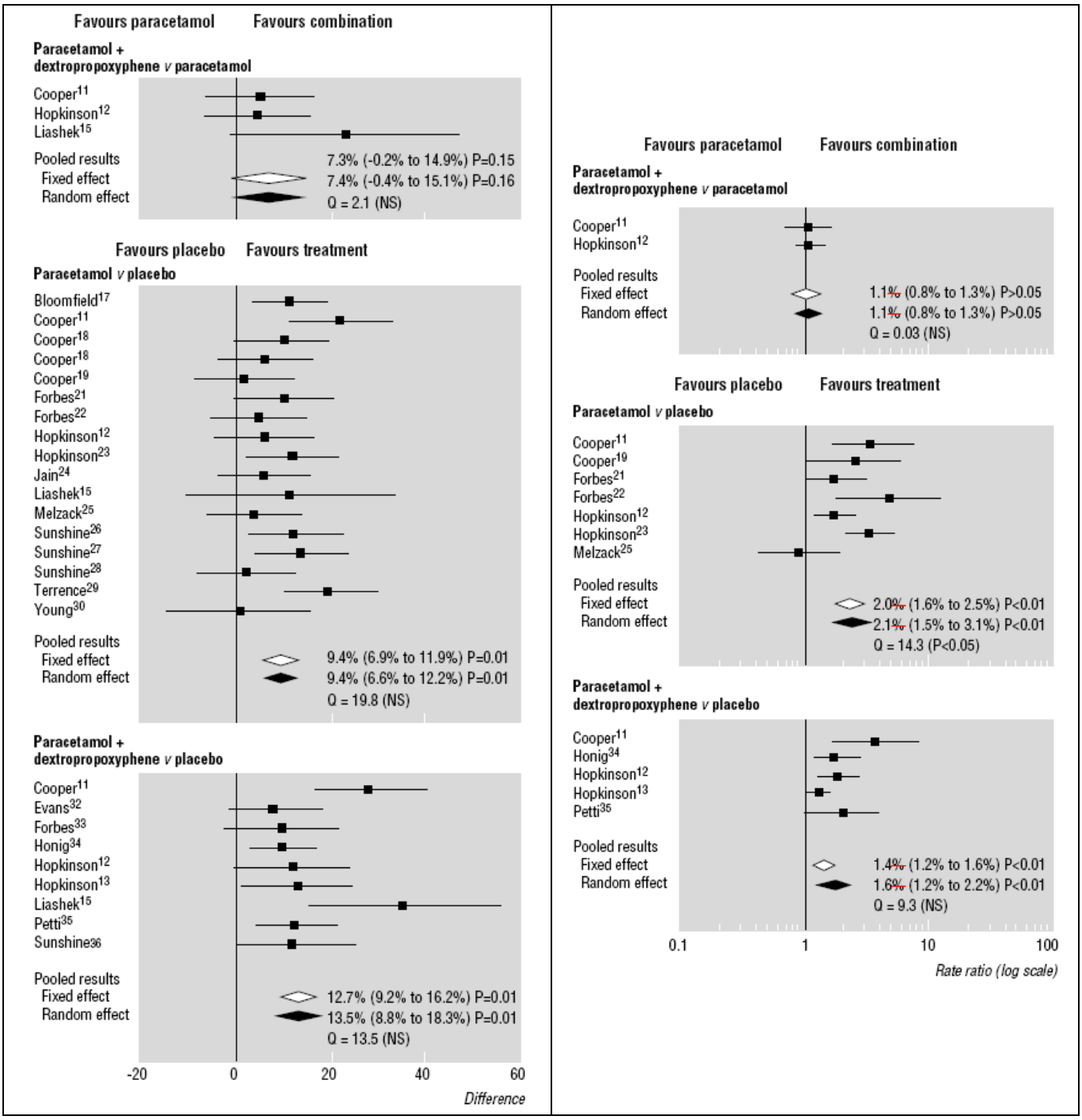
Analysis:

- A standardized SPID based upon previously-established method by Eisenberg *et. al.* 1994[19] was used.
- A standardized baseline pain score was calculated by taking the mean baseline score reported in any given trial divided by the maximum score possible on the scale used.
- The response rate ratio was calculated as proportion of patients with more than 50% pain relief during the observation period in the treatment group relative to the control group.
- Comparisons between APAP and PPX/APAP combination were made:
- The authors used both fixed and random effects modeling for pooling analyses

Results:
The standardized SPID and response rate ratio analyses (Figure 3) showed:

- Both PPX and APAP in combination and single-ingredient APAP were statistically superior to placebo in the pooled SPID or response rate ratio.
- The PPX/APAP combination was numerically, but not statistically, more effective than single-ingredient APAP in head-to-head comparisons of SPID, and was not different in the response rate ratio compared to single-ingredient APAP.
- The PPX/APAP combination was numerically, but not statistically, more effective than single-ingredient APAP based on comparisons of the placebo-referenced SPID or response rate ratio (the overlap of pooled 95% CI).

Figure 3. **Mean differences in the standardized SPID (*Left*) and response rate ratio (*Right*) between PPX/APAP combination and APAP alone after a single oral dose in patients with acute pain.** The bar represents the 95% confidence interval (CI). The response rate ratio was the ratio of the response (moderate pain relief or greater) rate of patients with treatment vs. with control (or other treatment). From Po and Zhang, 1997[6].



In 1998, Hanks and Forbes published a commentary in *BMJ*[20] on the Po and Zhang meta-analysis, which was cited in the 2006 Citizen's Petition. They pointed out that

propoxyphene products have been used extensively for management of chronic pain and that Po and Zhang's conclusion for acute pain with a single dose of PPX/APAP combination can not be extrapolated to chronic pain practice. The authors believed that repeat doses of PPX and APAP in combination were likely to be more effective than a single dose but lacked evidence from randomized controlled trials to support that assertion.

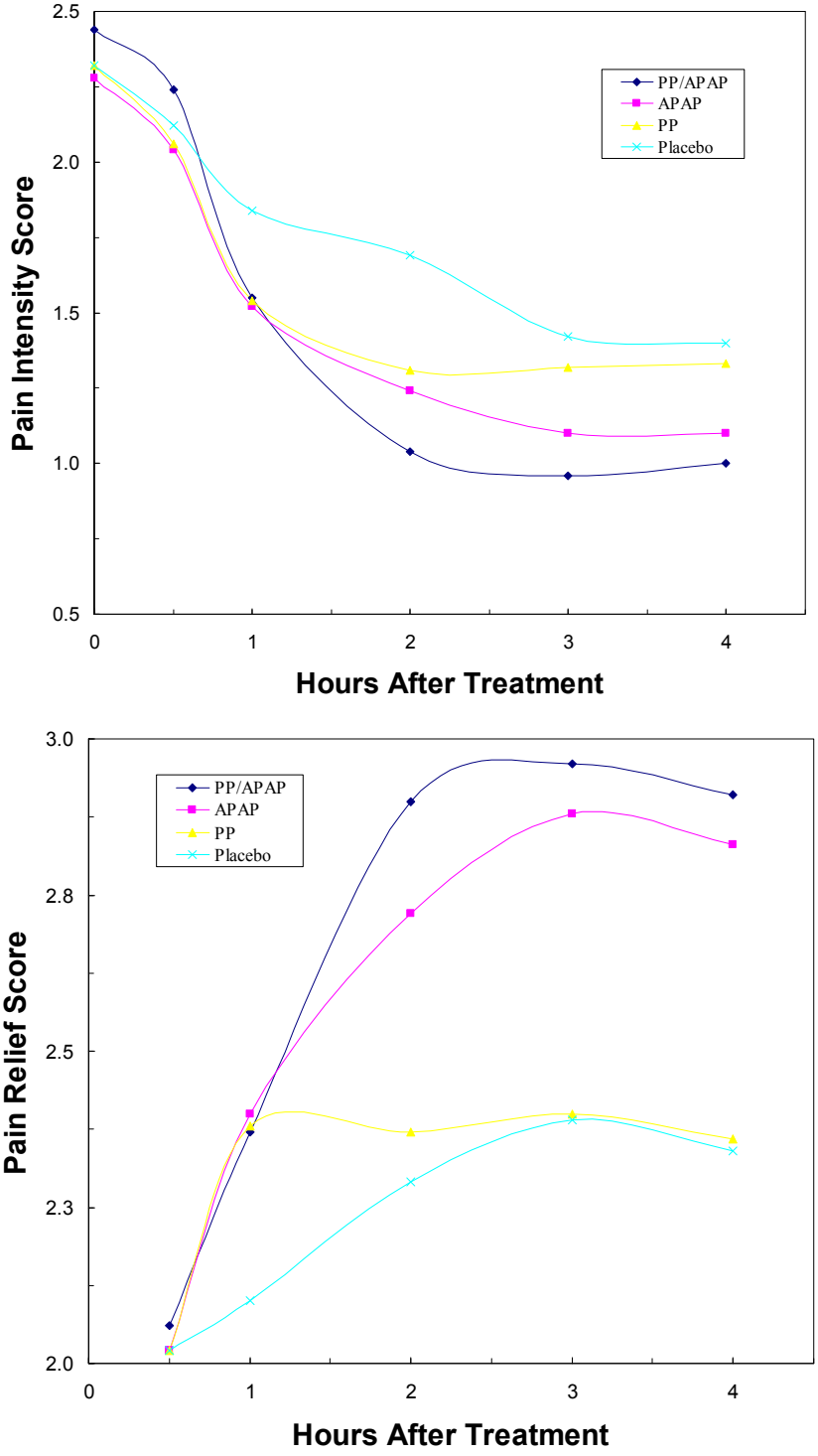
Efficacy data from the literature – Individual Study Reports

We identified one full factorial and some partial factorial design studies in the literature, which were also cited by published meta-analyses[3, 6].

Hopkinson et. al. 1973[23] reported a randomized, single-dose, double-blind, parallel-group trial in patients with moderate to severe postpartum pain using a full factorial design. Fifty patients received either a single oral dose of APAP 650 mg, propoxyphene 65 mg, propoxyphene/APAP 65 mg/650 mg or placebo. The pain assessment included pain intensity on a 5-point scale and pain relief score on a 4-point scale collected for 4 hours after dosing.

- The time-response curves for PI and PR showed that the propoxyphene/APAP combination was slightly more effective than single-ingredient APAP (Figure 4).
- The following statistically significant differences in the total PI and PR scores between treatments were found:
  - The propoxyphene/APAP combination was statistically superior to single-ingredient APAP in total PI reduction but not PR.
  - Single-ingredient propoxyphene was statistically superior to placebo for total PI reduction and numerically inferior to placebo in total PR.
  - Single-ingredient APAP was statistically superior to single-ingredient propoxyphene and placebo in both total PI reduction and total PR
- A global evaluation at the end of treatment (4 hours) showed no difference between the PPX/APAP combination and the single-ingredient APAP in the percentage of patients reporting "effectiveness:"
  - 64% in the combination group
  - 62% in the single-ingredient APAP group
  - 34% in the single-ingredient propoxyphene group
  - 30% in the placebo group

Figure 4. **Pain intensity score (*upper*) and pain relief score (*lower*) over four hours.** Based on data extracted from Tables Viii-Xi, Hopkinson *et. al.*, 1973[23]; the variability at each time-point and statistical analysis are not presented in the report.

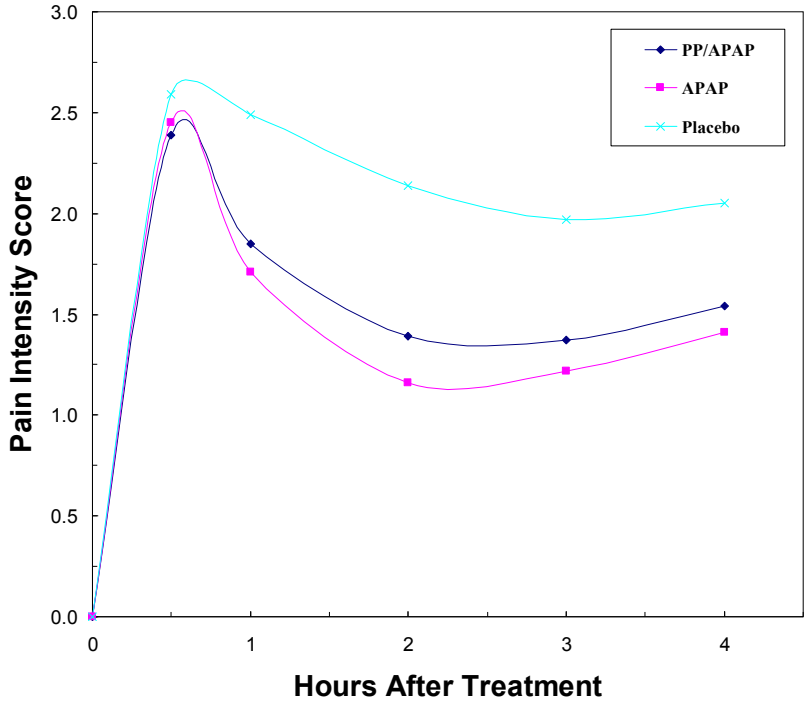


Hopkinson *et. al.* 1976[24] was a randomized, double-blind, single-dose, partial factorial study in patients with moderate to severe postpartum pain. Seventy five patients were treated with either a single oral dose of propoxyphene napsylate/APAP 100 mg/650 mg, APAP 1000 mg or placebo. The analgesic assessment was the same as in their 1973 study. Hopkinson *et. al.* reported:

- Slight separation between the pain intensity curves in comparing the combination and single-ingredient APAP.
- Both propoxyphene-N/APAP (100 mg/650 mg) and single-ingredient APAP (1000 mg) were superior to placebo in PID and PR scores.
- Single-ingredient APAP (1000 mg) was statistically superior to the propoxyphene/APAP combination

The authors concluded that the pain relief experienced by patients treated with the combination of propoxyphene napsylate and APAP was attributable in large measure to the therapeutic effects of APAP. They commented that these results were consistent with their previous study (Hopkinson *et. al.* 1973)[23].

Figure 5. **Pain intensity scores over four hours.** The data are extracted from the Table II of Hopkinson *et. al.* in 197)[24]; the variability at each time-point and statistical analysis was not reported in the paper.



Cooper *et. al.* 1981[25] conducted a randomized, double-blind, placebo- and active-controlled, single-dose, partial factorial study in patients with moderate to severe pain due to dental surgery. Approximately 200 patients received a single oral dose of APAP 650 mg, propoxyphene-N/APAP 100 mg/650 mg, codeine/APAP 60/650 mg, indoprofen 200 mg, or placebo, followed by a 4-hour analgesic assessment (pain intensity, pain relief etc.). Cooper *et. al.* found:

- Slight separation in the PID curves between propoxyphene/APAP and single-ingredient APAP but with overlap in the pain relief scores between these arms (Figure 6).
- Propoxyphene/APAP was not statistically different from single-ingredient APAP in the SPID and total PR score.

Figure 6a. **Pain intensity difference** over four hours. The data were extracted from Table 2 (Cooper *et. al.* in 1981)[25]; the variability at each time-point and statistical analysis were not reported in the paper.

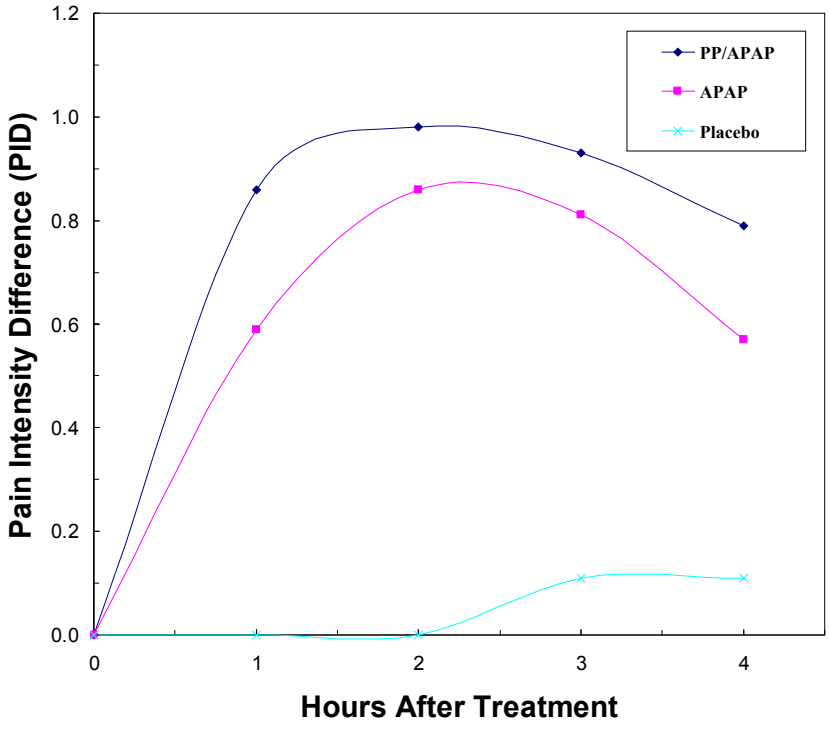
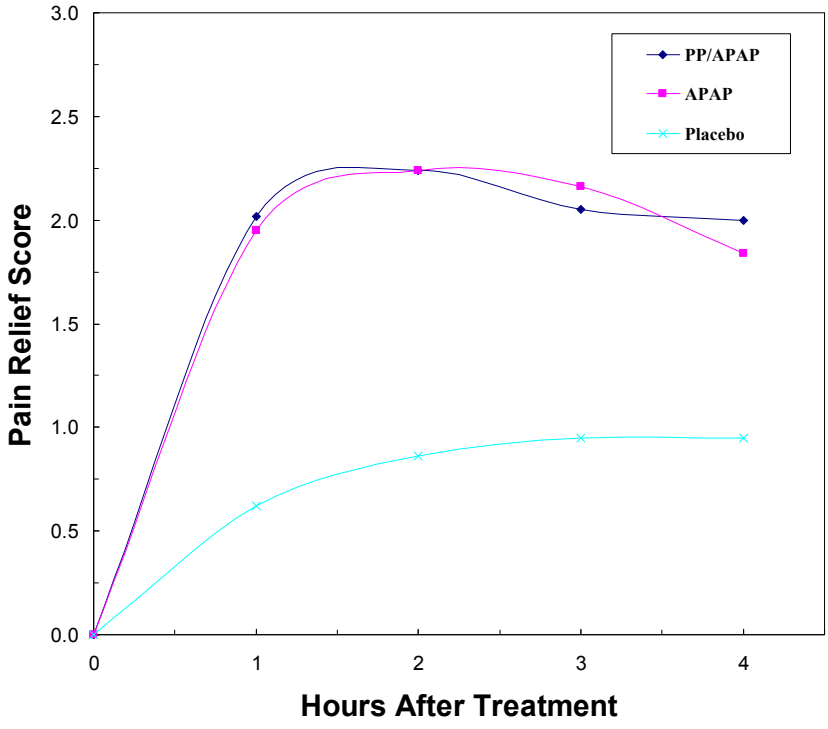


Figure 6b. **Pain relief score** over four hours. The data were extracted from Table 2 (Cooper *et. al.* in 1981)[25]; the variability at each time-point and statistical analysis were not reported in the paper.



There are few reports of studies of propoxyphene in chronic pain either as a single-ingredient product or in combination with other analgesics in the literature and no such data have been submitted to support an NDA. The few clinical trials in the literature that were conducted in patients with chronic pain were mostly active-controlled and compared propoxyphene or propoxyphene/APAP with other analgesics (Table 3 in Appendix 1). The duration of treatment was short, usually less than one week. Some of the trials were not randomized or were open-label. Based on the study designs, these trials are not able to provide much information that is useful in the discussion of the efficacy of propoxyphene products for the treatment of chronic pain.

OVERALL SUMMARY OF EFFICACY

Based on the information presented from the DESI review, the NDA submissions and the literature, there is evidence that propoxyphene possesses weak analgesic effects in patients with acute pain compared to placebo. While most of the studies show that in combination with acetaminophen, the propoxyphene component appears to contribute little or no additional analgesic effect beyond the efficacy of the acetaminophen when studied in patients with acute pain, there is at least one study that does support the contribution of propoxyphene to the efficacy of the combination.

ATTACHMENTS

Attachment-1: A notice of the FDA's DESI conclusion on propoxyphene products (Federal Register 1969 and 1972) and the efficacy report of National Academy of Science –National Research Council (NAS-NRC)

Attachment-2: Beaver WT: Mild analgesics, a review of their clinical pharmacology (Part II). ***Am J Med Sci*** 251: 576-599, 1966

Attachment-3: Lasagna L: Clinical Evaluation of morphine and its substitutes as analgesics. ***Pharmacol Rev*** 16: 47-83, 1964

Attachment-4: Moore RA *et. al.*: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain (Review) ***Cochrane Database of Systematic Reviews*** CD001440, 2008, Issue 3

Attachment-5: Collins SL *et. al.*: Single-dose dextropropoxyphene in post-operative pain: a quantitative systematic review ***Eur J Clin Pharmacol*** 54: 107-112, 1998

Attachment-6: Po ALW and Zhang WY: Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol ***BMJ*** 315: 1565-71, 1997

Attachment-7: Barden J *et. al.*: Single dose oral paracetamol (acetaminophen) for postoperative pain (Review) ***Cochrane Database of Systematic Reviews*** CD004602, 2004, Issue 1

APPENDIX 1. Summary of relevant clinical trials of propoxyphene products in the literature

Table 1. Review articles of clinical trials of propoxyphene products

Year	Author	No. of Trials	Subject	Treatment	Analysis	Outcome
2008	Moore *et. al.*[3] (Collins *et. al.* 1999)[4]	N=11 RCT (through 12/07) Single-dose	Post-operative pain	PPX 65mg PPX/APAP (65 mg/650mg), Placebo	Meta-analysis; RB & NNTB	Mixed results
1998	Collins *et. al.*[5]	N=11 RCT (through 11/96) Single-dose	Post-operative pain	PPX 65mg, PPX/APAP (65 mg/650mg), Placebo	Meta-analysis; RB & NNTB	Rank order of single dose analgesics: Ibuprofen 400mg >PPX/APAP >APAP>>PPX
1997	Moore *et. al.*[7]	N=18 RCT (through 1995) Single-dose pain	Post-operative pain (or dental)	PPX/APAP, codeine/ASA, tramadol, placebo	Single-patient meta-analysis RB & NNTB	Comparable NNTB of PPX/APAP with tramadol 100 mg and codeine/ASA
1997	Po & Zhang[6]	N=26 RCT (through 1997) Singe-dose	Postsurgery, arthritis, musculoskeletal	APAP 650 mg or 1000mg PPX/APAP 65 mg/650mg Placebo	Meta-analysis SPID and response rate ratio	PPX/APAP ≈ APAP >Placebo in SPID and response rate
1984	Beaver[10]	Additional RCTs after his 1966 review	Acute pain and chronic pain	APAP, PPX, PPX/APAP, Codeine, NSAIDs,	Review	Same conclusion as in the 1966's review
2005	Goldstein & Turk[11]	N=9 clinical trials in patients ≥55yo; published 1960-1998	Acute and chronic pain	PPX, AAP, PPX/APAP, codeine/APAP, codeine/ASA Placebo	Review	Efficacy of PPX was not different from active comparators; safety of PPX was comparable to other opioids.
1970	Miller *et. al.*[8]	N=20 RCTs (up to 1969)	Primarily acute pain	PPX, codeine, ASA	Review	PPX was not superior to codeine or ASA
1977	Miller[9]	N=13 RCTs (through 1977)	Acute and chronic pain	PPX, ASA, codeine, APAPA, placebo, ibuprofen	Review	PPX 65mg ≈ ASA 650mg; no conclusive evidence for PPX on chronic pain

Table 1. Review articles of clinical trials of propoxyphene products, continued

1966	Beaver[1]	N=18 RCTs (1956-1965)	Mostly acute pain	PPX, ASA, codeine, placebo	Review	PPX 65mg <codeine <ASA >placebo
1964	Lasagna[2]	N=13 RCTs (1955-1962)	Mostly acute pain	PPX, ASA, codeine, placebo	Review	PPX < codeine and ASA

RCT: randomized, double-blind, placebo-controlled trial
PPX: propoxyphene; PH: propoxyphene HCl; PN: propoxyphene napsylate (100 mg PN has equivalent molar to 65 mg PH)
RB: relative benefit; RR: relative risk; NNTB: number-needed-to-treat-to-benefit

Table 2. Individual trials on propoxyphene products in acute pain patients

Year	author	Study design	Subject	Treatment	Outcome
1994	Naidu *et. al.*[26]	R/DB Single-dose, 6 hr	N=160 postsurgery	Ketorolac 10mg Ibuprofen/APAP 400/325mg PPX/APAP 65/400mg	Analgesic response (PI and PR): Ketorolac>Ib/APAP≈PPX/APAP
1987	Liashek *et. al.*[27]	R/DB, single-dose, 4 hr	N=54 postsurgical dental pain	PPX-N/APAP 100 mg/650mg PPX-N 100mg APAP 650mg Placebo	PID and PR score: PPX-N ≥ PPX-N/APAP > APAP > placebo Longer analgesic duration with PPX-N and PPX-N/APAP
1986	Cooper *et. al.*[28]	R/DB, parallel, single-dose, 6hr	N=212 periodontal surgery	Suprofen 200mg Codeine 60mg PPX 65mg placebo	Time-course for PID and PR: Suprofen > PPX ≈ codeine > placebo
1982	Brooks *et. al.*[29]	R, DB, crossover (≥1 wk interval), single-dose, 4 hr	N=24 (12 each RA & OA)	PPX 65mg APAP 650 mg PPX/APAP 65 mg/650mg PPX/ASA 65 mg/650mg Placebo	PPX slightly less average pain score (0-4 hr) than placebo and other Txs. Overall, all 4 txs were comparable to placebo.
1982	Evans *et. al.*[30]	R/DB/PC Single-dose, 4 hr	N=120 Orthopedic surgery 30/arm	Single-dose PH/APAP 65 mg/650mg Zomepirac 50 & 100mg placebo	PI (PID, SPID), PR (TOTPAR) Zomepirac-50>PH/APAP>zomepirac-100>placebo
1981	Honig *et. al.*[31]	R/DB/PC Single-dose, 6 hr	N=196 postsurgery,	Single-dose PN/APAP 100 mg/650mg Zomepirac 50 & 100mg Placebo	PI (PID, SPID), PR (TOTPAR) Zomepirac 100 >zomepirac 50 > PN/APAP>placebo

Table 2. Individual trials on propoxyphene products in acute pain patients, continued

1981	Cooper *et. al.*[25]	R/DB, partial factorial, single-dose	N=200 postsurgical dental pain	PPX-N/APAP 100 mg/650mg APAP 650mg Codeine/APAP 60/650mg Indoprofen 200mg placebo	SPID all active tx > placebo Overall analgesic response: Indoprofen > PPX/APAP ≈ codeine/APAP ≈ APAP
1980	Cooper[32]	R/DB/PC, single-dose, 6 hr	N=179 postsurgical dental pain	Single-dose PN/APAP 100 mg/650mg Zomepirac 50 & 100mg Placebo	PI (PID, SPID), PR (TOTPAR) Zomepirac>PN/APAP>placebo
1980	Bloomfield *et. al.*[33]	R/DB/PC, single-dose, 6 hr	N=100 postpartum pain	Nefopam 45 & 90 mg PPX 65 mg placebo	Nefopam 45 & 90 mg >PPX >placebo in analgesic response
1979	Messick[34]	R? DB? Crossover (2-day tx for each of 4 txs)	N=32 chronic pain (musculoskeletal)	PPX-N/APAP 100 mg/650mg PPX-N 100mg APAP 650mg Placebo 4-6 times/day x 2days each	Phone report of duration (hours) of different PI levels daily and % PR (pre-24-hr). PPX/APAP > PPX ≈ APAP > placebo
1979	Trop *et. al.*[35]	R/DB, single-dose, 6 hr	N=125 postoperative pain	PPX 65mg or 130mg Nefopam 60mg or 90mg placebo	SPID and time-course of PID & PR in ITT population: PPX 130mg ≈ nefopam 60mg > PPX 65 mg > nefopam 90 mg > placebo
1976	Hopkinson *et. al.*[24]	R/DB, partial factorial, single-dose	N=224 post-partum pain	PPX-N/APA 100 mg/650mg APAP 1000mg Placebo	Analgesic response: APAP 1000mg > PPX-N/APAP > Placebo
1976	Coutinho A *et. al.*[36]	R/DB, single-dose, 5 hr	N=90 postoperative pain	PPX 65mg Fenbufen 400mg or 800mg Codeine 30mg ASA 600mg placebo	SPID in ITT population and completers: Fenbufen ≈ ASA ≈ codeine > PPX ≈ placebo

Table 2. Individual trials on propoxyphene products in acute pain patients, continued

1975	Berry *et. al.*[37]	R/DB, single-dose, 4 hr	N=225 post-partum pain	PPX 65mg APAP 1000mg placebo	PI decrease, Pt global and rescue meds: APAP >(statistically) PPX > (slightly) placebo
1974	Huskisson[38]	R/DB, single-dose	N=23 RA	APAP 650mg PPX/APAP 65 mg/650 mg Pentazocine 50mg Placebo	Mean total pain relief score: PPX/APAP > APAP ≈ pentazocine
1973	Hopkinson *et. al.*[23]	R/DB, full factorial, single-dose	N=200 postpartum pain	PPX/APAP 65 mg/650mg PPX 65mg APAP 650mh Placebo	Analgesic response: PPX/APAP slight >APAP APAP > PPX and placebo
1971	Staden[39]	R/DB, crossover, 8 hr	N=80 Ob/Gyn procedure pain	PPX 65mg Glifanan 200mg placebo	PID time-curve, total PID score: Glifanan > PPX ≈ placebo

R: randomize; DB: double-blind; PC: placebo-controlled; AC: active-controlled
SPID: sum of PID (pain intensity difference from baseline)
PN: propoxyphene napsylate; PH: propoxyphene HCl; APAP: acetaminophen

Table 3. Individual trials of propoxyphene products in chronic pain patients

Year	Author	Study Design	Subject	Treatment	Outcome
1998	Mercadante *et. al.*[14]	R/AC/OL	N=32 cancer pain	PPX 120-240mg/day MS-ER 10mg bid >10 days, till death	Comparable in pain intensity; PPX more tolerable
1992	Boissier *et. al.*[15]	R/DB/AC	N=141 OA	PPX/APAP 30/400mgx2 tid Codeine/APAP 30/500mg x2 tid	Comparable analgesic effects; Patient's acceptability PPX/APAP superior to codeine/APAP
1984	Mitchell *et. al.*[40]	DB, crossover	N=24 RA or OA	APAP 650mg; PPX 65mg PPX/APAP 65 mg/650mg; Placebo q4-hr prn x4 days	1PPX had marginal pain relief; addition of APAP had more negative than positive effects on pain score and well-being
1989	Parr *et. al.*[12]	R/DB	N=846 OA	Diclofenac 100 mg PPX/APAP 180/1950 mg qd x 4wwks	Diclofenac superior to PPX/APAP in pain relief and physical mobility of joints
1983	Salzman and Brobyn[18]	R, SB?	N=114 OA	Suprofen 200 mg PPX 65 mg Qid x 24 week	61% patients completed the 24-week tx; PPX was slightly less effects (PR and PI) than suprofen over 24-wk
1980	Owen & Hill[41]	R/DB, crossover	N=31 RA	PPX/APAP 65 mg/650mg APAP 500mg Up to 2 doses/day, prn x 1 wk	PPX/APAP (n=22) was superior to APAP (n=5) in efficacy, but no more details reported.
1982	Price & Latham[42]	R/DB	N=136 acute and chronic pain	Meptazinol 400mg PPX/APAP 65/400mg Q3-6hr, prn, x 14 days	PI daily (2 hour post dosing) No difference over 14 days
1984	Oro[17]	R/DB crossover	N=32 elderly (mean 74 yo) musculoskeletal pain	Meptazinol 200mg PPX/APAP 65 mg/650mg Qid x5 days	No difference between txs

Table 3. Individual trials of propoxyphene products in chronic pain patients, continued

1982	Rao & Sharma[16]	R/SB (to investigator)	N=40 traumatic pain (age>65 yr); (20/arm)	Diflunisal 500mg bid PPX/APAP 65 mg/650mg qid x 5 days	Daily pain assessment (spontaneous pain, night pain, pain on passive movement, tenderness), overall diflunisal was superior to PPX/APAP.
1992	Lloyd *et. al.*[13]	R/DB	N= 86 hip OA	Dihydrocodeine CR 60-120mg bid PPX/APAP 650/650mg tid to qid x 2 weeks	Pain diary qid; pain on passive movement at baseline and end of tx. More pts withdraw from CR (43%due to AEs) than from PPX/APAP (21%); overall CR superior to PPX/APAP.

R: randomize; DB: double-blind; SB: single-blind; OL: open-label; PC: placebo-controlled; AC: active-controlled
SPID: sum of PID (pain intensity difference from baseline)
PN: propoxyphene napsylate; PH: propoxyphene HCl; APAP: acetaminophen

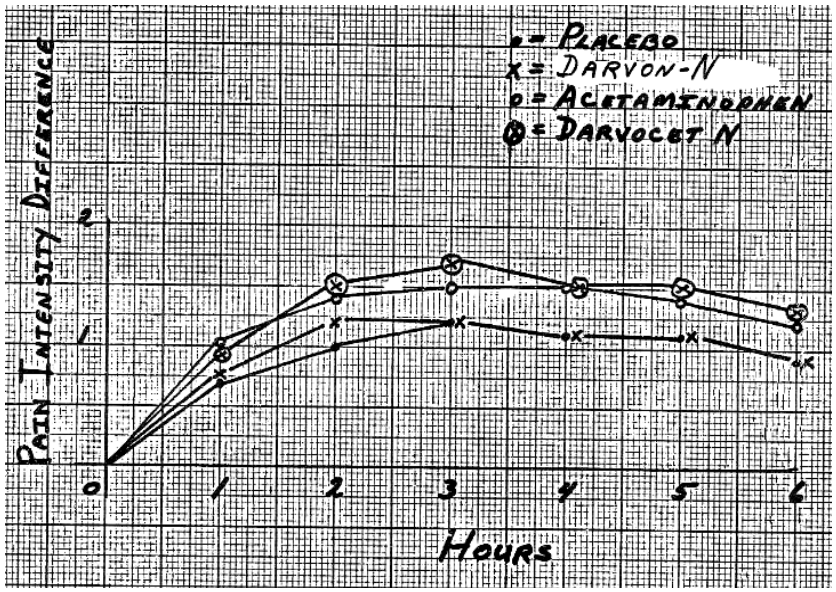
APPENDIX 2. Time-course of analgesic response in seven acute pain trials submitted to NDA 16-844 and NDA 17-122 in 1971

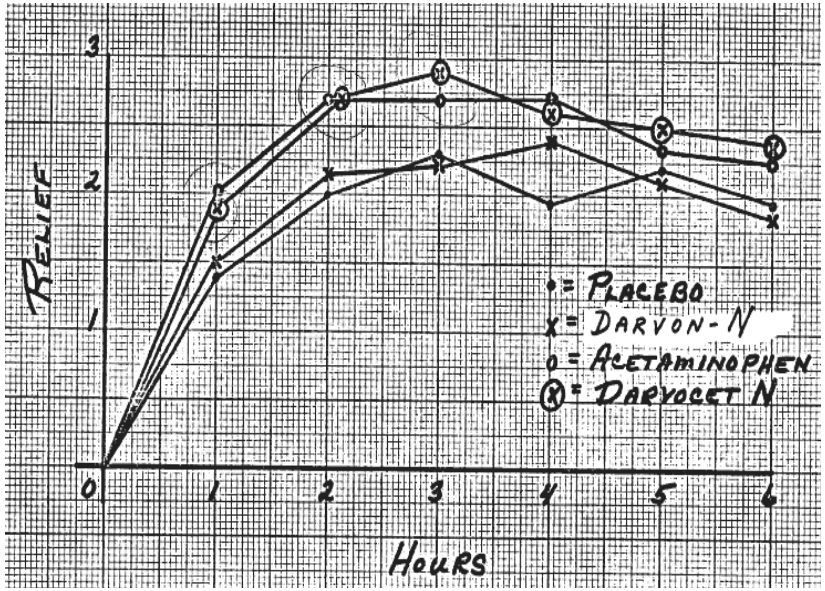
The following seven figures were taken from the clinical study reports submitted to NDA 16-844 (Darvocet) and NDA 17-122 (Darvocet-N) in December 17, 1971.

Figure 1. **Single dose analgesic response over six hours from Study #1 submitted to NDA 16-844 and NDA 17-122 in December 17, 1971** (Sponsor: Eli Lily and Company. Investigator: Dr. Lash AF)

Upper right: Pain intensity difference (PID) time curves
Lower left: Pain relief (PR) time curves
Lower right: Analgesic score (PID+PR) time curves

Treatment (n=48/arm):
Darvon-N (propoxyphene napsylate): 100 mg
Acetaminophen (APAP): 650 mg
Darvocet-N (propoxyphene napsylate/APAP): 100 mg/650 mg





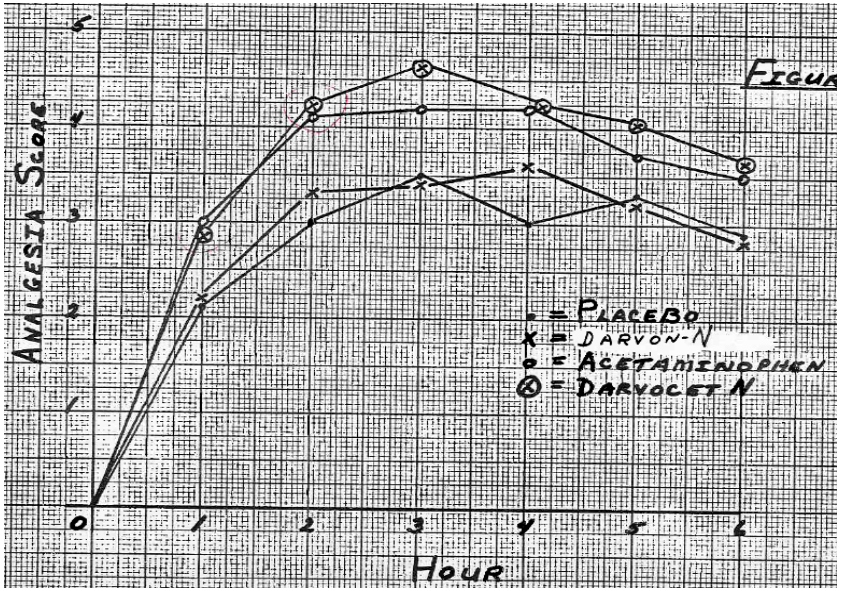
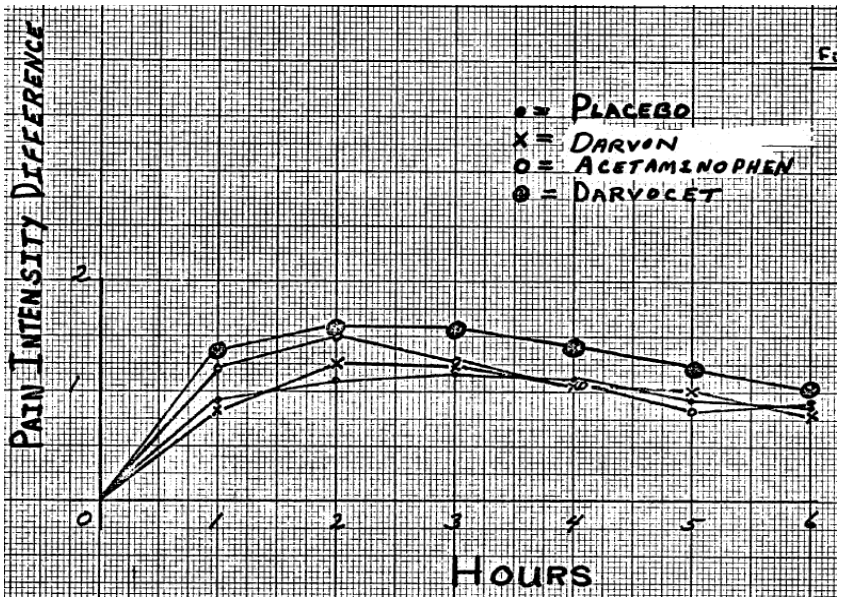
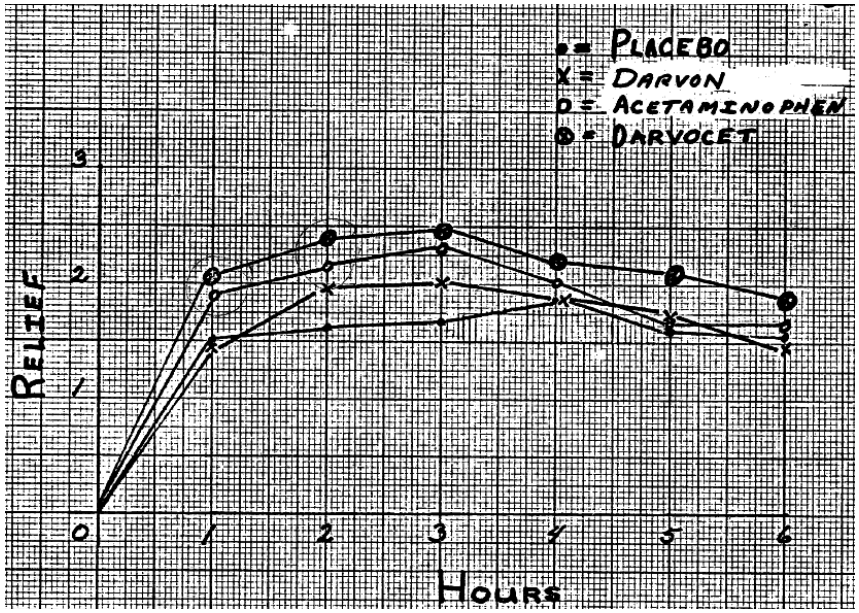


Figure 2. **Single dose analgesic response over six hours from Study #2a submitted to NDA 16-844 and NDA 17-122 in December 17, 1971** (Sponsor: Eli Lily and Company. Investigator: Dr. Lash AF)

Upper right: Pain intensity difference (PID) time curves
Lower left: Pain relief (PR) time curves
Lower right: Analgesic score (PID+PR) time curves

Treatment (n=48/arm):
Darvon (propoxyphene HCl): 65 mg
Acetaminophen (APAP): 650 mg
Darvocet-N (propoxyphene HCl/APAP): 65 mg/650 mg





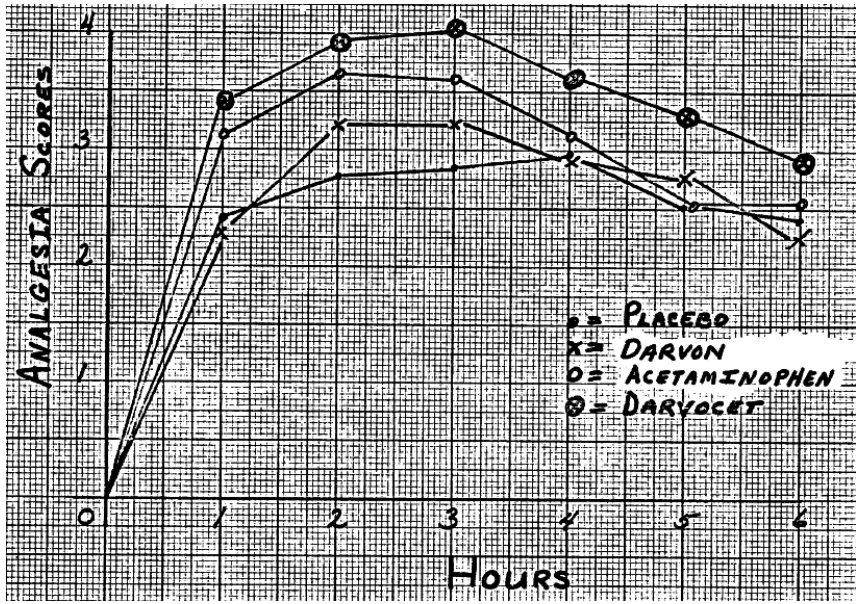
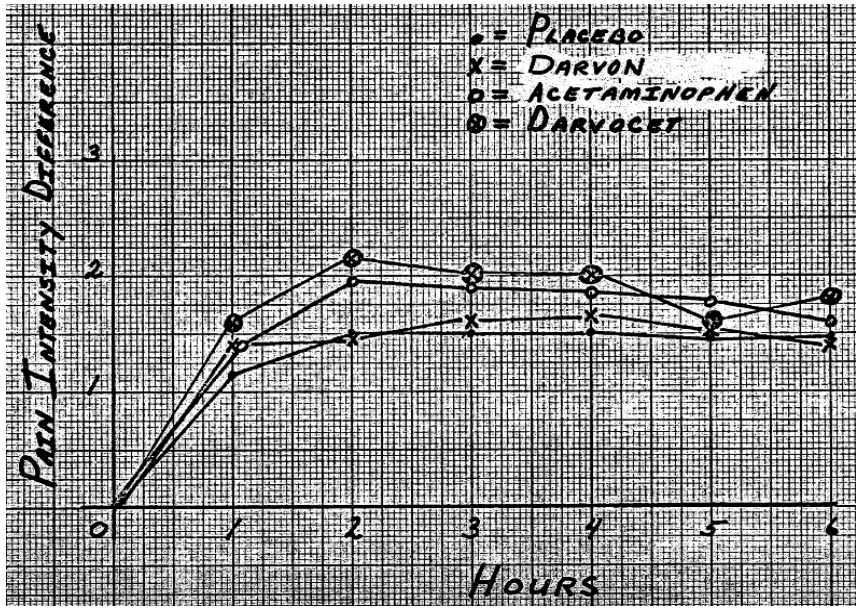
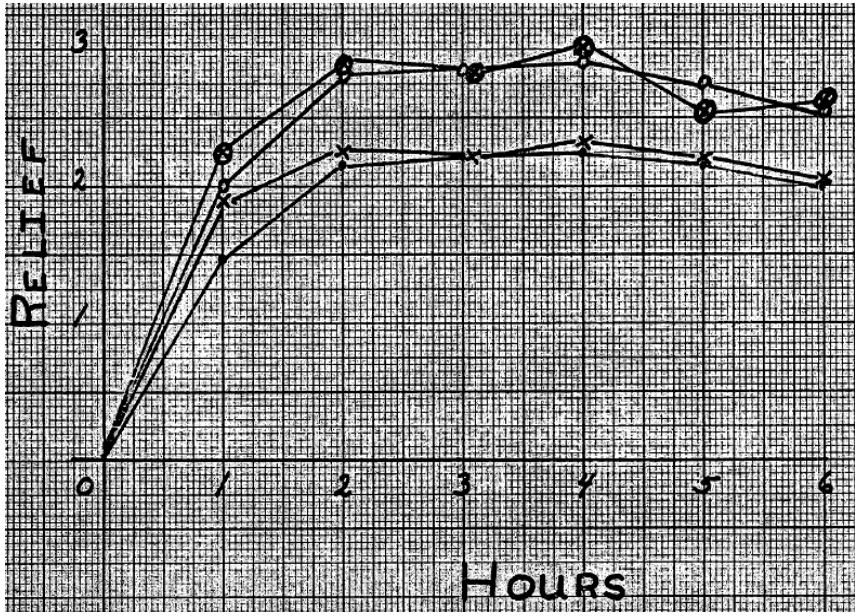


Figure 3. **Single dose analgesic response over six hours from Study #2b submitted to NDA 16-844 and NDA 17-122 in December 17, 1971** (Sponsor: Eli Lily and Company. Investigator: Dr. Lash AF)

Upper right: Pain intensity difference (PID) time curves
Lower left: Pain relief (PR) time curves
Lower right: Analgesic score (PID+PR) time curves

Treatment (n=48/arm):
Darvon (propoxyphene HCl): 65 mg
Acetaminophen (APAP): 650 mg
Darvocet-N (propoxyphene HCl/APAP): 65 mg/650 mg





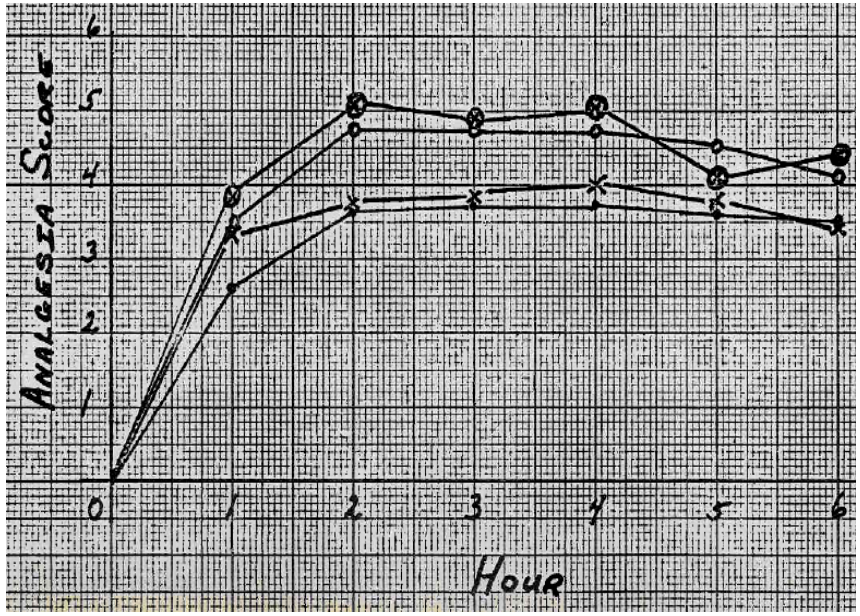
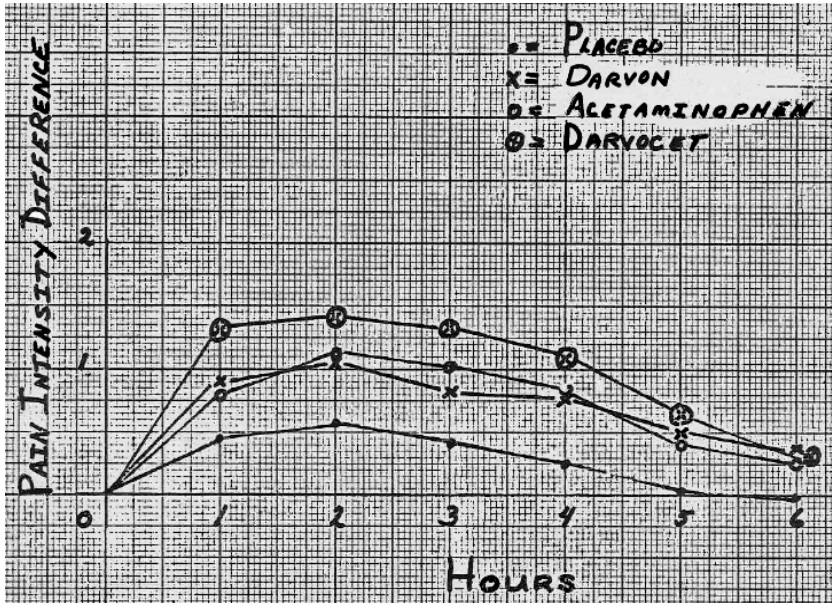
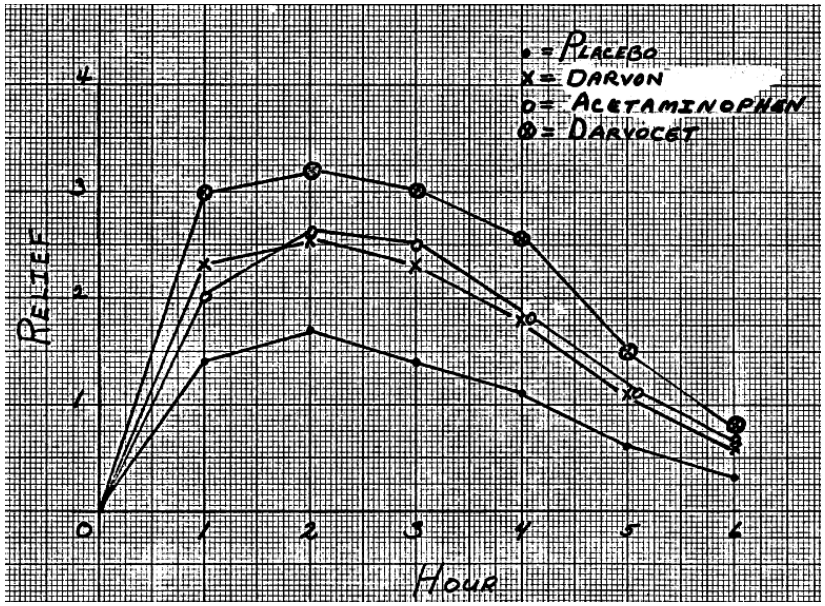


Figure 4. **Single dose analgesic response over six hours from Study #3a submitted NDA 16-844 and NDA 17-122 in December 17, 1971** (Sponsor: Eli Lily and Company. Investigator: Dr. Bauer RO)

Upper right: Pain intensity difference (PID) time curves
Lower left: Pain relief (PR) time curves
Lower right: Analgesic score (PID+PR) time curves

Treatment (n=30-32/arm):
Darvon (propoxyphene HCl): 65 mg
Acetaminophen (APAP): 650 mg
Darvocet-N (propoxyphene HCl/APAP): 65 mg/650 mg





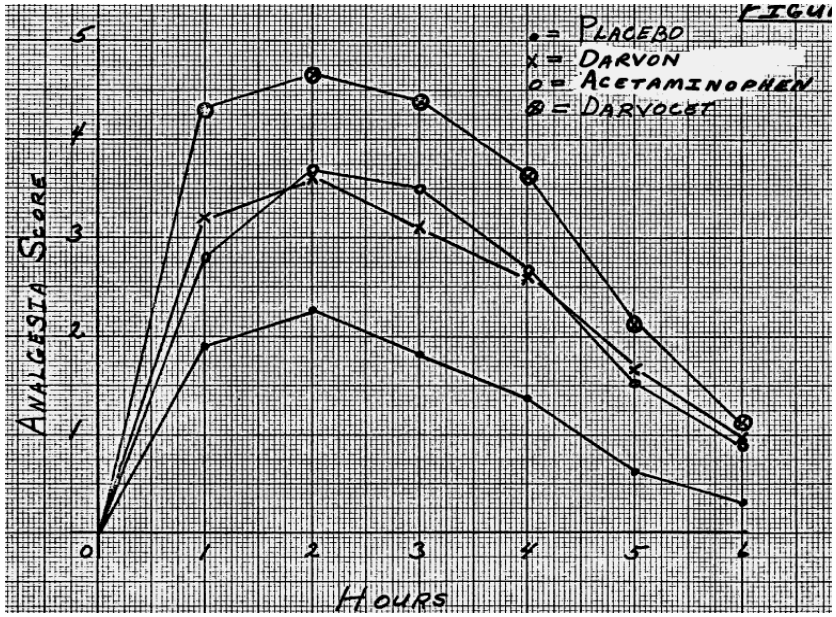
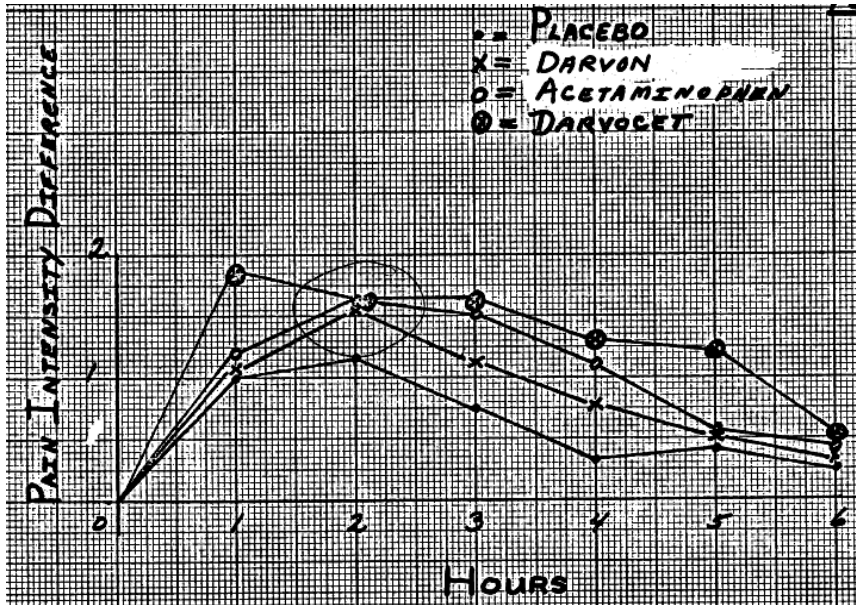
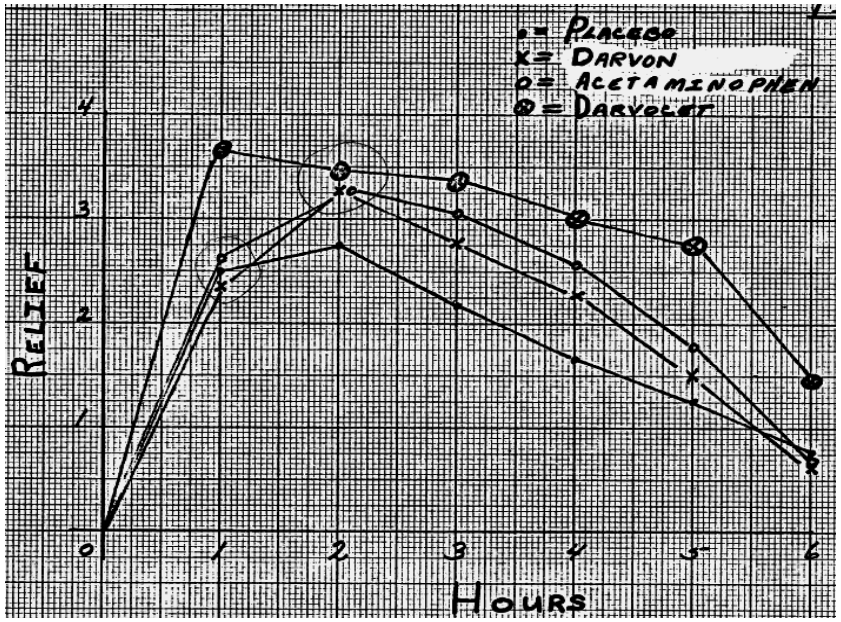


Figure 5. **Single dose analgesic response over six hours from Study #3b submitted to NDA 16-844 and NDA 17-122 in December 17, 1971** (Sponsor: Eli Lily and Company. Investigator: Dr. Bauer RO)

Upper right: Pain intensity difference (PID) time curves
Lower left: Pain relief (PR) time curves
Lower right: Analgesic score (PID+PR) time curves

Treatment (n=12-14/arm):
Darvon (propoxyphene HCl): 65 mg
Acetaminophen (APAP): 650 mg
Darvocet-N (propoxyphene HCl/APAP): 65 mg/650 mg





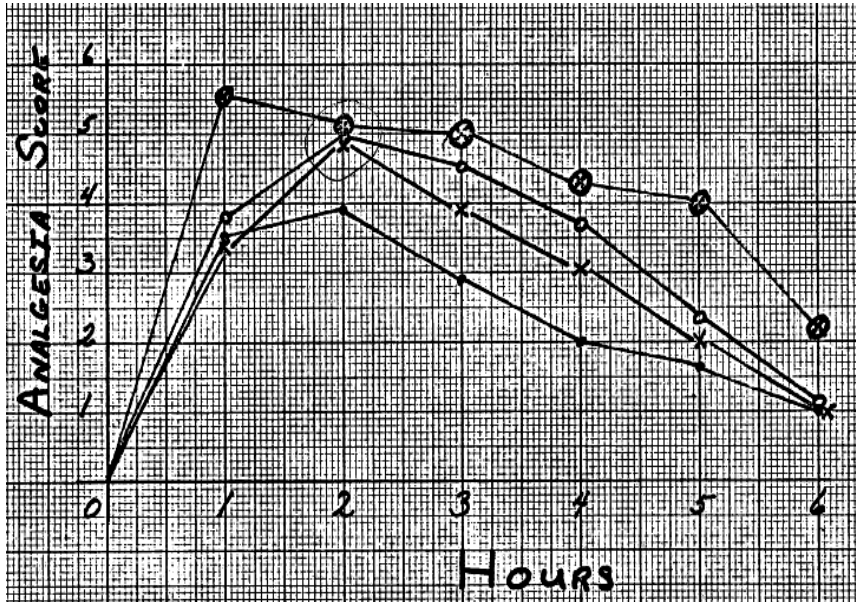
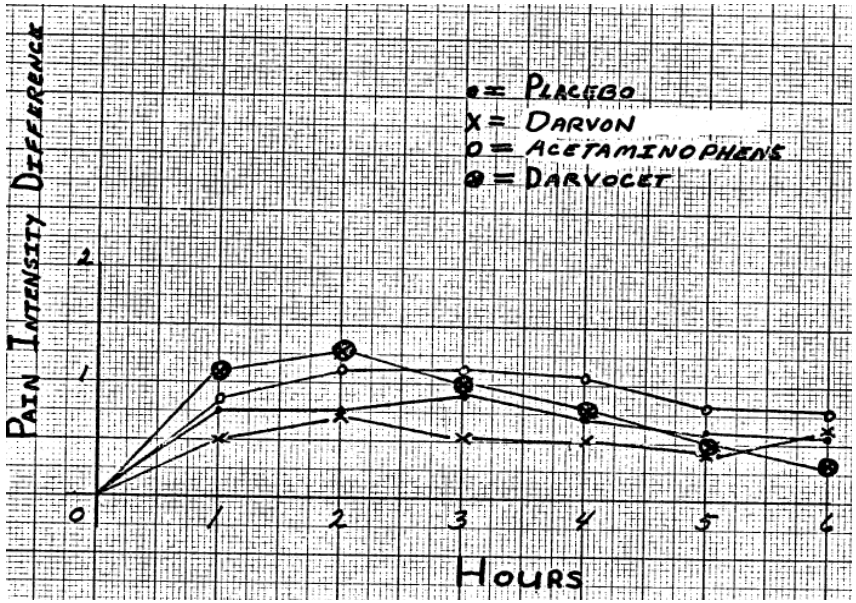
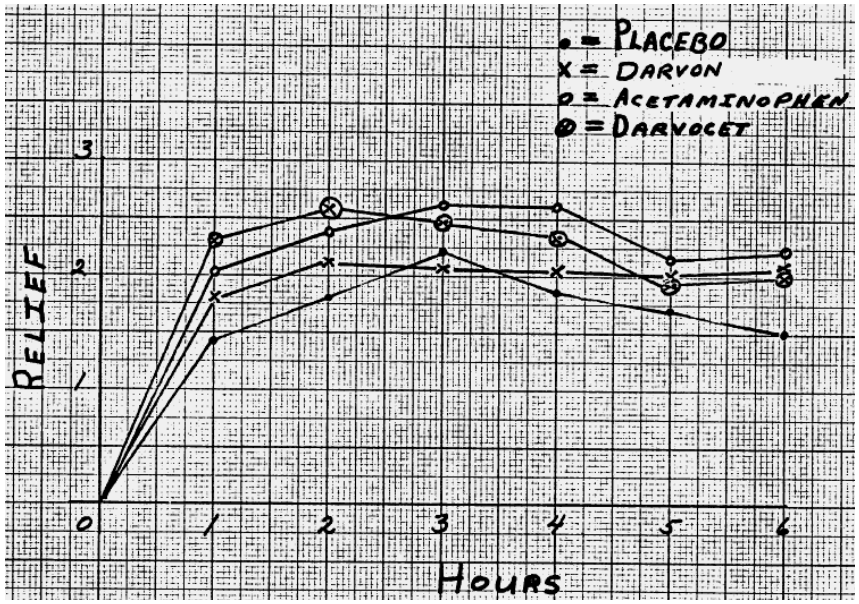


Figure 6. **Single dose analgesic response over six hours from Study #4a submitted to NDA 16-844 in December 17, 1971** (Sponsor: Eli Lily and Company. Investigator: Dr. Johnson W)

Upper right: Pain intensity difference (PID) time curves
Lower left: Pain relief (PR) time curves
Lower right: Analgesic score (PID+PR) time curves

Treatment (n=34-36/arm):
Darvon (propoxyphene HCl): 65 mg
Acetaminophen (APAP): 650 mg
Darvocet-N (propoxyphene HCl/APAP): 65 mg/650 mg





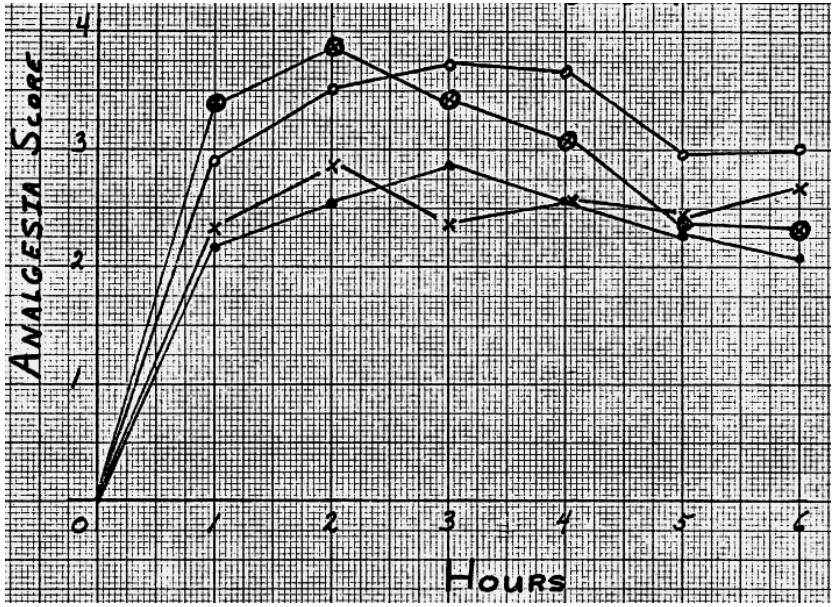
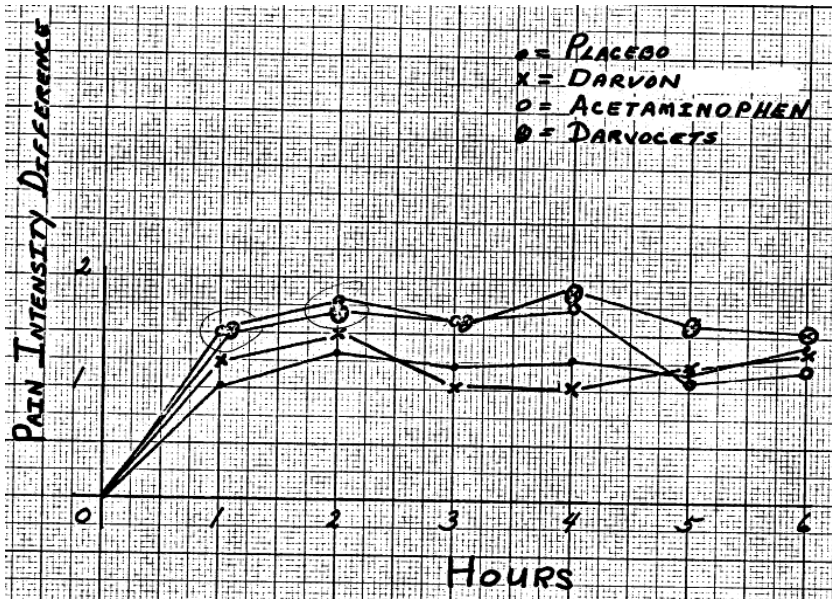
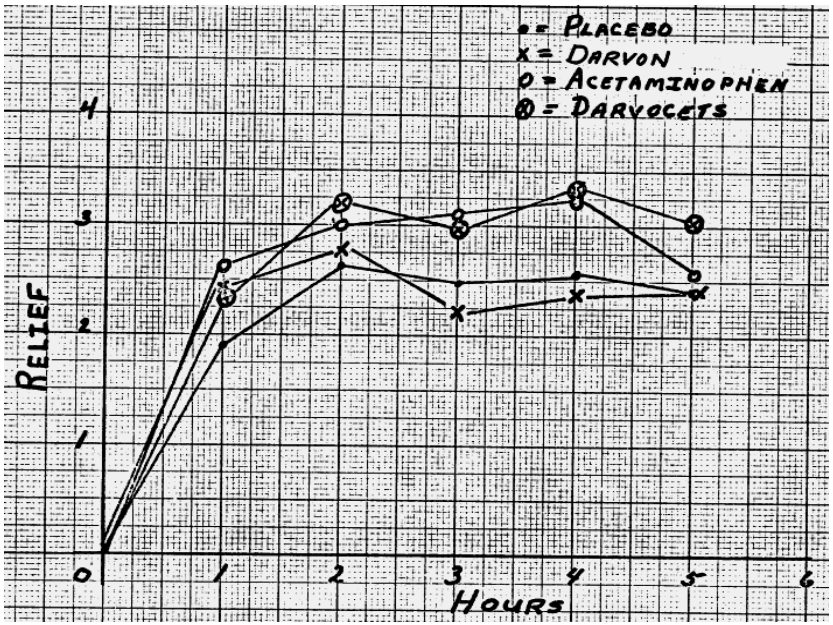


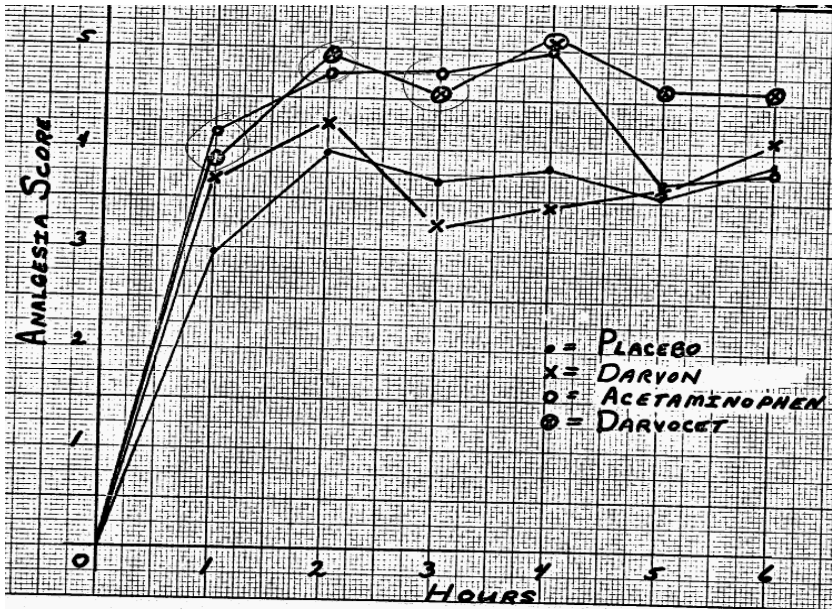
Figure 7. **Single dose analgesic response over six hours from Study #4b submitted to NDA 16-844 in December 17, 1971** (Sponsor: Eli Lily and Company. Investigator: Dr. Johnson W)

Upper right: Pain intensity difference (PID) time curves
Lower left: Pain relief (PR) time curves
Lower right: Analgesic score (PID+PR) time curves

Treatment (n=24-25/arm):
Darvon (propoxyphene HCl): 65 mg
Acetaminophen (APAP): 650 mg
Darvocet-N (propoxyphene HCl/APAP): 65 mg/650 mg







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Attachment-1

and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: April 1, 1969.

HERBERT L. LEY, Jr.,
Commissioner of Food and Drugs.

[F.R. Doc. 69-4102; Filed, Apr. 7, 1969; 8:48 a.m.]

DESI 10996

PROPOXYPHENE HYDROCHLORIDE; PROPOXYPHENE HYDROCHLORIDE WITH ASPIRIN; PROPOXYPHENE HYDROCHLORIDE WITH ASPIRIN, PHENACETIN, AND CAFFEINE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on the following analgesic preparations marketed by Eli Lilly & Co., 740 South Alabama Street, Indianapolis, Ind. 46206:

1. Darvon; 32 and 65 milligrams of propoxyphene hydrochloride per capsule (NDA 10–997).

2. Darvon Compound; 32 milligrams of propoxyphene hydrochloride, 227 milligrams of aspirin, 162 milligrams of phenacetin, and 32.4 milligrams of caffeine, per capsule (NDA 10–996).

3. Darvon Compound-65; 65 milligrams of propoxyphene hydrochloride, 227 milligrams of aspirin, 162 milligrams of phenacetin, and 32.4 milligrams of caffeine per capsule (NDA 10–996).

The Food and Drug Administration concludes that these drugs when given in adequate dosage are effective for the relief of mild to moderate pain, but that there is lack of substantial evidence of effectiveness of a 32-milligram dose of propoxyphene hydrochloride. Although the labeling of Darvon with A.S.A. (65 milligrams of propoxyphene hydrochloride with 325 milligrams of aspirin (NDA 10–995)), was not submitted for review by the Academy, the Food and Drug Administration also concludes that this combination is effective for relief of mild to moderate pain. Because of the close relationship of this combination to the other preparations reviewed by the Academy, it is appropriate to include it in this announcement.

The drugs continue to be regarded as new drugs (21 U.S.C. 321(p)). Supplemental new-drug applications are required to revise the labeling in and to update previous approved applications providing for such drugs. A new-drug application is required from any person marketing such drugs without approval.

The Food and Drug Administration is prepared to approve new-drug applications and supplements to previously approved new-drug applications under conditions described in this announcement.

PROPOXYPHENE HYDROCHLORIDE; PROPOXYPHENE HYDROCHLORIDE WITH ASPIRIN; AND PROPOXYPHENE HYDROCHLORIDE WITH ASPIRIN, PHENACETIN, AND CAFFEINE

A. *Effectiveness classification.* The Food and Drug Administration has considered reports of the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, as well as other available evidence, and concludes that propoxyphene hydrochloride, propoxyphene hydrochloride with aspirin, and propoxyphene hydrochloride with aspirin, phenacetin, and caffeine are effective for the relief of mild to moderate pain when administered in adequate dosages as described in the labeling guidelines in paragraph E below.

B. *Form of drug.* Propoxyphene hydrochloride preparations are in capsule form suitable for oral administration and contain per dosage unit an amount appropriate for administration in the dosage range described in the labeling conditions in this announcement.

C. *Previously approved applications.*

1. Each holder of a "deemed approved" new-drug application (that is, an application that became effective on the basis of safety prior to Oct. 10, 1962) for such drug is requested to seek approval of the claims of effectiveness and bring the application into conformance by submitting a supplement containing:

a. Revised labeling as needed to conform with the labeling conditions described herein for the drug.

b. Adequate data to assure the biologic availability of the drug in the formulation marketed; if such data are already included in the application, specific reference thereto may be made.

c. Updating information as needed to make the application current in regard to items 6 (components) and 7 (composition) of new-drug application form FD–356H and, to the extent described below for new applications, item 8 (methods, facilities, and controls) of FD–356H.

2. Such supplements should be submitted within the following time periods after the date of publication of this announcement in the FEDERAL REGISTER:

a. Sixty days for revised labeling—the supplement should be submitted under the provisions of § 130.9 (d) and (e) of the new-drug regulations (21 CFR 130.9) which permit certain changes to be put into effect at the earliest possible time.

b. One hundred and eighty days for biologic availability data.

c. Sixty days for updating information.

3. Marketing of the drug may continue until the supplemental applications submitted in accordance with the preceding paragraphs C–1 and C–2 are acted upon, provided that within 60 days after the date of this publication the labeling of the preparation shipped within the jurisdiction of the Federal Food, Drug, and Cosmetic Act is in accord with the labeling conditions described in this announcement.

D. *New applications.*

1. Any other person who distributes or intends to distribute such drug intended for the conditions of use for which it has been shown to be effective, as described under paragraph A above, should submit a new-drug application meeting the conditions specified in this announcement.

2. Such applications should include:

a. Proposed labeling in accord with the labeling conditions herein.

b. Adequate data to assure the biologic availability of the drug in the formulation marketed or proposed for marketing.

c. Satisfactory information of the kinds described in items 1 (table of contents), 4 (label and all other labeling), 5 (R_x or OTC statement), 6 (components), and 7 (composition), of new-drug application form FD–356H and, in lieu of full information described under item 8 (methods, facilities, and controls) of FD–356H, brief statements that:

i. Identify the place where the drug will be manufactured, processed, packaged, and labeled.

ii. Identify any person other than the applicant who performs a part of those operations and designate the part.

iii. Include certification from the applicant and from any person identified in ii above that the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and holding of the drug are in conformity with current good manufacturing practice in accord with Part 133 (21 CFR Part 133).

iv. Assure that the drug dosage form and components will comply with the specifications and tests described in an official compendium, if such article is recognized therein, or if not listed, or if the article differs from the compendium drug, that the specifications and tests applied to the drug and its components are adequate to assure their identity, strength, quality, and purity.

v. Outline the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug.

3. Distribution of any such preparation currently on the market without an approved new-drug application may be continued provided that:

a. Within 60 days from the date of publication hereof in the FEDERAL REGISTER, the labeling of such preparation shipped within the jurisdiction of the act is in accord with the labeling conditions described herein.

b. The manufacturer, packer, or distributor of such drug submits, within 180 days from the date of publication hereof, a new-drug application to the Food and Drug Administration.

c. The applicant submits within a reasonable time additional information that may be required for the approval of the application as specified in a written communication from the Food and Drug Administration.

d. The application has not been ruled incomplete or unapprovable.

E. *Labeling conditions.*

1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the act and regulations promulgated thereunder and those parts of its labeling indicated below are substantially as follows (optional additional information, applicable to the drug, may be proposed under other appropriate paragraph headings and should follow the information set forth below):

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

ACTIONS

Propoxyphene hydrochloride is an analgesic estimated to be approximately one-half to two-thirds as effective on a milligram basis as codeine. The combination of propoxyphene hydrochloride with aspirin and/or phenacetin results in greater analgesia than that achieved by either drug administered alone. Propoxyphene hydrochloride is structurally closely related to the narcotic analgesics methadone and isomethadone, and its general pharmacologic properties are those of the narcotics as a group.

INDICATION

For the relief of mild to moderate pain.

CONTRAINDICATIONS

Hypersensitivity to propoxyphene hydrochloride or to the other ingredients (aspirin, phenacetin, caffeine) in the propoxyphene hydrochloride combination products.

Concomitant administration with orphenadrine-containing compounds.

WARNINGS

Salicylates should be used with caution in the presence of peptic ulcer.

Phenacetin may damage the kidneys when used in large amounts or taken over a long period of time.

USAGE IN PREGNANCY: The safety of the use of this agent during pregnancy has not been established. The potential hazards of the drug must be weighed against the possible benefits.

USAGE IN CHILDREN: This agent should not be used in children since adequate data to establish safe conditions of use are lacking.

DRUG DEPENDENCE: Tolerance, psychological dependence, and physical dependence have been reported; the abuse liability of propoxyphene hydrochloride is qualitatively similar to that of codeine although quantitively less.

This agent may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

PRECAUTIONS

Patients who have received narcotic drugs for long periods of time may have developed physical dependence, and the sudden substitution of ordinary doses of propoxyphene hydrochloride may result in an acute withdrawal syndrome. These symptoms may be avoided by gradually reducing the dose of the prior medication as propoxyphene hydrochloride is substituted.

ADVERSE REACTIONS

Dizziness, headache, sedation, somnolence, paradoxical excitement, insomnia, skin rashes, gastrointestinal disturbances (including nausea, vomiting, abdominal pain, and constipation) may occur with the recommended doses of the drug.

Euphoria may occasionally occur.

DOSAGE AND ADMINISTRATION

Propoxyphene hydrochloride is given orally. The usual dose is 65 milligrams three to four times daily.

Propoxyphene hydrochloride with aspirin is given orally. The usual dose is 65 milligrams of propoxyphene hydrochloride and 325 milligrams of aspirin three to four times daily.

Propoxyphene hydrochloride with aspirin, phenacetin, and caffeine is given orally. The usual dose is 65 milligrams of propoxyphene hydrochloride, 227 milligrams of aspirin, 162 milligrams of phenacetin, and 32.4 milligrams of caffeine three or four times daily.

OVERDOSAGE

Manifestations of accidental or intentional overdosage with propoxyphene are similar to those of narcotic overdosage and include convulsions (more common than is usually noted in cases of narcotic poisoning), coma, respiratory depression, and circulatory collapse. When combination products containing salicylates as well as propoxyphene have been ingested, the clinical picture may be complicated by salicylism.

Analeptic drugs (for example, caffeine or amphetamine) should NOT be used because of their tendency to precipitate fatal convulsions. Narcotic antagonists (nalorphine and levallorphan) are the drugs of choice to reverse signs of intoxication. Gastric lavage may also be helpful. In addition, supportive measures such as assisted ventilation and intravenous fluids should be used as indicated.

Dialysis is of limited value with respect to propoxyphene alone; salicylate and phenacetin are dialyzable.

F. *Exemption from periodic reporting.* The periodic reporting requirements of §§ 130.35(e) and 130.13(b)(4) of the new-drug regulations (21 CFR 130.35(e), 130.13(b)(4)) are waived in regard to applications approved for this drug for the conditions of use described herein.

G. *Unapproved use or form of drug.*

1. If the article is labeled or advertised for use in any condition other than those provided for in this announcement, it will be regarded as an unapproved new drug subject to regulatory proceedings until such recommended use is approved in a new-drug application or is otherwise in accord with this announcement.

2. If the article is proposed for marketing in another form or for a use other than the use provided for in this announcement, appropriate additional information as described in § 130.4 or § 130.9 of the new-drug regulations (21 CFR 130.4, 130.9) may be required, including results of animal and clinical tests intended to show whether the drug is safe and effective.

Representatives of the Administration are willing to meet with any interested person who desires to have a conference concerning proposed changes in the labeling set forth in this announcement. Requests for such meetings should be made to the Special Assistant for Drug Efficacy Study Implementation, at the address given below, within 30 days after publication hereof in the FEDERAL REGISTER.

A copy of the subject NAS-NRC reports has been furnished to the firm referred to above. Any other manufacturer, packer, or distributor of a drug of similar composition and labeling to the drugs listed above or any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be directed to the attention of the following appropriate office and addressed to the Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204:

Requests for NAS-NRC reports: Press Relations Office (CE-300).

Supplements: Office of Marketed Drugs (MD-300), Bureau of Medicine.

Original new-drug applications: Office of Marketed Drugs (MD-300), Bureau of Medicine.

Comments on this announcement: Special Assistant for Drug Efficacy Study Implementation (MD-16), Bureau of Medicine.

This notice is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: April 1, 1969.

HERBERT L. LEY, Jr.,
Commissioner of Food and Drugs.

[F.R. Doc. 69-4103; Filed, Apr. 7, 1969; 8:48 a.m.]

ATOMIC ENERGY COMMISSION

CHARLES WINTER

Certification

Pursuant to the proviso contained in section 207 of title 18 U.S.C. (Public Law 87-849, 76 Stat. 1124), having found that Charles Winter, formerly Deputy Director of the Division of Military Application, Atomic Energy Commission, and presently an employee of the Sandia Corp., possesses outstanding scientific qualifications, I certify that the national interest would be served by the said Charles Winter acting as agent for or appearing personally before the Atomic Energy Commission on behalf of the Sandia Corp. in connection wth the performance of work under the Sandia Corp.-Western Electric Co., Inc., Contract No. AT(29-1)-789 with the Atomic Energy Commission, on matters in which he participated personally and substantially as an employee of the Atomic Energy Commission or which were under his official responsibilty as an AEC employee.

This publication is directed to be published in the FEDERAL REGISTER.

Dated: March 26, 1969.

R. E. HOLLINGSWORTH,
General Manager.

[F.R. Doc. 69-4068; Filed, Apr. 7, 1969; 8:46 a.m.]

[DESI 10996]

PROPOXYPHENE HYDROCHLORIDE; PROPOXYPHENE HYDROCHLORIDE WITH ASPIRIN; PROPOXYPHENE HYDROCHLORIDE WITH ASPIRIN, PHENACETIN, AND CAFFEINE

Followup Notice and Amendment—Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration published an announcement in the FEDERAL REGISTER of April 8, 1969 (34 F.R. 6264), regarding the efficacy of the following analgesic preparations marketed by Eli Lilly & Co., 740 South Alabama Street, Indianapolis, Ind. 46206:

1. Darvon; 32 and 65 milligrams of propoxyphene hydochloride per capsule (NDA 10-997).

2. Darvon Compound; 32 milligrams of propoxyphene hydrochloride, 227 milligrams of aspirin, 162 milligrams of phenacetin, and 32.4 milligrams of caffeine per capsule (NDA 10-996).

3. Darvon Compound-65; 65 milligrams of propoxyphene hydrochloride, 227 milligrams of aspirin, 162 milligrams of phenacetin, and 32.4 milligrams of caffeine per capsule (NDA 10-996).

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug applications reviewed and are subject to this notice. See 21 CFR 130.40 (37 F.R. 23185, October 31, 1972). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Office of Compliance (BD-300), 5600 Fishers Lane, Rockville, Md., 20852.

Upon the basis of recent studies and reconsideration of the reports from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, concerning the 32-mg. dose of propoxyphene hydrochloride, the Commissioner finds it appropriate to revise the second paragraph of the announcement of April 8, 1969, to read as follows:

The Food and Drug Administration concludes that these drugs are effective for the relief of mild to moderate pain. In regard to the 32-mg. dose of propoxyphene, recent studies have shown that this dose does have an analgesic effect in a certain fraction of the population of patients with mild to moderate pain. While 32 mg. of propoxyphene is a weak analgesic dose, only the physician attending a particular patient can determine by titrating the dose whether that individual patient is one of the minority who will respond adequately to the 32-mg. dose, or is one of the majority who will require at least 65 mg. to achieve adequate analgesia. It is therefore appropriate that the 32-mg. dose remain available for those patients in whom it represents an adequate analgesic. On the other hand, because this patient group represents a small fraction of the total population of patients with mild to moderate pain, it is likewise appropriate to state that the usual dose of propoxyphene is 65 mg. Although the labeling of Darvon with A.S.A. (65 mgs. of propoxyphene hydrochloride with 325 mg. of aspirin (NDA 10-995)), was not submitted for review by the Academy, the Food and Drug Administration also concludes that this combination is effective for relief of mild to moderate pain. Because of the close relationship of this combination to the other preparations reviewed by the Academy, it is appropriate to include it in this announcement.

The announcement of April 8, 1969, is further amended to require that adequate data to show the biologic availability of the drug be submitted only with respect to the combination products. For holders of "deemed approved" new drug applications (i.e., an application that became effective on the basis of safety prior to October 10, 1962), clinical trials which have established effectiveness of the drug may also serve to establish the bioavailability of the drug if such trials were conducted on the currently marketed formulation.

The conditions for marketing and for approval of propoxyphene hydrochloride in 32 mg. oral dosage form are the same as the conditions stated for the higher strength dosage form in the FEDERAL REGISTER of April 8, 1969, except that an abbreviated new drug application is required within 60 days after publication of this notice in the FEDERAL REGISTER from any manufacturer or distributor of the drug who does not now hold an approved application. Bioavailability data are not required.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and the Administrative Procedure Act (5 U.S.C. 554) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: December 7, 1972.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.72-21381 Filed 12-12-72;8:45 am]

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NATIONAL ACADEMY OF SCIENCES—NATIONAL RESEARCH COUNCIL

Division of Medical Sciences

DESI 10,996

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DRUG EFFICACY STUDY

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Form A

(To be submitted in duplicate by applicant)

1. NDA Number 10997 Eol 2. Date Originally Approved 8-16-57 3. Rx ☒ OTC ☐

4. Brand Name Darvon, Propoxyphene Hydrochloride Capsules, U.S.P., 32 mg.

5. Applicant's Name Eli Lilly and Company

and Address Post Office Box 618, Indianapolis, Indiana 46206

6. Quantitative Formula

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label)	Amount (per tablet, per ml., etc.)
Propoxyphene Hydrochloride	32 mg./Pulvule

7. Dosage Form (tablets, etc.) Pulvules #364

8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Oral

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

Blue copy is original

The back of this form may be

DARVON
NDA 10997
LOG 454

This drug has been evaluated by the following Panels:

1. Panel on Drugs for Relief of Pain
2. Panel on Drugs Used in Rheumatic Diseases.

Evaluations follow:

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DARVON
NDA 10997
LOG 454

Panel on Drugs for Relief of Pain

There is one insert for three different preparations; Darvon (NDA 10997), Darvon Compound (10996), and Darvon Compound-65 (10996). When the indication is just for one of these preparations, this will be designated by the NDA number of that preparation.

INDICATIONS

I. "Darvon /NDA 10997/ is indicated for the reduction or amelioration of pain."

EVALUATION: Effective.

COMMENTS: Dextropropoxyphene in doses of 65 mg to 100 mg has usually, but not always, proved superior to placebo in reasonably sensitive human analgesic assays; however, the 32-mg dose has often been found indistinguishable from placebo.

DOCUMENTATION:
1. Beaver, W. T. Mild analgesics, a review of their clinical pharmacology (Part II). Amer. J. Med. Sci. 251:576-599, 1966.
2. Lasagna, L. Clinical evaluation of morphine and its substitutes as analgesics. Pharmacol. Rev. 16:47-83, 1964.

II. "It /Darvon, NDA 10997/ is of particular value for pain associated with recurrent or chronic disease. This is true even in such conditions as migraine in which specific therapy sometimes fails to produce immediate or complete relief."

EVALUATION: Effective, but . . . .

COMMENTS: Although Darvon is an effective analgesic and can be used for recurrent or chronic pain, there is no evidence of its "particular value for pain."

DOCUMENTATION: Same as for Indication I.

III. "Darvon Compound and Darvon Compound-65 /NDA 10996/ provide the total analgesic effects of Darvon and A.S.A. Compound plus the anti-inflammatory and antipyretic activity of salicylates. This combination may be especially valuable in the symptomatic relief of such conditions as headache, dysmenorrhea, or various inflammatory states, e.g., arthritis and fibrositis."

EVALUATION: Effective, but . . . .

COMMENTS: In frankly febrile and inflammatory states, this combination is effective. However, it is not clear that the conditions cited above qualify. The Panel knows of no controlled studies using Darvon in dysmenorrhea.

DOCUMENTATION: Same as for Indication I.

GENERAL COMMENTS

I. Under "Description of Drug," the statement is made: "Milligram for milligram, Darvon is equal to codeine in intensity and duration of analgesic action, yet it has fewer side-effects."

This claim is misleading and therefore unjustifiable. If all the suitably controlled analgesic assays comparing Darvon and codeine with which the Panel is familiar are considered, Darvon appears to be less potent than codeine; the best available estimates of the relative potency of the two drugs indicate that dextropropoxyphene is approximately one-half to two-thirds as potent as codeine. The side effects produced by the two drugs are qualitatively similar. When the two drugs are administered in equal doses on a milligram basis, codeine is more likely to cause nausea and vomiting than dextropropoxyphene and is possibly more likely to cause sedation and dizziness. However, because estimates of relative side-effect liability are meaningful only if made at equianalgesic doses, the significance of the relative side-effect incidence observed at equimilligram doses is debatable.

DOCUMENTATION: Same as for Indication I.

II. Under "Indications," the statement is made: "When Darvon /NDA 10997/ is given in therapeutic doses, euphoria is not observed, tolerance does not occur, and physical dependence does not develop."

The statement is inadequate concerning the abuse liability and dependence-producing properties of dextropropoxyphene and appears unwarranted in the face of the paucity of suitable studies exploring such factors as the occurrence of euphoria and the development of tolerance, psychic dependence, or physical dependence when therapeutic doses of any of the narcotics, including Darvon, are administered chronically to representative populations of patients with pain. A possibly significant incidence of euphoria has been noted by Gruber (10) on administration of therapeutic doses of racemic propoxyphene, and Cass (2) have noted signs and symptoms suggestive of minimal physical dependence after allyl tests or drug withdrawal in some patients who were on Darvon 65 mg (presumably q.i.d.) for 3 months. The matter of tolerance development to the analgesic effects of any of the mild analgesics has, to the Panel's knowledge, never been explored using a satisfactory experimental design. However, Chernish and Gruber (3,10) have produced some evidence indicating that long-term therapy with oral meperidine induced more tolerance than long-term therapy with similar doses of Darvon to the analgesic effect of subsequent parenteral administration of either drug.

A statement concerning the abuse liability of Darvon is certainly indicated at this point in the package insert. Studies by Fraser (7-9) and his associates in "post-addicts" at Lexington indicate that although an abuse potential for dextropropoxyphene exists, it is slight, substantially less even than that of codeine. This prediction has been substantiated by the fact that, in spite of widespread use of this drug, reports of abuse have been few. When Darvon has been given in therapeutic doses, there has been no evidence that significant physical dependence on the drug or tolerance to its analgesic effects develops. Although a few cases of Darvon dependence have been reported, its abuse potential is considered to be slight.

DOCUMENTATION:

1. Beaver, W. T. Mild analgesics; a review of their clinical pharmacology (Part II). Amer. J. Med. Sci. 251:576-599, 1966.
2. Cass, L. J., J. T. Laing, and W. S. Frederik. Physical dependence potentiality of analgesics. Curr. Ther. Res. 3:289-299, 1961.
3. Chernish, S. M., and C. Gruber, Jr. A comparison of dextro-propoxyphene hydrochloride and meperidine hydrochloride. J. Amer. Geriat. Soc. 12:249-254, 1964.
4. Chernish, S. M., and C. M. Gruber, Jr. Demonstration of absence of physical dependence to therapeutic doses of dextropropoxyphene hydrochloride (darvon) using the "allyl test". Antibiot. Med. Clin. Ther. 7:190-192, 1960.
5. Claghorn, J. L., and J. C. Schoolar. Propoxyphene hydrochloride, a drug of abuse. J.A.M.A. 196:1089-1091, 1966.
6. Elson, A., and E. F. Domino. Dextro-propoxyphene addiction; observations of a case. J.A.M.A. 183:482-485, 1963.
7. Fraser, H. F., and H. Isbell. Pharmacology and addiction liability of dl- and d-propoxyphene. U. N. Bull. Narcotics 12(1):9-14, 1960.
8. Fraser, H. F., W. R. Martin, A. B. Wolbach, and H. Isbell. Addiction liability of an isoquinoline analgesic, 1-(p-chlorophenethyl) -2-methyl-6, 7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Clin. Pharmacol. Ther. 2:287-299, 1961.
9. Fraser, H. F. Addictiveness of 1,2-dimethyl, 3-phenyl, 3-propionoxy pyrrolidine hydrochloride (ARC I-O-1). U. N. Bull. Narcotics 16(1): 37-43, 1964.
10. Gruber, C. M., Jr., E. P. King, M. M. Best, J. F. Schieve, F. Elkus, and E. J. Zmolek. Clinical bio-assay of oral analgesic activity of propoxyphene (lilly), acetylsalicylic acid, and codeine phosphate, and observations on placebo reactions. Arch. Int. Pharmacodyn. Ther. 104:156-166, 1955.
11. Lasagna, L. Clinical evaluation of morphine and its substitutes as analgesics. Pharmacol. Rev. 16:47-83, 1964.

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III. Under "Adverse Reactions," the statement is made: "Huge doses may be accompanied by dizziness, sedation and somnolence."

This statement is inadequate because narcosis, respiratory depression, convulsions, and death may also result from massive overdosage.

DOCUMENTATION:
1. Beaver, W. T. Mild analgesics; a review of their clinical pharmacology (Part II). Amer. J. Med. Sci. 251:576-599, 1966.

IV. Under "Treatment of Overdosage," the statements are inadequate. It should be clearly stated that overdosage with Darvon presents essentially the same clinical picture and management problem as acute overdosage with any other narcotic drug, complicated by a more frequent occurrence of convulsions than is usually noted in the case of narcotic poisoning. The predominant features are coma, respiratory depression, convulsions, and circulatory collapse. Salicylism may complicate the picture if Darvon Compound or Darvon with A.S.A. was the preparation ingested.

DOCUMENTATION: Same as for General Comment III.

V. Under "Administration and Dosage," it should be pointed out that dextropropoxyphene is less than equianalgesic with codeine on a milligram basis and a single 32 mg dose of Darvon is often ineffective. Although most published clinical trials have used doses of 32 and 65 mg, many physicians currently use 65 to 130 mg doses.

DOCUMENTATION: Same as for General Comment III.

VI. Under "Description," the statement is made: "When inflammation is present, the combination /Darvon Compound, NDA 10996/ reduces discomfort to a greater extent than does either analgesic given alone."

There is reason to believe, on the basis of either actual clinical studies and theoretical considerations, that the combination of Darvon with an antipyretic-analgesic of the aspirin type results in analgesia superior to that achieved by either drug administered alone.

DOCUMENTATION:
1. Beaver, W. T. Mild analgesics; a review of their clinical pharmacology. Amer. J. Med. Sci. 250:577-604, 1965 and 251:576-599, 1966.

VII. In the "Indications" section, the statement is made: "It /Darvon, NDA 10997/ can be used with other analgesics to augment their effectiveness."

If this is meant to indicate that a combination of dextropropoxyphene with aspirin or other antipyretic-analgesics yields greater analgesia than the antipyretic-analgesic alone, there is reasonable evidence that this claim is true. However, the Panel is not aware of evidence that the analgesic effectiveness of other analgesics such as morphine, meperidine, etc., would be augmented by the concomitant administration of dextropropoxyphene.

DOCUMENTATION: None applicable.

VIII. Although the package insert is in general acceptable, with the reservations noted above, one disturbing feature comes to mind when the insert is considered as a whole. An obvious effort has been made to avoid pointing out that dextropropoxyphene is structurally closely related to the narcotic analgesics methadone and isomethadone, that its general pharmacologic properties are those of the narcotics as a group, that poisoning produced by dextropropoxyphene is essentially typical of narcotic overdose (complicated by convulsions) and should be treated as such, and that the distinction in dependence-producing properties and abuse liability between dextropropoxyphene and various other narcotics is essentially quantitative, rather than qualitative.

That this effort, unfortunately, appears to have been successful, is attested to by the fact that the majority of house staff and attending physicians who make liberal use of Darvon assume that its pharmacology is basically similar to that of aspirin or phenacetin, rather than to that of the narcotics.

IX. The revised insert of March 1967 has also been reviewed by the Panel. Justifiably, the company has elected to delete claims made in General Comments I, II, VI, and VII. Under "Adverse Reactions," the claim was made: "When recommended doses are given, euphoria and tolerance have been reported rarely. Dependence (addiction) has not been reported with therapeutic dosages." This claim has been commented on in General Comment II.

X. See general statements on analgesic preparations.

Approved by _____
Chairman

GENERAL STATEMENTS ON ANALGESIC PREPARATIONS

I. Evidence for General Analgesic Effect.

It is the recommendation of the Panel that, when a drug has been shown to be an effective analgesic in several different kinds of clinical pain, by suitably controlled trials using modern criteria, such a drug be entitled to consideration as an "all-purpose analgesic" unless special considerations indicate that this is not appropriate. In such cases, it would seem desirable to allow the drug to be marketed for the relief of most kinds of pain, thus avoiding the necessity for listing specific conditions.

II. Analgesic Mixtures.

There is increasing evidence, which has accumulated particularly within the past few years, that it is not always easy to predict the effects of adding one drug to another. Thus, drugs may merely summate in their activities, antagonize each other, or produce true potentiation. Since adequate trials on the relative efficacy of single drugs and mixtures are usually unavailable, it is hard for the Panel to be both fair and scientific in the evaluation of many of the mixtures which it has been asked to review.

Furthermore, some ingredients appear to have been added to these mixtures on the basis of a rationale that is not evident to the Panel. On other occasions, the rationale seems evident, but the reason for the particular doses chosen (especially those which seem homeopathic) is not clear.

In addition to the well-known objections that fixed-ratio mixtures do not allow flexibility in the doses of individual ingredients, one can object to many analgesic mixtures because they contribute little additional therapeutic benefit while increasing the risks of side effects, allergic sensitization, etc. One can perhaps justify the use of some of these mixtures when pain is present with some other symptom, such as a stuffy nose, and both symptoms can be handled reasonably well by the mixture. However, to promote such a mixture as an all-purpose remedy for all kinds of pain, including those which cannot possibly be aided by one or more of the ingredients, is, in the view of the Panel, to encourage bad therapeutics.

III. Semantic Confusion.

The words "synergism" and "potentiation" are subject to multiple interpretations, even among professional pharmacologists. It would seem desirable to avoid their use, focusing instead on a description of what actually was achieved in the clinical setting. The word "potency" also has different meanings to different persons. If one is talking simply about milligram potency, this is actually a trivial matter in the clinical setting and, therefore, the term "potency" should probably be avoided.

IV. Irrelevant Information.

Many package inserts contain material of no relevance to most practitioners. For example, the animal data are often not helpful, and are not always clearly identifiable as such. This material often seems to be used as a substitute for clinical data. Also irrelevant and not particularly helpful to the reader is a long list of clinical testimonials, only some of which bear on the points at issue, and most of which are uninterpretable because of defects in clinical design.

V. Drug Dependence and Abuse.

The following statement is proposed to bring uniformity to the claims made concerning the dependence-producing properties of narcotic analgesics and preparations containing narcotic analgesics. It is recognized that many of the claims concerning a lesser dependence-producing liability of specific narcotic analgesics reflect the fact that the particular agents are not commonly abused. However, it must also be recognized that the actual abuse rates do not accurately reflect dependence-producing potential. It is known that agents and preparations that have not been commonly abused in some social settings at some times, have been extensively abused in other settings at other times.

One of the major purposes of the existing laws and regulations concerning narcotic analgesics is to prevent abuse. Therefore, all agents that have been shown to produce morphine-like physiologic and subjective changes when administered chronically, that will produce morphine-like dependence, or that will substitute for morphine in morphine-dependent subjects, shall carry the following recommended warning:

"(Name of agent) can produce dependence of the morphine type and therefore has the potential for being abused."

The only exceptions to this recommendation are substances specifically exempted from bearing the label "Warning -- may be habit forming" required by federal law or regulation.

VI. Rigid Dose Recommendations.

The Panel believes that doctors should not be bound legally by dose recommendations in package inserts. These recommendations represent advice as to the dose at which most patients can be started, and the range at which the needs of most patients can be met. However, it is good practice to manipulate the dose in the event of a therapeutic failure, or in the event of untoward effects. Furthermore, tolerance to a drug may develop, and may require an increase in dose. It is the Panel's observation that some of the recommended doses are too low.

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DARVON
NDA 10997
LOG 454

VII. Deficiencies of Methodology.

There is a need for additional methodology for the study of pain. Thus, for example, there is a paucity of information available on the comparative effects of analgesics given repeatedly to patients with chronic pain. The result with single doses may or may not be transferable to such situations. Another area of deficiency is the evaluation of topical ointments that produce obvious sensations of cooling or warmth. Such limitations in methodology should be kept in mind by the Food and Drug Administration when evaluating data on drugs, both old and new.

Approved by _____

Chairman

DARVON
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16

Panel on Drugs Used in Rheumatic Diseases

GENERAL COMMENTS

The Panel on Drugs Used in Rheumatic Diseases recommends that certain ill-defined and vague claims be modified or deleted. The following is a list of these claims.

1. Fibrositis, myositis, arthritis, spondylitis, and torticollis.

2. Lumbago, "stiff neck," whiplash injury, rheumatism, rheumatic, and arthritides.

The claims in the first category are of such different etiologies that it would be better to specify the diseases (e.g., osteo-arthritis, rheumatoid arthritis, and ankylosing spondylitis) or modify the claims to specify the etiology. The claims in the second category are imprecise and unscientific terms which are objectionable to the Panel and should be deleted. Because these claims are vague and ill-defined, the objective criteria necessary to evaluate the efficacy of a drug is greatly compromised.

Approved by Charles Rayer
Chairman

The Drug Efficacy Study of the National Academy of Sciences - National Research Council has requested that the following qualifying addendum be conveyed with their reports to the ultimate recipients of these reports:

> "Drugs of identical chemical composition (so-called generic drugs) formulated and marketed by numerous individual firms under generic or trademarked names have been evaluated for efficacy as a group without consideration of 'therapeutic equivalence.' In the event that no evidence for pharmacological availability or therapeutic efficacy in man can be presented for any of the indications claimed for the use of any of the drugs in the attached listing, their classifications of effectiveness may need to be modified if regulations of the Food and Drug Administration require such proof."

NATIONAL ACADEMY OF SCIENCES—NATIONAL RESEARCH COUNCIL

Division of Medical Sciences

DRUG EFFICACY STUDY

Form A

(To be submitted in duplicate by applicant)

Ref# 437

1. NDA Number 10-996 2. Date Originally Approved 8-14-57 3. Rx ☒ OTC ☐

4. Brand Name Darvon® Compound (Propoxyphene Hydrochloride, Aspirin, Phenacetin, and Caffeine

5. Applicant's Name EU LILLY AND COMPANY
~~P. O. Box 618~~
Indianapolis, Indiana
U. S. A. 46206
and Address

6. Quantitative Formula

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label)	Amount (per tablet, per ml., etc.)
Propoxyphene Hydrochloride	32.0 mg./Pulvule
Aspirin	227.0 mg./Pulvule
Phenacetin	162.0 mg./Pulvule
Caffeine (Anhydrous)	32.4 mg./Pulvule

7. Dosage Form (tablets, etc.) Pulvules #368

8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Oral

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

Blue copy is original

The back of this form may be

DARVON COMPOUND
NDA 10996
LOG 27

This drug has been evaluated by the following Panels:

1. Panel on Drugs for Relief of Pain

2. Panel on Drugs Used in Rheumatic Diseases

Evaluations follow:

DARVON COMPOUND
NDA 10996
LOG 27

Panel on Drugs for Relief of Pain

There is one insert for three different preparations; Darvon (NDA 10997), Darvon Compound (10996), and Darvon Compound-65 (10996). When the indication is just for one of these preparations, this will be designated by the NDA number of that preparation.

INDICATIONS

I. "Darvon /NDA 10997/ is indicated for the reduction or amelioration of pain."

EVALUATION: Effective.

COMMENTS: Dextropropoxyphene in doses of 65 mg to 100 mg has usually, but not always, proved superior to placebo in reasonably sensitive human analgesic assays; however, the 32-mg dose has often been found indistinguishable from placebo.

DOCUMENTATION:
1. Beaver, W. T. Mild analgesics, a review of their clinical pharmacology (Part II). Amer. J. Med. Sci. 251:576-599, 1966.
2. Lasagna, L. Clinical evaluation of morphine and its substitutes as analgesics. Pharmacol. Rev. 16:47-83, 1964.

II. "It /Darvon, NDA 10997/ is of particular value for pain associated with recurrent or chronic disease. This is true even in such conditions as migraine in which specific therapy sometimes fails to produce immediate or complete relief."

EVALUATION: Effective, but . . . .

COMMENTS: Although Darvon is an effective analgesic and can be used for recurrent or chronic pain, there is no evidence of its "particular value for pain."

DOCUMENTATION: Same as for Indication I.

III. "Darvon Compound and Darvon Compound-65 /NDA 10996/ provide the total analgesic effects of Darvon and A.S.A. Compound plus the anti-inflammatory and antipyretic activity of salicylates. This combination may be especially valuable in the symptomatic relief of such conditions as headache, dysmenorrhea, or various inflammatory states, e.g., arthritis and fibrositis."

EVALUATION: Effective, but . . . .

COMMENTS: In frankly febrile and inflammatory states, this combination is effective. However, it is not clear that the conditions cited above qualify. The Panel knows of no controlled studies using Darvon in dysmenorrhea.

DOCUMENTATION: Same as for Indication I.

GENERAL COMMENTS

I. Under "Description of Drug," the statement is made: "Milligram for milligram, Darvon is equal to codeine in intensity and duration of analgesic action, yet it has fewer side-effects."

This claim is misleading and therefore unjustifiable. If all the suitably controlled analgesic assays comparing Darvon and codeine with which the Panel is familiar are considered, Darvon appears to be less potent than codeine; the best available estimates of the relative potency of the two drugs indicate that dextropropoxyphene is approximately one-half to two-thirds as potent as codeine. The side effects produced by the two drugs are qualitatively similar. When the two drugs are administered in equal doses on a milligram basis, codeine is more likely to cause nausea and vomiting than dextropropoxyphene and is possibly more likely to cause sedation and dizziness. However, because estimates of relative side-effect liability are meaningful only if made at equianalgesic doses, the significance of the relative side-effect incidence observed at equimilligram doses is debatable.

DOCUMENTATION: Same as for Indication I.

II. Under "Indications," the statement is made: "When Darvon /NDA 10997/ is given in therapeutic doses, euphoria is not observed, tolerance does not occur, and physical dependence does not develop."

The statement is inadequate concerning the abuse liability and dependence-producing properties of dextropropoxyphene and appears unwarranted in the face of the paucity of suitable studies exploring such factors as the occurrence of euphoria and the development of tolerance, psychic dependence, or physical dependence when therapeutic doses of any of the narcotics, including Darvon, are administered chronically to representative populations of patients with pain. A possibly significant incidence of euphoria has been noted by Gruber (10) on administration of therapeutic doses of racemic propoxyphene, and Cass (2) have noted signs and symptoms suggestive of minimal physical dependence after allyl tests or drug withdrawal in some patients who were on Darvon 65 mg (presumably q.i.d.) for 3 months. The matter of tolerance development to the analgesic effects of any of the mild analgesics has, to the Panel's knowledge, never been explored using a satisfactory experimental design. However, Chernish and Gruber (3,10) have produced some evidence indicating that long-term therapy with oral meperidine induced more tolerance than long-term therapy with similar doses of Darvon to the analgesic effect of subsequent parenteral administration of either drug.

A statement concerning the abuse liability of Darvon is certainly indicated at this point in the package insert. Studies by Fraser (7-9) and his associates in "post-addicts" at Lexington indicate that although an abuse potential for dextropropoxyphene exists, it is slight, substantially less even than that of codeine. This prediction has been substantiated by the fact that, in spite of widespread use of this drug, reports of abuse have been few. When Darvon has been given in therapeutic doses, there has been no evidence that significant physical dependence on the drug or tolerance to its analgesic effects develops. Although a few cases of Darvon dependence have been reported, its abuse potential is considered to be slight.

DOCUMENTATION:

1. Beaver, W. T. Mild analgesics; a review of their clinical pharmacology (Part II). Amer. J. Med. Sci. 251:576-599, 1966.
2. Cass, L. J., J. T. Laing, and W. S. Frederik. Physical dependence potentiality of analgesics. Curr. Ther. Res. 3:289-299, 1961.
3. Chernish, S. M., and C. Gruber, Jr. A comparison of dextro-propoxyphene hydrochloride and meperidine hydrochloride. J. Amer. Geriat. Soc. 12:249-254, 1964.
4. Chernish, S. M., and C. M. Gruber, Jr. Demonstration of absence of physical dependence to therapeutic doses of dextropropoxyphene hydrochloride (darvon) using the "allyl test". Antibiot. Med. Clin. Ther. 7:190-192, 1960.
5. Claghorn, J. L., and J. C. Schoolar. Propoxyphene hydrochloride, a drug of abuse. J.A.M.A. 196:1089-1091, 1966.
6. Elson, A., and E. F. Domino. Dextro-propoxyphene addiction; observations of a case. J.A.M.A. 183:482-485, 1963.
7. Fraser, H. F., and H. Isbell. Pharmacology and addiction liability of dl- and d-propoxyphene. U. N. Bull. Narcotics 12(1):9-14, 1960.
8. Fraser, H. F., W. R. Martin, A. B. Wolbach, and H. Isbell. Addiction liability of an isoquinoline analgesic, 1-(p-chlorophenethyl)-2-methyl-6, 7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Clin. Pharmacol. Ther. 2:287-299, 1961.
9. Fraser, H. F. Addictiveness of 1,2-dimethyl, 3-phenyl, 3-propionoxy pyrrolidine hydrochloride (ARC I-O-1). U. N. Bull. Narcotics 16(1): 37-43, 1964.
10. Gruber, C. M., Jr., E. P. King, M. M. Best, J. F. Schieve, F. Elkus, and E. J. Zmolek. Clinical bio-assay of oral analgesic activity of propoxyphene (lilly), acetylsalicylic acid, and codeine phosphate, and observations on placebo reactions. Arch. Int. Pharmacodyn. Ther. 104:156-166, 1955.
11. Lasagna, L. Clinical evaluation of morphine and its substitutes as analgesics. Pharmacol. Rev. 16:47-83, 1964.

III. Under "Adverse Reactions," the statement is made: "Huge doses may be accompanied by dizziness, sedation and somnolence."

This statement is inadequate because narcosis, respiratory depression, convulsions, and death may also result from massive overdosage.

DOCUMENTATION:
1. Beaver, W. T. Mild analgesics; a review of their clinical pharmacology (Part II). Amer. J. Med. Sci. 251:576-599, 1966.

IV. Under "Treatment of Overdosage," the statements are inadequate. It should be clearly stated that overdosage with Darvon presents essentially the same clinical picture and management problem as acute overdosage with any other narcotic drug, complicated by a more frequent occurrence of convulsions than is usually noted in the case of narcotic poisoning. The predominant features are coma, respiratory depression, convulsions, and circulatory collapse. Salicylism may complicate the picture if Darvon Compound or Darvon with A.S.A. was the preparation ingested.

DOCUMENTATION: Same as for General Comment III.

V. Under "Administration and Dosage," it should be pointed out that dextropropoxyphene is less than equianalgesic with codeine on a milligram basis and a single 32 mg dose of Darvon is often ineffective. Although most published clinical trials have used doses of 32 and 65 mg, many physicians currently use 65 to 130 mg doses.

DOCUMENTATION: Same as for General Comment III.

VI. Under "Description," the statement is made: "When inflammation is present, the combination /Darvon Compound, NDA 10996/ reduces discomfort to a greater extent than does either analgesic given alone."

There is reason to believe, on the basis of either actual clinical studies and theoretical considerations, that the combination of Darvon with an antipyretic-analgesic of the aspirin type results in analgesia superior to that achieved by either drug administered alone.

DOCUMENTATION:
1. Beaver, W. T. Mild analgesics; a review of their clinical pharmacology. Amer. J. Med. Sci. 250:577-604, 1965 and 251:576-599, 1966.

VII. In the "Indications" section, the statement is made: "It /Darvon, NDA 10997/ can be used with other analgesics to augment their effectiveness."

If this is meant to indicate that a combination of dextropropoxyphene with aspirin or other antipyretic-analgesics yields greater analgesia than the antipyretic-analgesic alone, there is reasonable evidence that this claim is true. However, the Panel is not aware of evidence that the analgesic effectiveness of other analgesics such as morphine, meperidine, etc., would be augmented by the concomitant administration of dextropropoxyphene.

DOCUMENTATION: None applicable.

VIII. Although the package insert is in general acceptable, with the reservations noted above, one disturbing feature comes to mind when the insert is considered as a whole. An obvious effort has been made to avoid pointing out that dextropropoxyphene is structurally closely related to the narcotic analgesics methadone and isomethadone, that its general pharmacologic properties are those of the narcotics as a group, that poisoning produced by dextropropoxyphene is essentially typical of narcotic overdose (complicated by convulsions) and should be treated as such, and that the distinction in dependence-producing properties and abuse liability between dextropropoxyphene and various other narcotics is essentially quantitative, rather than qualitative.

That this effort, unfortunately, appears to have been successful, is attested to by the fact that the majority of house staff and attending physicians who make liberal use of Darvon assume that its pharmacology is basically similar to that of aspirin or phenacetin, rather than to that of the narcotics.

IX. The revised insert of March 1967 has also been reviewed by the Panel. Justifiably, the company has elected to delete claims made in General Comments I, II, VI, and VII. Under "Adverse Reactions," the claim was made: "When recommended doses are given, euphoria and tolerance have been reported rarely. Dependence (addiction) has not been reported with therapeutic dosages." This claim has been commented on in General Comment II.

X. See general statements on analgesic preparations.

Approved by _____

Chairman

GENERAL STATEMENTS ON ANALGESIC PREPARATIONS

I. Evidence for General Analgesic Effect.

It is the recommendation of the Panel that, when a drug has been shown to be an effective analgesic in several different kinds of clinical pain, by suitably controlled trials using modern criteria, such a drug be entitled to consideration as an "all-purpose analgesic" unless special considerations indicate that this is not appropriate. In such cases, it would seem desirable to allow the drug to be marketed for the relief of most kinds of pain, thus avoiding the necessity for listing specific conditions.

II. Analgesic Mixtures.

There is increasing evidence, which has accumulated particularly within the past few years, that it is not always easy to predict the effects of adding one drug to another. Thus, drugs may merely summate in their activities, antagonize each other, or produce true potentiation. Since adequate trials on the relative efficacy of single drugs and mixtures are usually unavailable, it is hard for the Panel to be both fair and scientific in the evaluation of many of the mixtures which it has been asked to review.

Furthermore, some ingredients appear to have been added to these mixtures on the basis of a rationale that is not evident to the Panel. On other occasions, the rationale seems evident, but the reason for the particular doses chosen (especially those which seem homeopathic) is not clear.

In addition to the well-known objections that fixed-ratio mixtures do not allow flexibility in the doses of individual ingredients, one can object to many analgesic mixtures because they contribute little additional therapeutic benefit while increasing the risks of side effects, allergic sensitization, etc. One can perhaps justify the use of some of these mixtures when pain is present with some other symptom, such as a stuffy nose, and both symptoms can be handled reasonably well by the mixture. However, to promote such a mixture as an all-purpose remedy for all kinds of pain, including those which cannot possibly be aided by one or more of the ingredients, is, in the view of the Panel, to encourage bad therapeutics.

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One of the major purposes of the existing laws and regulations concerning narcotic analgesics is to prevent abuse. Therefore, all agents that have been shown to produce morphine-like physiologic and subjective changes when administered chronically, that will produce morphine-like dependence, or that will substitute for morphine in morphine-dependent subjects, shall carry the following recommended warning:

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The only exceptions to this recommendation are substances specifically exempted from bearing the label "Warning -- may be habit forming" required by federal law or regulation.

VI. Rigid Dose Recommendations.

The Panel believes that doctors should not be bound legally by dose recommendations in package inserts. These recommendations represent advice as to the dose at which most patients can be started, and the range at which the needs of most patients can be met. However, it is good practice to manipulate the dose in the event of a therapeutic failure, or in the event of untoward effects. Furthermore, tolerance to a drug may develop, and may require an increase in dose. It is the Panel's observation that some of the recommended doses are too low.

DARVON COMPOUND
NDA 10996
LOG 27

VII. Deficiencies of Methodology.

There is a need for additional methodology for the study of pain. Thus, for example, there is a paucity of information available on the comparative effects of analgesics given repeatedly to patients with chronic pain. The result with single doses may or may not be transferable to such situations. Another area of deficiency is the evaluation of topical ointments that produce obvious sensations of cooling or warmth. Such limitations in methodology should be kept in mind by the Food and Drug Administration when evaluating data on drugs, both old and new.

Approved by _____

Chairman

DARVON COMPOUND
NDA 10996
LOG 27

11

Panel on Drugs Used in Rheumatic Diseases

GENERAL COMMENTS

The Panel on Drugs Used in Rheumatic Diseases recommends that certain ill-defined and vague claims be modified or deleted. The following is a list of these claims.

1. Fibrositis, myositis, arthritis, spondylitis, and torticollis.

2. Lumbago, "stiff neck," whiplash injury, rheumatism, rheumatic, and arthritides.

The claims in the first category are of such different etiologies that it would be better to specify the diseases (e.g., osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis) or modify the claims to specify the etiology. The claims in the second category are imprecise and unscientific terms which are objectionable to the Panel and should be deleted. Because these claims are vague and ill-defined, the objective criteria necessary to evaluate the efficacy of a drug is greatly compromised.

Approved by Charles Rheyer
Chairman

The Drug Efficacy Study of the National Academy of Sciences - National Research Council has requested that the following qualifying addendum be conveyed with their reports to the ultimate recipients of these reports:

> "Drugs of identical chemical composition (so-called generic drugs) formulated and marketed by numerous individual firms under generic or trademarked names have been evaluated for efficacy as a group without consideration of 'therapeutic equivalence.' In the event that no evidence for pharmacological availability or therapeutic efficacy in man can be presented for any of the indications claimed for the use of any of the drugs in the attached listing, their classifications of effectiveness may need to be modified if regulations of the Food and Drug Administration require such proof."

Attachment-2

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

HARRY GOLD, M.D.
PROFESSOR OF CLINICAL PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE

AND

MCKEEN CATTELL, M.D.
PROFESSOR OF PHARMACOLOGY, EMERITUS, CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK, NEW YORK

MILD ANALGESICS
A REVIEW OF THEIR CLINICAL PHARMACOLOGY (Part II)

(Continued from November, 1965 issue)

BY WILLIAM T. BEAVER, M.D.*

(From the Division of Clinical Investigation, Sloan-Kettering Institute for Cancer Research, and the Department of Pharmacology, Cornell University Medical College, New York, New York)

B. "WEAK" NARCOTICS AND CHEMICALLY RELATED NONNARCOTICS. The decision to include oral codeine as a "weak" narcotic in a review on mild analgesics and to exclude closely related compounds such as dihydrocodeine, hydrocodone (dihydrocodeinone) and oxycodone, or other narcotics such as meperidine and anileridine which are often administered in oral form for the relief of moderate pain, is admittedly arbitrary. This decision was based on the following considerations: (1) It is my impression that, as a matter of clinical usage, most physicians tend to think of and to prescribe oral codeine as a "mild" analgesic, in contradistinction to the other narcotics noted above (with the possible exception of dihydrocodeine) which are usually considered by the physician as "strong" analgesics. (2) Most aspects of the clinical pharmacology of the strong analgesics have been quite adequately considered by Lasagna in an excellent critical review[214]. Moreover, clinical experience regarding comparative analgesic effectiveness, side-effect liability, and addiction potential of the synthetic substances with morphine-like effect has been extensively reviewed by Eddy *et al.*[104]. (3) Dihydrocodeine, hydrocodone, and oxycodone seem to be available in America only as constituents of drug mixtures, and with the exception of one study in out-

*Sec. 5607, Sloan-Kettering Institute for Cancer Research, 410 East 68th Street, New York, New York 10021.

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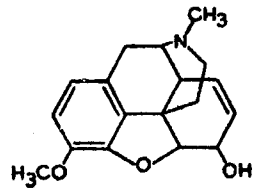

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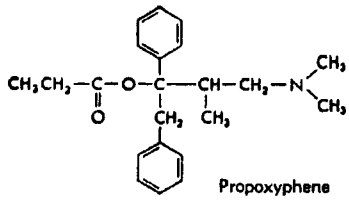

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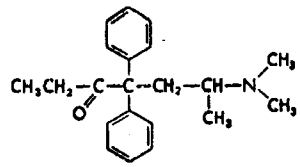

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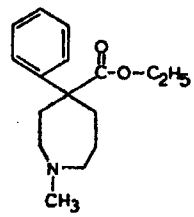

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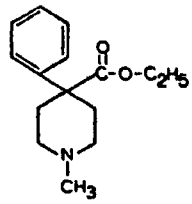

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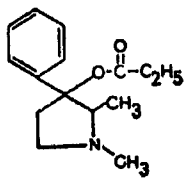
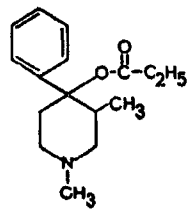


Prodilidine



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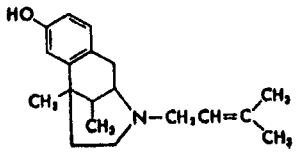
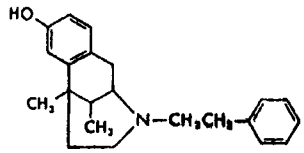


Pentazocine



Phenazocine

Fig. 5.—"Weak" narcotics and chemically related nonnarcotics. The formulae of corresponding potent narcotics are illustrated for comparison.

TABLE 2.—CONTROLLED HUMAN ANALGESIC ASSAYS INCORPORATING ORAL CODEINE

Investigator(s)	*Reference*	*Type of Patient or Etiology of Pain, or Both*	*Schedule of Administration*	*Results*
Beecher *et al.*	20	postoperative	single dose, p.r.n., crossover	cod. 60 ns> placebo
Boyle *et al.*	34	mixed chronic	multiple dose, p.r.n. × 1 week, crossover	cod. 65 s> placebo, cod. 65 ns> aspirin 650
Cass & Frederik	62	mixed chronic	t.i.d. × 6 days, crossover	cod. 60 s> placebo, cod. 60 ns> aspirin 600
Cass & Frederik	59	mixed chronic	t.i.d. × 6 days, crossover	cod. 30 s> placebo, cod. 30 s> aspirin 600
Cass & Frederik	57	mixed chronic	t.i.d. × 6 days, crossover	cod. 32 s> placebo, cod. 130> cod. 64> cod. 32> placebo
Chilton *et al.*	72	dental outpatients	single dose, p.r.n.	cod. 60 s> placebo
Corgill *et al.*	78	mixed pain, inpatients & outpatients	multiple dose, p.r.n. × 4 days	cod. 60 s> placebo, cod. 60 ns> aspirin 600
DeKornfeld & Lasagna	88	postpartum	single dose, p.r.n.	cod. 60 s> placebo, aspirin 600 ns> cod. 60
Forrest	112	mixed acute	single dose, p.r.n., crossover	cod. 90 s> placebo ns> cod. 30, aspirin 900 s> cod. 90 aspirin 300 s> cod. 30
Gruber	144	mixed chronic	4–6 doses/day × 3 days	cod. 32.5 s> placebo, cod. 65s> cod. 32.5
Gruber *et al.*	145	postpartum	single dose, p.r.n.	cod. 32 ns> placebo, A.P.C. s> placebo
Gruber *et al.*	146	postpartum	q.i.d. × 1–3 days	cod. 32 ns> placebo, A.P.C. s> placebo
Gruber *et al.*	147	mixed chronic	q.i.d. × 3 days, crossover	cod. 32 & cod. 65 s> placebo, cod. 65> cod. 32
Houde & Wallenstein	175,179	cancer	single dose, p.r.n., crossover	cod. 32 s> placebo, aspirin 600 ns> cod. 32
Howard *et al.*	183	orthopedic conditions	q.i.d., crossover	cod. 65 s> placebo
Kantor *et al.*	191	postoperative & fracture	single dose, p.r.n.	cod. 60 s> placebo, cod. 60 ns> aspirin 600
Magee & De Jong	250	headache, outpatients	multiple dose, p.r.n.	cod. 32 or 65 s> placebo
Marrs *et al.*	253	mixed chronic & acute	q. 4 h.	placebo ns> cod. 32, aspirin 325 s> placebo
Prockop	295	postpartum	t.i.d.	cod. 32 s> placebo, A.P.C. s> cod. 32
Sadove *et al.*	313	orthopedic conditions	single dose, p.r.n., partial crossover	cod. 32 s> placebo, cod 65 s> cod. 32
Seed	325	cancer	single dose, p.r.n., crossover	cod. 60 s> cod. 30 s> placebo
Van Bergen *et al.*	357	postoperative	q. 4 h.	cod 65 s> placebo

cod. = codeine; s> = significantly superior to; ns> = not significantly superior to; > = significance of difference in response uncertain.

patients with alveolar osteitis, which demonstrated that dihydrocodeine 30 mg. was an analgesic superior to placebo with a substantially higher incidence of side effects than aspirin 600 mg.[107], no suitably controlled clinical experiments to determine the oral efficacy of these compounds seem to have been performed. (4) While all narcotics possess both the ability to induce physical dependence on prolonged administration and varying degrees of abuse potential, oral codeine has substantially less liability in this regard than such drugs as hydrocodone, oxycodone, and meperidine.

1. *Codeine.* With the exception of aspirin, codeine (Fig. 5) has perhaps been the most widely used oral analgesic and is generally accepted as the alternative to aspirin as a standard of comparison for drugs in this category. As in similar studies with aspirin, well-controlled comparisons have usually shown codeine 65 mg. to be significantly superior to placebo as an analgesic, and sensitive assays have likewise demonstrated the superiority of 32 mg. of codeine to placebo (Table 2).

Beecher *et al.*[20] have reported that while they were not able to demonstrate a superiority of codeine 60 mg. by mouth over placebo, they could distinguish aspirin 600 mg. from placebo. Their paper has been cited on numerous occasions as evidence that the usually prescribed oral doses of codeine are without analgesic effect. However, Beecher's group only considered an administered dose of drug analgesic if the patient reported at least 50% pain relief at *both* one hour and two hours after medication. This criterion for analgesia could result in underestimation of the effectiveness of drugs with a delayed onset and peak of action, a characteristic of orally administered narcotics in general. Furthermore, this type of quantal or all-or-none measure of analgesia is a less sensitive indicator of drug effect than the use of quantitative or graded estimates of effect made at frequent intervals after drug administration. This factor was recognized and discussed by these investigators, but apparently ignored by most workers who have subsequently cited this study. Another possible explanation for Beecher's discrepant results with oral codeine may lie in the fact that his data apparently represent the results of a series of separate comparisons of drug and placebo (that is, placebo vs. aspirin 300 mg., placebo vs. aspirin 600 mg., placebo vs. codeine 60 mg., and the like.). Since treatments do not seem to have been randomly assigned to patients *between* series, but only *within* series, the validity of inter-series comparisons, in the absence of a common standard medication in addition to placebo, is questionable. Putting the matter in another way, the fact that a population sample in one experiment was able to discriminate between aspirin 600 mg. and placebo in no way proves that the population sample in another experiment (that is, codeine 60 mg. vs. placebo) would have likewise been able to discriminate between placebo and aspirin.

Since there is a generally held impression, which has been abetted by the results of studies using experimentally induced pain in man, that there is a ceiling for codeine's analgesic effect at about 60 mg. and that higher doses cause no increase in analgesia, controlled clinical studies germane to this point are of considerable interest.

An extensive series of studies on the dose-response relationships of oral and parenteral codeine have been carried out by Houde and his co-workers in patients with chronic pain due to cancer. On intramuscular administration, graded doses of codeine produced progressively increasing analgesia up to doses in the range of 180 mg. to 240 mg., beyond which point there was some evidence of a leveling off of effect with still higher doses[172,176,179] p. 92.[181] This failure to find a clear-cut ceiling

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effect for parenteral codeine, except possibly with doses substantially above those usually employed therapeutically, was confirmed in a subsequent study comparing parenteral codeine in doses of 30 mg., 60 mg., and 180 mg. with oral codeine 60 mg., 120 mg., and 360 mg.[178]. No evidence of a ceiling effect was noted on administration of codeine by either route, and the drug was found to be 0.68 times as potent when given orally as when administered by intramuscular injection. For a narcotic, this represents an excellent oral: parenteral efficiency ratio, the similar figure for the oral: parenteral potency of morphine being 0.17[172].

Lasagna[214] has criticized Houde's data in relation to the ceiling effect of codeine on the grounds that the population of patients used by Houde had varying degrees of prior narcotic experience and hence possible tolerance to these drugs, a factor which would admittedly tend to obscure the existence of a ceiling effect at lower doses. However, on examination of the records of the patient population in question, the degree of analgesic experience and evidence of tolerance does not appear to be sufficient to account for Houde's failure to find a ceiling effect for quite large doses of codeine, if such in fact exists. Lasagna and Beecher[215] compared the effect of graded doses of parenteral codeine 30, 60, 90, and 120 mg. with morphine 10 mg. in postoperative patients. Although the authors interpreted their results as indicating a relative decrease in analgesia with doses greater than 60 mg., when their data are plotted in the conventional way on a log dose scale, their results are not inconsistent with the hypothesis of a linear dose regression within the range of doses studied.

Positive dose-effect slopes have been obtained by Gruber and his associates[144,147], Seed[325], and Sadove *et al.*[313] on comparing 32.5 (30) mg. and 65 (60) mg. of codeine in patients with various types of chronic pain. Doses of 30 mg. and 90 mg. of codeine have likewise yielded a positive slope when compared in patients with acute and chronic pain of various etiologies[112]. Cass and Frederik[57] found an increment of analgesia produced by each increment of drug dose on comparing codeine 32 mg., 65 mg., and 130 mg., and placebo in a study in which the drugs were administered t.i.d. for alternate one-week periods to patients with chronic pain. Specifically these investigators did not find any sloping-off of the dose-response curve between codeine 65 mg. and codeine 130 mg.

Efforts to determine the relative potency of codeine and aspirin, the two generally accepted standards of comparison for the mild analgesics, have met with only incomplete success. Few investigators have attempted to compare graded doses of each drug, and the dose-response curve for aspirin alone has proved difficult to establish with certainty. A further complicating factor is that the mechanism of analgesic action of the two drugs is most likely different, and this may result in different estimates of their relative potency in patient populations which differ in the etiology of their pain.

Codeine 65 (60) mg. produced analgesia not significantly different from aspirin 650 (600) mg. in five of the studies noted in Table 2[34,62,78,88,191]. Houde *et al.* [175] ([179]p.90) found that aspirin 600 mg. provided somewhat superior relief than codeine 32 mg. in patients with pain due to cancer, but the difference was not statistically significant. In one study, Cass and Frederik[59] found codeine 30 mg. superior to aspirin 600 mg., but considering both the response to other drugs in the study and their subsequent work, the poor performance of aspirin in this study is decidedly atypical. Several workers have found the response to codeine 32 (30) mg. to be significantly less than that to aspirin

330 mg.[253] or to A.P.C. compound (227 mg. aspirin, 160 mg. acetophenetidin, and 32 mg. caffeine)[145,146,205].

The Veterans Administration Cooperative Analgesic Study Group[112] is currently engaged in a crossover comparison of aspirin 300 mg. and 900 mg., codeine 30 mg. and 90 mg., and placebo in a large number of patients with pain of varied etiology. An analysis of the incomplete data from this experiment reveals that both drugs are giving significant dose-effect slopes, their respective regressions do not seem to differ significantly from parallelism, and aspirin appears to be about 1/5 as potent as codeine (that is, aspirin 300 mg. is approximately equivalent to 60 mg. of codeine). Considering all of the above comparisons, aspirin is probably from 1/5 to 1/10 as potent as oral codeine when usual therapeutic doses of both drugs are administered.

Codeine 60 mg. does not seem to differ significantly from aspirin 600 mg. in terms of their respective time-action curves[88,101]; however, codeine 32 mg. appears to have a somewhat shorter duration of action than aspirin 600 mg.[175,(170p. 90)].

There are two interrelated, but in many respects quite distinct, aspects of addiction liability which must be considered when discussing the clinical pharmacology of codeine or of any drug with a potential for inducing some type of drug dependence. (1) What is the comparative risk, relative to other agents used for similar therapeutic purposes, that the drug in question will produce tolerance and physical dependence when administered in usual therapeutic doses to patients under suitable medical supervision? (2) Does the drug have properties which are likely to make it an attractive drug of abuse in settings which are unrelated to its medical employment?

Unfortunately, very little information is available, particularly of a quantitative sort, concerning the absolute or relative dependence-producing properties of the narcotics when used clinically. In comparative studies in postaddicts, the emphasis has been placed on using maximum tolerated doses of drugs, and an effort is made to induce tolerance and physical dependence as rapidly as possible, rather than administering the agents being compared in equianalgesic doses and at intervals comparable to a clinical regimen. The results of such studies have been excellent predictors of *abuse* liability but have only limited relevance to what may be expected in clinical use of an agent. For example, certain modified narcotics were found in these assays to have less abuse potential than oral codeine, because, as the doses of these agents were increased, severe toxic effects became manifest, discouraging the use of doses which would give opiate-like effects equivalent to those produced by doses of codeine which are well tolerated[113,115]. However, while toxic effects which serve to limit abuse potential may be an asset when considering the problem of diversion of medical stores into illicit channels, these effects may become a distinct liability when attempting to obtain adequate pain relief with a drug in situations where deliberate abuse is unlikely.

Cass *et al.*[55] administered codeine 32 mg. q.i.d. for 3-month periods to 23 patients with chronic pain. Allyl (Nalline) tests were performed on these patients at 2-week intervals to detect evidence of the development of physical dependence, and at the end of 3 months the drug was discontinued unbeknownst to the patients, and they were observed for signs of withdrawal. Little evidence was found that physical dependence had developed under the conditions of the study.

In an extensive monograph on the subject of codeine addiction, Himmelsbach *et al.*[164] reviewed the literature

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prior to 1940 and found 99 cases of codeine addiction reported, of which 25 were regarded as definite and 74 presumptive. In only about 20% of these cases was the primary drug of addiction codeine. Of 44,146 addicts reported to the bureau of narcotics during 1953-1957 in the United States, only 118 (0.27%) used codeine[10]. This low incidence should be contrasted with the extremely wide use of the drug as an analgesic and antitussive. Most addicts who have resorted to codeine have done so because nothing "better" was available and have deserted the drug as soon as they have had access to stronger narcotics.

Although large doses of codeine can prevent withdrawal reactions in patients physically dependent on morphine[115,119,164] and can induce primary physical dependence[116,118,121,164], the drug does not seem to produce the psychic effects which most opiate addicts consider desirable[164] and has proved quite unacceptable to post-addicts when given intravenously[119]. To summarize, while there have been occasional cases of primary codeine addiction reported, and while the drug can support a pre-existing physical dependence to a certain extent, the danger of inducing drug dependence with the usual oral doses of codeine administered under medical supervision is slight indeed.

Tolerance presumably develops, albeit very slowly, to repeated therapeutic doses of oral codeine, but there seems to be no quantitative data available concerning this matter. In addition to drug dependence, codeine is capable of producing all of the side effects characteristic of the narcotics as a group; however, when the drug is administered orally in usual therapeutic doses, the incidence of side effects is not high, and the ones that occur are, almost always, annoying rather than serious. Even when administered orally, codeine 60 mg. can depress respiration to a measurable extent[23,155], but the degree of respiratory depression produced is of little significance clinically. In those studies which compared oral codeine 32 or 65 mg. with placebo (Table 2) and contained an analysis of side-effect frequency in a sufficient number of patients, nausea, vomiting, sedation, and dizziness were generally seen more often after codeine 32 mg. than after placebo, and more often after codeine 65 mg. than after codeine 32 mg. These side effects were more often observed in ambulatory patients than in those confined to bed. Constipation has also been noted in those studies in which repeated doses of codeine were administered. Codeine may also produce uncommon acute allergic reactions characterized by giant urticaria, and rarely angioneurotic edema, laryngeal edema, or anaphylactic shock[317].

Acute poisoning resulting from a large overdose of codeine is quite uncommon ([205]p. 843) but presents a picture not unlike that resulting from intoxication with other narcotics ([260]p. 505). In an adult patient who was semicomatose and breathing four times per minute after receiving a single dose of codeine phosphate 360 mg., nalorphine (Nalline) 5 mg. intravenously produced an immediate and dramatic improvement in both respiratory rate and level of consciousness (personal observation).

2. *Dextropropoxyphene* (Darvon) The synthesis and preliminary animal pharmacology of racemic alpha-propoxyphene, a compound closely related structurally to the potent narcotics methadone and isomethadone (Fig. 5), was reported in 1953[290]. Material relevant to chemistry and structure-activity relationships[154]p. 256,[291] animal pharmacology[290] p. 384,[304] and biological disposition[223] has since been presented or summarized. The analgesic activity of the racemate was shortly found to reside in the dextro isomer[291], and it is this compound, dextropropoxyphene, which is currently widely used as a mild analgesic. The levo isomer, which lacks analgesic activity, has been recently introduced as an antitussive (Novrad).

TABLE 3.—CONTROLLED HUMAN ANALGESIC ASSAYS INCORPORATING ORAL DEXTROPROPOXYPHENE

Investigator(s)	*Reference*	*Type of Patient or Etiology of Pain, or Both*	*Schedule of Administration*	*Results*
Bensen	25	postpartum	p.r.n. & by-the- clock	dex. 65 s> placebo
Boyle *et al.*	34	mixed chronic	2–4 x/day, p.r.n. (?), × 5–7 days, partial crossover	dex. 65 s> placebo, cod. 65 s> dex. 65, aspirin 650 ns> dex. 65
Cass & Frederik	57	mixed chronic	t.i.d. × 7 days, crossover	(I) dex. 32> dex. 65> dex. 130> placebo (reverse slope) cod. 65 s> dex. 65 & dex. 130 cod. 65 ns> dex. 32 (II) dex. 32 s> placebo (III) dex 32> dex. 65> dex. 130> placebo (reverse slope) (IV) dex. 130> dex. 65> dex. 32> placebo. All doses dex. inferior to respective codeine doses.
Chilton *et al.*	72	oral surgery, outpatients	multiple dose, p.r.n. × 2 days	dex. 65 ns> placebo, cod. 60 s> dex. 60
DeKornfeld & Lasagna	88	postpartum	single dose, p.r.n.	placebo ns> dex. 60, cod. 60 s> dex. 60, aspirin 60 s> dex. 60
Gruber	144	mixed chronic	4–6 ×/day × 3 days, crossover	dex. 65 ns> dex. 32 s> placebo, cod. 65 ns> dex. 65, dex. 32 ns> cod. 32
Gruber *et al.*	145	postpartum	single dose, p.r.n.	dex. 65 ns.> placebo, placebo ns> dex. 32 & cod. 32, A.P.C. s> placebo
Gruber *et al.*	146	postpartum	q.i.d. × 1–3 days	dex. 32 ns> placebo, placebo ns> cod. 32, A.P.C. s> placebo
Gruber *et al.*	147	mixed chronic	q.i.d., crossover	dex. 32 & 65 s> placebo, dex. 65 ns> dex. 32, cod. 65 ns> dex. 65, dex. 32 ns> cod. 32
Howard *et al.*	183	mixed	q.i.d., crossover	dex. 65 s> placebo, dex. 65 ns> cod. 60
Magee & De Jong	250	headache, outtients	multiple dose, p.r.n.	dex. 32 or 65 s> placebo
Marrs *et al.*	253	mixed	q. 4 h.	placebo ns> dex. 65, aspirin 325 s> placebo
Prockop *et al.*	295	postpartum	t.i.d.	dex. 32 ns> placebo, cod. 32 s> placebo, A.P.C. (1 tab) s> cod. 32
Reiss & Aufses	303	postoperative	q.i.d.	dex. 100 s> placebo, dex. 100 ns> meperidine 100
Sadove *et al.*	313	mixed orthopedic	single dose, p.r.n., incomplete crossover	dex. 65 s> placebo, dex. 32 ns> placebo, dex. 65 s> dex. 32, cod. 60 ns> dex. 65, cod. 30 ns> dex. 32
Sadove & Bruce	310	mixed	p.r.n., partial crossover	dex. 60 s> placebo
Seed	325	cancer	single dose, p.r.n., crossover	see text
Van Bergen *et al.*	357	postoperative	q. 4 h.	dex. 100 s> placebo, dex. 100 ns> cod. 65

cod. = codeine; dex. = dextropropoxyphene; s> = significantly superior to; ns> = not significantly superior to; > = significance of difference in response uncertain.

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Studies of apparently suitable design comparing dextropropoxyphene with placebo, codeine, aspirin, or A.P.C. are listed in Table 3. While the results of these various studies are to a degree contradictory, certain statements concerning the analgesic effectiveness of dextropropoxyphene appear justified. Dextropropoxyphene in doses of 65 mg. or 100 mg. has usually, but not always[72, 88], proved superior to placebo in reasonably sensitive assays; however, the 32 mg. dose has quite often failed to demonstrate a similar superiority.

In two of a series of three studies in patients with chronic pain, Cass and Frederik[57] found a reverse slope for graded doses of the drug; however, in the one trial which did show a positive slope, a more sensitive assay method had been utilized. In two studies, also using patients with chronic pain, Gruber *et al.*[144,147] demonstrated greater mean relief scores for 65- than for 32.5-mg. doses of dextropropoxyphene, but this difference in means was not statistically significant in either case. Sadove *et al.*[313] found the effect of 65 mg. of dextropropoxyphene to be significantly greater than that of 32 mg., but the 32-mg. dose yielded analgesia not significantly greater than placebo. In a crossover study employing patients with chronic pain due to cancer, Seed[325] found a significant positive regression for dextropropoxyphene in doses of 30 mg., 60 mg., and 130 mg. No reliable data seems to be currently available concerning the time-action curve of dextropropoxyphene.

In eight of the studies noted in Table 3, codeine proved significantly superior to dextropropoxyphene in equal doses, and in three others, the effects of the two drugs were not significantly different. In no study was dextropropoxyphene shown to be superior to codeine in potency. Seed[325] found, on comparing the effects of codeine 30 mg. and 60 mg. with dextropropoxyphene 30 mg., 60 mg., and 120 mg., that the respective dose-response curves did not diverge significantly from parallelism, and his best estimate of relative potency was that codeine was approximately twice as potent as dextropropoxyphene on a milligram basis. This estimate agrees well with the result obtained on plotting the data of Sadove *et al.*[313], which shows codeine to be 1½ times as potent as dextropropoxyphene. Although Cass and Frederik obtained positive slopes for both codeine and dextropropoxyphene using doses of 32 mg., 65 mg., and 130 mg. of each drug ([57]study IV), they present insufficient data to allow calculation of a relative potency estimate. Nevertheless, inspection of their dose-response curves suggests a relative potency for the two drugs not inconsistent with the findings of Seed or Sadove *et al.* (that is, codeine is 1½ to 2 times as potent as dextropropoxyphene).

In the few studies which have been done (see Table 3) comparing dextropropoxyphene with aspirin or A.P.C. (a mixture containing acetophenetidin 160 mg., aspirin 227 mg., and caffeine 32 mg.), dextropropoxyphene 32.5 to 65 mg. has consistently proven inferior to aspirin (325 mg. to 650 mg.) or A.P.C. (1 or 2 tablets).

In summary, dextropropoxyphene is a mild oral analgesic which has proven superior to placebo in doses of 65 mg. or more but which is of questionable efficacy in doses lower than 65 mg. The drug is definitely less potent than codeine, the best available estimates of the relative potency of the two drugs indicating that dextropropoxyphene is approximately ½ to ⅔ as potent as the latter drug. Likewise, dextropropoxyphene in 32-mg. to 65-mg. doses is certainly no more, and possibly less, effective than the usually used doses of aspirin or A.P.C.

Chernish and Gruber[69] administered dextropropoxyphene 65 mg. q.i.d. to 12 patients, and 195 mg. q.i.d. to one patient, for 6 months, at the end of which time nalorphine 3 mg. was administered intramuscularly (the allyl

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test), and a few days later dextropropoxyphene was suddenly withdrawn. There was no evidence of withdrawal phenomena precipitated by nalorphine injection or sudden discontinuance of dextropropoxyphene in any of the 12 patients receiving the lesser dose of the drug and, at most, only suggestive evidence of withdrawal on discontinuance of the drug in the patient receiving 195 mg. q.i.d. In another study, the same workers[70] presented data which I would interpret as consistent with the hypothesis that long-term therapy with oral meperidine induced considerably more tolerance than long-term therapy with similar doses of dextropropoxyphene to the analgesic effect of subsequent parenteral administration of either drug.

Fraser and his associates[113,115,119] have examined the properties of dextropropoxyphene in postaddicts in relation to various drug effect parameters associated with abuse potential. These investigators found that dextropropoxyphene was similar to narcotics in that: (1) large single oral (that is, >300 to 350 mg.) or intravenous (180 mg.) doses of the drug were identified as "dope" and produced pleasurable opiate-like subjective effects in a substantial number of subjects, (2) in large oral or parenteral doses the drug was capable of partially suppressing withdrawal symptoms in patients dependent on morphine, and (3) a slight but significant abstinence syndrome was observed on drug withdrawal in patients taking 600 mg. to 825 mg. of the drug daily for 53 days. However; (1) on repeated doses the subjects expressed increasing dissatisfaction with the subjective effects of dextropropoxyphene, (2) oral doses of 800 mg. per day did not surpress the morphine abstinence syndrome as well as 1500 mg. of codeine, and efforts to suppress abstinence more completely by increasing the dose of dextropropoxyphene resulted in toxic psychoses and other severe side-effects, and (3) parenteral administration of the drug produced intense tissue irritation, and intravenous administration of large or repeated doses caused thrombophlebitis, nervousness, toxic psychoses, and, occasionally, convulsions. It was, therefore, felt that the abuse potential of dextropropoxyphene was slight, substantially less than even that of codeine. The drug is not considered a narcotic by the U.S. Bureau of Narcotics and is no longer held by the World Health Organization to present a sufficient addiction hazard to require international narcotics control[389]. These predictions seem to have been substantiated thus far by the fact that, in spite of the extremely wide use of dextropropoxyphene, only one case of dependency on the drug has been reported in the literature[106].

The side effects noted on therapeutic administration of dextropropoxyphene have been qualitatively quite similar to those associated with the use of codeine (that is, nausea, vomiting, sedation, dizziness, constipation, and, occasionally skin rashes)[72,144,146,205,357], but side-effects have generally not proved to be a really serious problem with either drug. When the two drugs are administered in *equal milligram doses*, codeine seems definitely more likely to cause nausea and vomiting than dextropropoxyphene and possibly more likely to cause sedation and dizziness. However, as has been noted before, estimates of relative side-effect liability are only meaningful if made at *equianalgesic* doses, and since dextropropoxyphene seems to be less potent than codeine as an analgesic, the significance of the relative side-effect incidence noted above is debatable.

A number of cases of acute poisoning due to accidental or suicidal dextropropoxyphene overdosage have been reported[49,122,153,186,262,297,348], and two of these have terminated fatally[122,262]. These cases have presented a picture similar to that seen in acute narcotic intoxication, except for a greater incidence of convulsions. Nalorphine has

proven useful in the treatment of several of these patients, as would be expected on the basis of animal studies[68,304]. Although oral dextropropoxyphene 130 mg. did not cause a significant shift in the ventilation-response curve in an apparently uncontrolled study in normal adult volunteers[44], respiratory depression was a prominent feature in the above noted cases of poisoning, and it has also been noted in postaddicts receiving daily doses of the drug in excess of 800 mg.[115].

It would appear that although dextropropoxyphene is legally a "non-narcotic" analgesic and has even less abuse liability than codeine, the properties of this compound are not *qualitatively* different from those of the narcotics.

3. *Ethoheptazine* (Zactane). Ethoheptazine is a mild analgesic with a structure closely related to that of meperidine (Demerol), in which a seven-membered hexamethyleneimine ring is substituted for meperidine's six-numbered piperidine ring (Fig. 5). Material relevant to the chemistry ([154] p. 206), animal pharmacology[132,133,241] and biological disposition of the drug in animals[361] and man[11] has been published, as has an early brief review of its properties[104].

Cass *et al.*[64] found both aspirin 600 mg. and ethoheptazine 100 mg. significantly superior analgesics to placebo, and the ethoheptazine dose superior to the aspirin dose, when the drugs were administered q.i.d. by-the-clock for alternate 7-day periods to patients with chronic pain of mixed etiology.

However, DeKornfeld and Lasagna[89] found that both 75-mg. and 150-mg. doses of ethoheptazine could scarcely be distinguished from placebo, while aspirin 600 mg. was clearly superior to placebo, in a comparison of the four treatments in patients with postpartum pain. In a further study in a similar patient population, Lasagna and DeKornfeld[218] found that the addition of 150 mg. of ethoheptazine to aspirin 600 mg. resulted in analgesia in no way superior to that provided by aspirin 600 mg. alone. Similarly, Brenman[36], using postoperative dental patients, and Bruni and Holt[42], using patients with postpartum pain, were unable to demonstrate any superiority of a mixture of aspirin and ethoheptazine over aspirin administered in the same dose alone. The conclusions of these investigators differ from the findings of Cass *et al.*[58,64] who, in two separate studies reported that the addition of ethoheptazine 100 mg. or 150 mg. to aspirin yielded an increase in analgesia over that produced by the aspirin alone. The cause of these discrepancies is not clear at present, but perhaps it relates to the differences in the patient populations used and the fact that only Cass and his co-workers administered the drug on a chronic basis.

Ethoheptazine does not seem to have produced significant side effects when administered in doses of from 75 mg. to 150 mg. The drug has little or no tendency to induce physical dependence, even when administered for extended periods of time to patients with chronic pain[55], and is considered to have minimal abuse potential, as central nervous system excitation and other toxic effects preclude the use of excessive doses[117]. This drug is thus not considered to be a narcotic and is not subject to the record-keeping requirements and controls attendant on the use of codeine. This may be a possible explanation for the continued use of ethoheptazine in view of its equivocal performance in controlled studies of its analgesic effects.

4. *Prodilidine*. Prodilidine, although not currently available, is of interest in that, like ethoheptazine, its structure represents a slight modification of a potent narcotic, in this case alphaprodine (Nisentil) (Fig. 5). Data concern-

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ing prodilidine's actions[201,378] and biological disposition[368] in animals have been published, as has a review of the chemical and pharmacologic properties of the drug ([154]p. 211).

Boyle *et al.*[35] found that prodilidine 200 mg. was superior to placebo when administered repeatedly to patients with chronic pain of varied etiology, but the drug also produced a significant incidence of dyspepsia. Houde and his co-workers[172], in a crossover comparison of prodilidine 300 mg., aspirin 600 mg., and placebo in patients with pain due to cancer, found that the analgesia produced by the two active drugs was significantly greater than that produced by placebo, but the two drugs produced essentially the same degree of analgesia in the doses used.

A second study comparing aspirin 300 mg. and 600 mg. with 150 mg. and 300 mg. of prodilidine in a similar patient group confirmed these workers' findings that prodilidine was about twice as potent as aspirin on a milligram basis, and equi-effective doses of the drugs had comparable dose-response curves. However, prodilidine 300 mg. produced more nausea, vomiting, and dizziness than placebo or the equi-effective dose of aspirin 600 mg.

Cass and Frederik have reported on two studies using prodilidine in patients with chronic pain. In the first of these[59], they found prodilidine 50 mg. and aspirin 600 mg. to be equi-effective as analgesics. Prodilidine 100 mg. and codeine 30 mg. were likewise equi-effective and superior in performance to both aspirin 600 mg. and prodilidine 50 mg. However, in a second study in a similar patient population[62], prodilidine in 50-mg. and 100-mg. doses, while superior to placebo, proved inferior to both aspirin 600 mg. and codeine 60 mg. The discrepancy seems to be due to the relatively poor performance of aspirin in the first study.

Prodilidine is incapable of suppressing withdrawal phenomena in morphine-dependent monkeys[93], and the drug has been found by Fraser[113] to be substantially less addictive than codeine, and probably less addictive than dextropropoxyphene, when administered to former opiate addicts. Although high oral doses of the drug were frequently identified as "dope" by these postaddicts, a very high incidence of unpleasant side effects, particularly persistent nausea and vomiting, caused all 5 patients on the study to discontinue the drug of their own volition.

5. *Pentazocine* (Talwin). Pentazocine is a mild narcotic antagonist structurally related to the strong narcotic phenazocine (Prinadol) (Fig. 5)[156]. Virtually all of the published material to date concerning pentazocine has dealt with the parenteral form of the drug, which is a strong analgesic ½ to ¼ as potent as morphine[21,60,178,193,196]. Pentazocine produces some pharmacological effects characteristic of narcotics, such as respiratory depression[22,196,352] and certain subjective effects[22,120,196]. However, pentazocine is of particular significance in that it has been found to possess virtually no addiction potential (abuse liability) in studies in postaddicts[120], and, being a narcotic antagonist, it can in fact precipitate withdrawal phenomena in persons physically dependent on narcotics[178].

Kantor *et al.*[191] have compared oral pentazocine HCl 35 mg. and 50 mg. with aspirin 600 mg., codeine 60 mg., and placebo in patients with postoperative and fracture pain. They found pentazocine 50 mg. equivalent to codeine 60 mg. and perhaps slightly superior to aspirin 600 mg. Pentazocine 35 mg. produced less analgesia than aspirin 600 mg., but significantly greater effect than placebo. Side-effects with pentazocine 50 mg. were similar in type and frequency to those seen with codeine 60 mg., save that pentazocine produce an occasional transient mental aberration such as a

sensation of floating in space or "bad dreams." The drug is not yet marketed in either oral or parenteral form, but it is likely that at least the parenteral form will be in the near future.

E. MISCELLANEOUS MILD ANALGESICS. In recent years, a number or structurally unique compounds of groups of compounds which are neither antipyretic, antirheumatic or anti-inflammatory, nor pharmacologically or structurally related to the narcotics, have been advanced as being effective in the treatment of pain. In addition to their putative analgesic properties, many of these drugs are centrally acting muscle relaxants, some have tranquilizing or psychic-stimulant properties, and still others are parasympathetic blocking agents or agents first used in the treatment of Parkinsonism. In addition to these newer remedies, several older drugs not usually considered primarily as analgesics are prescribed, usually as components of mixtures, for the relief of mild to moderate pain.

1. *Muscle relaxants.* Many compounds are putative centrally acting skeletal-muscle relaxants. It is far from certain whether any of these drugs have nonspecific analgesic properties distinct from their effect on skeletal-muscle spasm. On the other hand, many workers in the field of skeletal-muscle hypertonia question whether these drugs, when administered *orally* in usual doses, have any selective skeletal-muscle relaxing activity which cannot be explained on the basis of their tranquilizing and general central-nervous-system-depressant effects[315]. Those muscle relaxants which have not been claimed to have nonspecific analgesic activity, such as meprobamate, methocarbamol, chlormezanone, chlorzoxazone, orphenadrine, or styramate, will not be considered in this review.

a. *Carisoprodol* (Soma, Rela). Carisoprodol (Fig. 6) is chemically related to both the internuncial blocking agent, mephenesin, and the tranquilizer, meprobamate. Extensive animal studies[26,27,91,92,126,246] revealed that carisoprodol depressed multineuronal reflexes to a greater extent than simple ones, exerted a specific suppressing action on reticulospinal facilitation, and possessed antinociceptive action in selected assays.

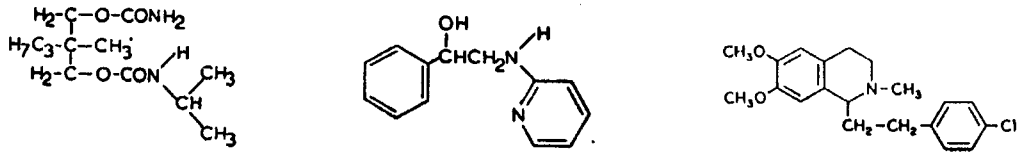

Fig. 6.—Miscellaneous mild analgesics.

Carisoprodol has been found to be superior to placebo in a number of studies in patients with musculoskeletal complaints, including leg cramps[71,341], low back pain[136] and musculoskeletal pain of mixed etiology[12,80,111,222]. In these studies, the drug was administered repeatedly for periods of several days to 4 weeks. Likewise, Cass and Frederik[61] found carisoprodol 350 mg. superior to placebo and equivalent in analgesic effect to aspirin 600 mg. when administered to patients with chronic pain of predominately musculoskeletal etiology. However, Schwartz *et al.*[319] were unable to demonstrate a significant difference between carisoprodol 350 mg. and placebo in the relief of temporomandibular joint pain and dysfunction.

In postpartum pain, Lasagna and DeKornfeld[218] were unable to demonstrate any superiority of carisoprodol in single doses of 350 mg. or 700 mg.

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over placebo. Similarly, in patients with postoperative pain, Adams and Holden[1] found that carisoprodol 1400 mg. did not yield greater relief than placebo, while oral meperidine 100 mg. was clearly superior to both.

The predominant side-effect associated with the use of carisoprodol has been sedation, and large doses produce subjective effects similar to those produced by the barbiturates[114] Occasional allergic reactions have also been noted. In experiments in former opiate addicts, the drug was not found to possess addictive properties of the opiate type[114].

b. *Phenyramidol* (Analexin). Phenyramidol (Fig 6) seems to be structurally unrelated to any other currently available analgesic. In animal assays, the drug was found to possess both antinociceptive activity of the order of codeine and interneuronal blocking activity[282,283], and it was felt that this combination of analgesic and muscle-relaxant effects might prove clinically useful. Unfortunately, although there have been a number of clinical trials with the compound, there seem to have been no properly controlled assays of its analgesic action in man.

Fraser *et al.*[114], in tests of abuse potential in postaddicts, did not find that the drug possessed addictive qualities of the opiate type, and they were impressed with "the absence of detectable objective or subjective pharmacologic effects" of the drug, even when administered in substantial doses.

2. *Methopholine* (Versidyne). Methopholine (Fig. 6) is a mild analgesic structurally related to the naturally occurring isoquinoline, papaverine. Brossi *et al.*[41] have extensively reviewed the chemistry and pharmacology of this class of compounds. The pharmacology of methopholine has also been discussed by Randall ([299]p. 390), and its biological disposition in man and animals elucidated by Schwartz *et al.*[318].

Studies of presumably suitable design have varied considerably in their appraisal of the analgesic activity of methopholine. Sadove *et al.*[309], in an early study in postoperative patients comparing methopholine 20 mg. and 40 mg., codeine 30 mg., and placebo, found the drug doses all superior to placebo, but not significantly different from each other. The same workers[313], in a subsequent study using a similar patient population, found methopholine 30 mg. and 60 mg. to be approximately as potent as codeine 30 mg. and 60 mg., and the respective doses of both drugs were superior to dextropropoxyphene 32 mg. and 65 mg. Sadove and Bruce[310] found methopholine 60 mg. significantly superior to both dextropropoxyphene in the same dose and to placebo in patients with pain of mixed etiology; and, in another study in patients with postoperative pain[311], they demonstrated a positive regression for 30-mg., 60-mg., and 120-mg. doses of methopholine. Chilton *et al.*[72] likewise found methopholine 60 mg. and codeine 60 mg. not significantly different in the relief of pain in postoperative dental patients, but both drugs were superior to dextropropoxyphene 65 mg. and to placebo. Cass and Frederik[56] demonstrated that methopholine 120 mg. yielded analgesia similar to that produced by two tablets of A.P.C. compound on repeated administration to patients with chronic pain of mixed etiology, and both drugs were superior to placebo.

On the other hand, while DeKornfeld and Lasagna[88] found aspirin 600 mg. and codeine 60 mg. to be equivalent and superior to placebo in the relief of postpartum pain, methopholine 60 mg. was indistinguishable from placebo in this study. In their initial study of this drug in cancer patients, Houde and his co-workers[178] found that methopholine 60 mg. appeared to yield pain relief equivalent to that produced by codeine 60 mg., but the poor performance of the 20-mg. doses of each drug and an unusually high placebo score make the significance of this

result doubtful. In a subsequent study these workers found[177] that while 40-mg. and 120-mg. doses of codeine were significantly superior to placebo and gave a very satisfactory dose-effect regression, both the 40-mg. and 120-mg. doses of methopholine were inferior to the lower dose of codeine, and even the higher methopholine dose was probably not superior to placebo. The reason for these discrepant results is not apparent.

The side-effects noted on administration of 60-mg. doses of methopholine have been few and generally less pronounced than those occurring after equal doses of codeine. Fraser *et al.*[119], in experiments in postaddicts, have found the drug, by every criterion customarily used, to be a compound of little or no abuse potential. "Its addiction liability, if any, is definitely less than that of d-propoxyphene and codeine . . ." Methopholine is not yet commercially available.

3. *Hypnotics, Sedatives, and Tranquilizers.* Considering the significance of the reaction component in the pain experience, it is possible that a degree of pain relief *might* be produced by any drug with a distinct effect on mood or mental state[16]. However, very few controlled studies have been performed to explore this possibility. Pentobarbital, in substantial intravenous doses, was found by Keats and Beecher[104] to be superior to placebo but inferior to 8 mg. morphine in the treatment of postoperative pain. However, in spite of the numerous citations of this work as justification for the widespread use of oral formulations containing small doses of hypnotics in combination with various analgesics, there does not seem to be even one suitably designed study to determine if these small oral doses of hypnotics have any analgesic effect by themselves or contribute to the analgesic effect of mild analgesics. There is likewise a paucity of dependable information on the effect of oral tranquilizers on pain, and considerable division of opinion even exists as to whether parenteral phenothiazines have any potentiating effect on the analgesia produced by narcotics.

4. *Amphetamines and Caffeine.* Like the central nervous system depressants noted above, the amphetamines have marked effects on the psyche, and their mood-elevating action could be expected to alter the patient's experience of pain. These stimulants have been found to potentiate the analgesic effect of narcotics and other drugs in *experimentally induced pain* in man and animals (for a review of this work see Evans[107,108]), and are, in fact, frequently employed in a variety of analgesic mixtures[8].

In what appears to be the only really suitable clinical study germane to this point, Tattersall[351] found two tablets of a mixture of amphetamine sulfate 2.5 mg., aspirin 160 mg., and acetophenetidin 160 mg. (Edrisal) significantly superior to aspirin 1 gm. in the relief of dysmenorrhea, which strongly suggests an analgesic or potentiating effect for amphetamine, at least in dysmenorrhea. Levinson[231] found a mixture of dextroamphetamine 5 mg., amobarbital ½ gr., aspirin 2½ gr., and acetophenetidin 2½ gr. (Daprisal) superior to placebo in a similar patient population, but this study provided no information as to what component or components of the mixture were responsible for this superiority. There seems to be no clinical evidence at all concerning the effect of combining amphetamines with barbiturates in analgesic mixtures.

Compared to the amphetamines, caffeine has a qualitatively similar, but quantitatively inferior, effect on mood[371]. The use of caffeine in vascular headache probably stems from its vasoconstrictive effect on cerebral blood vessels rather than from any specific analgesic action[274]. Indeed, repeated large doses of caffeine can induce a type of "physical dependence" on the drug manifested by severe headaches on withdrawal[101], and this phenomenon

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may be one of the causes of chronic use of caffeine-containing analgesic mixtures. In the rather small dose (½ gr.) present in an A.P.C. tablet, there is no evidence that caffeine either exerts a direct analgesic effect or potentiates the action of other analgesics (*vide infra*).

III. Analgesic Combinations and Mixtures. Although analgesic drug combinations, mainly in the form of drug mixtures*, are extremely widely used, little evidence exists from experiments in man as to the nature of the resultant drug interactions. Because of this lack of information and the plethora of drug mixtures, only certain general principles in the use of analgesic combinations will be discussed, and this discussion will be illustrated by consideration of a few well-known analgesic combinations.

It is my viewpoint that unless there is sufficient *evidence* that the use of a drug combination is likely to achieve therapeutic results unobtainable by the administration of a suitable dose of one of its constituents, a single drug alone should be used. The proof of superior efficacy of drug combinations lies with the proponents of their use. This approach to use of drug combinations is based both on the general scientific principle of parsimony and on a variety of practical considerations too extensive to be discussed in detail at this point, but most of which have been set forth in a penetrating analysis by Starr[340].

The object of the use of analgesic combinations is twofold: (1) achievement of more intense analgesia than can be provided by using a single agent, and (2) avoidance of side-effects by reducing the dose of any one analgesic. While these two objectives are admittedly interrelated, they may be discussed separately.

The slopes of the log dose-response curves of analgesic drugs are relatively flat, with the result that even successive doubling of the dose produces only modest increments of analgesic effect. If two drugs produce a similar degree of analgesia by different mechanisms and do not interact, the simple "additive" effect of the two drugs given together will be significantly greater than the analgesia achieved by doubling the dose of either drug administered alone. Furthermore, there may be a ceiling of analgesic effect for the antipyretic-analgesics, and this might be circumvented by combination with a compound which produces analgesia by a different mechanism. These are the considerations which provide a rational basis for the use of a combination of an antipyretic-analgesic, such as aspirin, with a narcotic-type analgesic, such as codeine or dextropropoxyphene, and several studies would indicate that such significant summation of analgesic effect does indeed occur[34,56,64,179,180,253,295,327]. A similar rationale might apply to the use of a combination of an antipyretic-analgesic with a drug having a pronounced effect on mood, such as amphetamines or sedatives, but the necessary experimental verification is lacking.

However, there seems to be no reason to believe that a similar advantage would accrue by combining two or more antipyretic-analgesics with each other. Similarly, the use of a combination of, say, codeine and dextropropoxyphene on this pretext would likewise appear irrational. Aspirin compound or A.P.C. compound (typically composed of aspirin 3½ gr., acetophenetidin 2½ gr., and caffeine ½ gr.) is a traditional analgesic mixture which has long been widely used on the assumption that it presents some advantage over plain aspirin. This mixture, how-

*In the context of this discussion, an "analgesic combination" will refer to the simultaneous administration of more than one drug for pain relief. A "mixture" will refer to the incorporation of such a drug combination in a single fixed-dose formulation, which practice "presents additional problems beyond the problems of drug combinations *per se*"[167].

ever, unlike most of its numerous counterparts, has been the subject of several suitably designed analgesic assays. In spite of the fact that a dose of A.P.C. compound contains a somewhat greater amount of analgesic than does the usual dose of aspirin, the mixture has not been found to be in any way superior to aspirin in extensive studies in patients with headache[84, 124], postpartum pain[90], chronic pain of mixed etiology[60], or acute and chronic pain of mixed etiology[253].

A second object in the use of analgesic combinations is the reduction of the incidence of side-effects or toxic reactions by reducing the dose of any one constituent. As Goodman and Gilman state ([185], p. 313): "The possibility of untoward reactions is also reduced (by prescribing an analgesic mixture) because the toxic effects of the salicylates, pyrazolon, and para-aminophenol derivatives differ somewhat from each other." The rationale behind this ostensibly reasonable maneuver does not, however, withstand pharmacologic scrutiny. It is based on the assumption that the major toxic effects of these drugs are dose-related within the usual therapeutic range of doses. The fact is, however, that when these compounds are administered as mild analgesics, the dose-related toxicity is extremely small. The salient danger of the above compounds is related to uncommon but potentially disastrous idiosyncratic or allergic reactions (that is, massive gastrointestinal hemorrhage or acute allergic reactions from the salicylates, sudden hemolytic reactions to the aniline derivatives, and agranulocytosis produced by the pyrazolones). There is no evidence that by reducing the individual dose of these drugs by one half, the danger of precipitating such reactions is materially lessened, but by taking a mixture of them, the risk of having an unfortunate reaction to one is unquestionably greater.

There is likewise no evidence that a mixed intoxication with these drugs, such as that arising from accidental acute overdosage, is any less dangerous than poisoning by one alone. In none of the analgesic studies noted in the preceding paragraph was A.P.C. compound found to produce fewer subjective side-effects than plain aspirin. Theoretical speculations on the relative likelihood of producing subjective side-effects by administration of analgesic drugs, be they mixtures or single drug entities, have little meaning unless substantiated by the results of suitable clinical experiments.

As noted above, a great number of analgesic mixtures are marketed, both on an over-the-counter and on a prescription basis. In addition to one or more antipyretic-analgesics, these mixtures may contain narcotics or similar compounds, hypnotics, sedatives, tranquilizers, muscle relaxants, amphetamines, caffeine, parasympathomimetics, anticholinergics, sympathomimetics, para-aminobenzoic acid, vitamin C, iodides, steroids, and colchicine. Mixtures containing five or six ingredients, apparently selected at random from the above list, are not at all uncommon. References are made to "synergistic" and "potentiating" actions; and many of these remedies have been thoughtfully formulated to contain both a psychic stimulant *and* a sedative, or a parasympathomimetic agent *and* a parasympatholytic, lest the physician be uncertain whether activation or suppression of certain of the vital functions is indicated.

Leaving aside the question of the analgesic merit of the various drug entities listed above, it is obviously impossible to adjust the size and frequency of the dose of each constituent of even a well-founded combination analgesic regimen, when these constituents are compounded in a mixture. It seems also appropriate to point out at this juncture, that in all probability, the etiology and pathogenesis of "analgesic nephropathy" would not be so uncertain if only single drug entities,

as opposed to mixtures, had been consumed by the patients in question.

It is not the intent of the above discussion to disparage all use of analgesic combinations, or combinations of analgesics with other types of drugs such as tranquilizers, sedatives, or stimulants, in the relief of pain. "What is to be deprecated is the concept that certain combinations of compounds in specific proportions provide in some mysterious way better analgesia than the analgesic potentials of the compounds contained. This "potentiation" could not be demonstrated whenever it was studied by properly controlled trial. [Drugs used in combination therapy] should be prescribed individually and in doses tailored to the patient and the therapeutic objective"[105].

IV. Concluding Remarks. After some consideration, I found no more satisfactory conclusion to this review than the following statement which appeared in a rather terse discussion of the same subject: "It may be disappointing that there are no therapeutic revolutions among the analgesic drugs, but it is also comforting that the most useful drugs are also very familiar and present only modest and well-known hazards"[9].

ACKNOWLEDGMENT: I would like to thank Miss Julie Franchi for her extensive assistance in the preparation of this manuscript, and Miss Ada Rogers and my wife, Nancy, for their aid in reading the proof.

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Attachment-3

THE CLINICAL EVALUATION OF MORPHINE AND ITS SUBSTITUTES AS ANALGESICS[1]

LOUIS LASAGNA

Departments of Medicine (Division of Clinical Pharmacology) and of Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine, Baltimore, Maryland

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". . . it is the mark of an educated man to look for precision in each class of things just so far as the nature of the subject admits . . ."

Aristotle, 4th Century B.C.

"A micrometer is not used to measure a football field."

Freis and Williams, 1961.

I. INTRODUCTION

There are few symptoms more urgent than severe pain, few classes of drugs more useful than the major analgesics. The world literature on morphine-like drugs is both voluminous and ancient, but until recent times one searched in vain for quantitative data on their clinical performance. The last two decades have witnessed not only the birth of many new pain-relieving compounds, but—

[1] Supported in part by grants from the National Institutes of Health.

more important—have seen the emergence of scientifically acceptable techniques for generating reliable and interpretable clinical data.

This review will attempt to summarize the information available on the relative merits of the individual morphine-like compounds, and on their drawbacks. Before this, however, it is necessary to discuss briefly the problems involved in evaluating the literature in this field.

II. PROBLEMS IN EVALUATING THE LITERATURE

The delineation of analgesic efficacy can be thought of at two different levels. The first, and more simple one, is exemplified in the question: "Does this drug clearly relieve human pain?" The second, more complex level—and one which is crucial if we are to evaluate side-action liability in any meaningful way—can be exemplified in a second question: "How does this analgesic drug compare with already available analgesics, especially the standard ones?"

The first question requires a comparison of drug and placebo, the second a comparison of two or more drugs. Both kinds of comparisons are optimally made by the use of clinical trials employing accepted principles of experimental design, including the randomization of subjects to reduce or eliminate bias in allocation; the "double blind" technique (in which neither subject nor observer is aware of the specific nature of the medication being exhibited at a given time) to reduce or eliminate bias in assessment; and statistical planning and analysis, to minimize the drawing of conclusions unjustified by the magnitude of differences obtained and the numbers of subjects studied.

It is no exaggeration to say that we do not, at the present time, possess an adequate amount of information for most of the compounds to be discussed. This lugubrious statement is made not so much because of our inability to answer the first question posed above, but because of problems in answering the second.

Difficulties arise from the following sources:

A. Dose-response problems

It is a truism that the evaluation of a drug in man, no less than in other species, requires knowledge of the effects achieved with a reasonably broad span of doses (114). For reasons of convenience, caution, and habit, it is still commonplace to have evaluations and comparisons of analgesic drugs made at single dose levels.

B. The semantics of "pain relief"

The inter-investigator comparisons that one might desire to make are often hampered by the use of different criteria of response. Thus one may find papers reporting on the analgesic power of a given agent with the emphasis being on complete disappearance of pain, "significant" pain relief (variously defined or undefined), or incidence of pain relief of any degree; on peak effects or total performance over a matter of hours or days; or even on scores representing a strange melange of pain relief and untoward effects, with points given for analgesia and subtracted for such things as nausea or dizziness.

C. Acute vs. chronic administration

The study of single doses of drugs is certainly simpler and tidier than the study of repeated doses, but it does not shed light on such problems as cumulation and tolerance. Fortunately, drugs like morphine are most often used on a short-term basis, so that results on single-dose studies appear readily transferable to much of clinical practice. Occasionally, problems arise even in acute studies from the prolonged effects of analgesics (*cf.* acetylmethadol) (84). There is a dearth of information on the effects of chronic dosage with morphine and its substitutes.

D. Oral vs. parenteral routes

There is evidence that most of the drugs in the category under consideration are probably much less effective by mouth than by injection. At the same time, reliable potency estimates for drug given by these two routes are rarely available for the simple reason that controlled trials of an agent given by different routes pose certain technical obstacles which, while not insuperable, constitute a significant deterrent to the investigator. For example, patients with postoperative pain are often used to assess injectable drugs, but such patients, with their recent surgery, anesthesia, indwelling tubes, *etc.*, are likely to be considered poor candidates for oral medication. Contrariwise, postpartum patients or ambulatory outpatients are candidates for oral medication, but it may be difficult to arrange to give such patients injections, or they may be unwilling to undergo the pain and apprehension caused by them. In addition, there is the difficulty of eliminating bias in oral *vs.* parenteral comparisons, since to maintain double blind conditions, it is necessary to use two kinds of placebos, one oral and one injectable.

E. Population differences

Pain occurs in many clinical situations. There is the pain of labor, the after-pains of the postpartum period, the pains after a host of different surgical procedures, the pain of cardiac infarct, the pain of biliary or renal or intestinal colic, the pain from primary or metastatic malignant invasion of soft tissues or bone. The possibility arises that analgesic data, no matter how precise, in one kind of pain may not be readily transferable to other kinds of discomfort. Fortunately, the evidence to date suggests that potency estimates in such entities as post-operative pain, postpartum pain, and pain of malignant disease are often in reasonably good agreement, although some kinds of pain (*e.g.*, of rheumatoid or gouty arthritis) theoretically and empirically are responsive to agents (such as cortisone or colchicine) which are considered of little or no use in painful states unaccompanied by inflammatory pathology of any degree. Although the concepts of specific and nonspecific pain relief (for example, atropine or nitrites *versus* morphine in relieving the pain of smooth muscle spasm) are by no means new or profound, this point is mentioned because of the fact that analgesic studies are still reported which either fail to describe patients adequately, or include varying (and often unspecified) proportions of patients (such as arth-

ritics) in whom pain relief could conceivably be more impressive with agents affecting basic pathogenetic processes rather than (or as well as) producing "central" pain relief.

Certain kinds of common clinical pain, such as headache, traumatic pain (nonsurgical), and labor pain (126a), have been the subject of extraordinarily few adequately controlled trials.

F. Individual differences in drug response

Most clinical trials are designed to measure and describe the "average" performance of a drug, rather than to answer the question of whether a given drug works better for one person than another drug. Even "cross-over" trials, unless specifically designed to study the problem, usually give only limited assurance that an individual will reproducibly prefer one agent to another for relief of pain. At present, therefore, it is usually possible to say only that if Drugs A, B, and C relieve, respectively, 90%, 60%, and 40% of a given population, one is well advised to use Drug A as the agent of choice. Such percentages do not tell us whether failures with Drug A *will* respond to Drug B or C; indeed, it is not unlikely that failures to Drug A will *not* respond to B and especially not to C.

Although it is unfortunate that we do not have reliable data on individuality of response, the practice of medicine is hardly paralyzed by the lack of such information. Indeed, even if we were sure that Drug C mentioned above would handle the pain problem of all failures on Drug A, one would not select C as the drug of first choice unless somehow there were a way of knowing in advance whether a patient was an "A-" or a "C-responder." Clinical medicine generally lacks such information, so that barring a clearcut history, from a patient, of poor analgesia (or untoward effects) from a known drug, one would still prescribe, in any given situation, the drug with the best "average" performance.

G. The delineation of side-action liability and addiction potential

The quantification of the limitations of morphine and its substitutes poses a dilemma for the clinical investigator. The most precise and careful studies on this problem are unfortunately performed under conditions considerably different from the conditions of ordinary medical usage. The potential of morphine-like drugs for producing respiratory depression, affecting pupil size, inducing nausea and vomiting, *etc.*, is often, for example, evaluated in healthy volunteers. The ability of drugs to produce physical dependence, tolerance, and euphoria is most readily studied in experienced "postaddicts," recidivist prisoner volunteers who may not even be representative of the general addict population, let alone the nonaddict patient in pain.

The reasons for preferring such volunteers to actual sick patients in evaluating side-action or addiction liability are numerous: 1) Patients are often in a state of flux because of improvement or deterioration in their basic disease, so that one is faced with the evaluation of drug-induced change superimposed on change of other sorts; 2) not only may the basic disease produce symptoms and signs, but other medications may be applied concurrently in the management of the pa-

tient's total problem (anesthetics, anticancer drugs, *etc.*); 3) the sick patient is often not as accurate or reliable an observer and reporter as the volunteer subject; 4) many of the investigations in question cannot ethically be carried out in populations other than those now used (*e.g.*, certain addiction studies).

The result of current practice is to provide the investigator with data that are in a way spuriously precise. Qualitative statements can be validly made; even crude quantitative statements are possible, such as: "When Drugs X and Y are given in equianalgesic dosage, Drug X will probably cause nausea more frequently than Drug Y." But one is hard put to go beyond this. That a drug can cause respiratory depression is easily determinable; how often it will cause *biologically significant* respiratory depression in ordinary clinical use is impossible to tell from studies in volunteers. That a drug is likely to be abused by addicts, or may produce primary addiction, is not impossible to predict, but the precise relative addiction liability of drugs under conditions of medical usage (or even illicit use) is not within our grasp. One thing seems relatively clear: facile generalizations from nonpatients to patients are likely to be accompanied by substantial error.

There have been attempts at determination of tolerance and physical dependence development in patients with chronic pain, in some instances by challenging periodically with nalorphine. These have been few, and for the most part we are left with an imperfect impression, based on "past experience," of the degree and rate of development of tolerance or the likelihood that a patient may become dependent upon a drug under conditions of prolonged clinical use.

III. INDIVIDUAL DRUGS

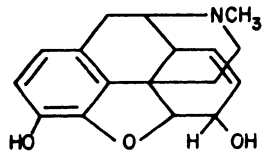
In the sections that follow, the major drugs used in the clinic for relief of severe pain will be discussed. Not all such drugs are included, and a few drugs not in the category of popular morphine substitutes will also be taken up. When one in clinical use is omitted, the reason is usually that there are no data on humans which satisfy modern criteria for a valid experiment. In addition, certain analgesics comparable to aspirin rather than morphine, or analgesics not in widespread clinical use, are discussed, usually either for theoretical reasons or in an attempt to correct widespread misconceptions about the drugs. The drugs are taken up in groups of similar molecular configuration.

The accent will be on clinical analgesic trials which appear interpretable by reason of apparently acceptable design and execution, and on the side-action liability of the drugs in man. (Of necessity, much of the interpretable literature on side effects is in healthy volunteers, as mentioned above.) No attempt is made to discuss such clinical matters as control of cough or diarrhea, *e.g.*, although the drugs to be discussed have broad applications in the management of these symptoms. Most of the so-called "mild" analgesics will not be taken up, except occasionally in statements about comparative efficacy. This omission reflects the desire to keep this review within reasonable limits, rather than a cavalier disaffection for these drugs. (Indeed aspirin—acetylsalicylic acid—remains

the standard of reference for oral analgesics in most laboratories concerned with controlled clinical assays.)

This review will not attempt to discuss addiction liability in detail, partly because of the absence of quantitative clinical data. Instead, addiction will be discussed under individual drugs when it is especially relevant to the evaluation of the compound, and very briefly for the drugs as a whole in Section IV.

Several sources should be listed for those interested in reading further in this area, either to fill in the gaps in this review, or to pursue related topics. The relationship between chemical structure and analgesic action has been summarized by Braenden *et al.* (19) and that between analgesic action and addiction liability by the same authors (43). A third and extremely useful reference by these workers deals with synthetic substances with morphine-like effect, and covers the clinical experience in regard to potency, side effects, and addiction liability (44). An additional source of references, although less satisfactory than the above, is the book on *Morphine and Allied Drugs* by Reynolds and Randall (140). A superb discussion of methods for measuring clinical pain, including related statistical problems, can be found in the review by Beecher (6); a shorter coverage of some of these problems is also available (105). Also recommended is the book by Beecher entitled *Measurement of Subjective Responses. Quantitative Effects of Drugs* (7). Those who wish to be apprised of current methods for assessing addiction liability are referred to the methodologic paper by Fraser *et al.* (49), and that by Halbach and Eddy (61).



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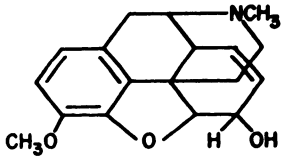

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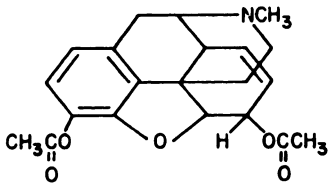
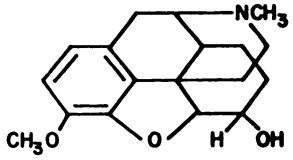


HEROIN
(DIACETYLMORPHINE)



DIHYDROCODEINE

A. Morphine

The beginning of the modern era in the clinical evaluation of analgesic drugs dates from 1949–1950, when a series of classic papers emerged from the Anesthesia Research Laboratory of Harvard University at the Massachusetts Gen-

eral Hospital. The key figures in this research were Henry K. Beecher, Jane E. Denton, Arthur S. Keats, and Frederick C. Mosteller.[2] Workers since that time—both in and out of the Harvard Laboratory—have modified and improved on the early protocols, but these subsequent modifications have been in the nature of refinements rather than complete reworkings. Since 1949, many papers have been published on analgesics which are as uninterpretable as those pre Beecher-Denton-Keats-Mosteller, but there has also been published an encouraging amount of data generated by experiments properly designed and executed. More important, the way is now clear for any who care to perform a properly controlled trial in this field.

The principles established by Denton and Beecher (35) were these: 1) because of inconsistencies in response of experimental pain to drugs, the proper appraisal of analgesics must be performed in humans with "natural" pain, *i.e.*, pain that is a consequence of disease or trauma, 2) the collection of data must not be biased by observers' knowledge of which drug the patient has received, 3) a dose-response curve for each drug must be determined, 4) the data collected should be subjected to statistical analysis, 5) the study of side effects in patients (post-operative, specifically) may be not sufficiently reliable to warrant recording and analysis, 6) side-action liability can be measured in healthy volunteers, 7) the performance of a good experiment in this field requires full-time attention and cannot easily be accomplished as a sideline in clinical practice, 8) appropriate measures must be taken to assure the safety of patients and volunteer subjects, 9) new agents must be compared with controls, *e.g.*, morphine, saline, or both, 10) sleep should not be confused with analgesia, 11) the comparative side-action liability of drugs, to be meaningful, must be assessed at equianalgesic doses.

In a second paper, Denton and Beecher (36) presented evidence that the analgesic dose-response curve for morphine reached a plateau at 7 to 9 mg. This dose seemed to provide acceptable relief in 90% of the patients, and further increase in dose did not improve on this performance. (In subsequent work from Beecher's laboratory, as certain kinds of surgery were eliminated from study because of the mild nature of the pain they produced, this figure changed somewhat, although the "optimal" dose of morphine remained at 10 mg per 70 kg; *vide infra.*) It was estimated that the mean interval between subcutaneous injection and onset of some degree of pain relief was 10 minutes, and the mean duration of analgesia was about 4 hours.

The paper by Keats *et al.* (85) further emphasized the reliability of clinical assays based on the principles outlined above. A study of saline, 5, 8, 10, 12, and 15 mg morphine, always pitted against 10-mg doses of morphine, produced a satisfactory dose-response curve with an assay error of approximately 10%. Further information was provided as to choice of patients, types of surgery, order of drug administration, variability in response to morphine, *etc.* The paper remains a classic one, and is a delight to read.

In 1954 Lasagna and Beecher re-examined the question of the "optimal" dose of morphine (108). They found that 10 mg of morphine per 70 kg body weight

[2] For the record: anesthetist, internist, anesthesiologist, statistician.

provided significant relief of pain in about two-thirds of patients. With 15 mg per 70 kg, a little over three-fourths of patients reported such relief. The higher dose also provided somewhat longer relief of pain. Counterbalancing the gains provided by the higher dose was a significant increase in side effects. Their review of the literature, plus the fact that the group studied by them was purposely selected as a group with severe pain, rather than the average group of patients likely to receive morphine-like compounds, led Lasagna and Beecher to conclude that 15-mg doses of morphine are probably unnecessary to relieve pain in most patients receiving this drug, and that the optimal parenteral dose is 10 mg per 70 kg body weight. (This dose has become the standard for comparison in most controlled trials.)

Houde *et al.* (74) have described their technique for the evaluation of analgesic drugs (both oral and parenteral) in man. Like the other workers described above, they present evidence for the reproducibility of analgesic effects in patients with pathologic pain (they use cancer patients with chronic pain), for the satisfactory dose-response curves obtainable with morphine, and for the performance of parenteral morphine and oral aspirin as controls.

In contrast to the excellent analgesia provided by 10 mg morphine given parenterally is the poor performance of this dose given by mouth. Beecher *et al.* (10), studying postoperative patients, found 10 mg oral morphine only 9% better than placebo capsules in relieving pain. Houde *et al.* (65), studying cancer patients, found that in terms of peak effects, oral morphine was $\frac{1}{15}$th as potent an analgesic as parenteral morphine. Because the effects with oral morphine have a delayed peak but also a more prolonged effect, the use of "total" pain relief scores over 6 hours changes this ratio to $\frac{1}{6}$th. Nevertheless, it is obvious that *single* doses of oral morphine are not very effective. (There are no adequate comparisons available on repeated doses of oral morphine *versus* repeated doses of parenteral drug.) Preliminary data from Houde and Wallenstein (73), on the other hand, indicate that this performance of oral morphine is nevertheless superior to that of oral codeine, milligram for milligram.

The subjective effects of morphine (nausea, vomiting, dizziness, sleepiness, "mental clouding," *etc.*) have been repeatedly reported (37, 54, 83, 88, 108, 115, 146, 156) in healthy volunteers and in patients. (Although most of these studies have been performed in males, it is perhaps worth observing that our own experience with thousands of female patients indicates that the oft-repeated canard that women are very likely to react to morphine with the excitement seen in cats and horses is another of those interesting myths that textbook writers are fond of repeating without evidence down through the years.)

The respiratory depressant capacity of clinical doses of morphine is easily demonstrable whether one simply measures minute ventilation or uses more complicated techniques such as displacement of ventilation-P_{CO_2} curves (39, 83, 118). Holford and Mithoefer (64) have presented evidence that in terms of respiratory effects healthy aged individuals respond no differently to 10 mg morphine than do healthy young adults.

Laidlaw and Read (101), and Laidlaw *et al.* (102) have stressed the greater

EEG response of cirrhotic patients to morphine, but their papers give no indication that even severely decompensated cirrhotics reacted catastrophically to 8 or 16 mg parenteral morphine. The original paper by Benedict (13) on the dangers of morphine in myxedema is unimpressive today, although its conclusions may be valid; comparative data on the effects of morphine in hypothyroid patients and matched controls are unavailable.

The effects of morphine on blood pressure and cardiovascular responses have been most easily shown in tilt-table experiments (38). Given to supine subjects intravenously, morphine produced only transient increases in cardiac rate and output. If subjects given morphine parenterally were put suddenly in a 75-degree head-up position, there was an increased incidence of fainting, when contrasted with the nonmorphine state.

The gastrointestinal effects of morphine in man are complex (155), but in general there appears to be an increase in intestinal tone different from normal coordinated propulsive activity, plus sphincteric spasm, with resultant diminution in peristalsis and the occurrence of constipation (1). The ability of morphine to produce spasm of smooth muscle also can cause increased pressure in the biliary system (52, 99), sufficient at times to produce biliary colic. Spasm may also occur in the vesical sphincter.

In summary, morphine is a good, reliable analgesic when given parenterally, but is considerably less effective when given by mouth. It can produce a variety of untoward side effects, but these are not of sufficient seriousness or frequency in most patients with severe pain to override the remarkable analgesia this drug can provide. Despite its drawbacks, and because no other established drug which can equal the analgesic performance of morphine is free of its undesirable qualities, morphine remains the standard against which all potential new morphine substitutes must be compared.

B. Codeine

Despite codeine's long use as an analgesic drug, it is amazing how little reliable information there is about its efficacy, particularly by the parenteral route. Beecher *et al.* (10) compared 60 mg codeine by mouth against placebo in the management of postoperative pain. The percent of doses providing analgesia was insignificantly higher (39%) after codeine than after placebo (34%).

Houde and Wallenstein (67) found 32 mg codeine given by mouth significantly better than placebo as an analgesic in patients suffering from pain of terminal cancer, but not significantly different from 600 mg of aspirin. Together, however, these two agents gave impressive summation of effect.

Gruber (57) studied patients with pain of various sorts: osteoarthritis, rheumatoid arthritis, cellulitis, bursitis, malignant neoplasm, peripheral neuritis, fractured femur, and "vascular" pain. Thirty-two mg codeine orally produced relief clearly superior to that seen after placebo, but 65-mg doses seemed to yield little additional benefit over that provided by the lower dose; in 3 of the subcategories of patients the pain relief scores were higher on 65 mg and in 3 lower. The lower dose of codeine in this study produced a very low incidence of nausea, vomiting,

or sleepiness; the higher dose caused a substantial increase in incidence of nausea, vomiting, anorexia, constipation, abdominal pain, dizziness, and sleepiness.

Cass and Frederik (24), in a group of patients with chronic pain, concluded that codeine by mouth in doses of 32 to 130 mg was better than either placebo or equal doses of *d*-propoxyphene.

Boyle *et al.* (18) also studied oral codeine in patients suffering from a variety of conditions causing chronic pain (arthritis, fractures, *etc.*). Sixty-five mg codeine provided pain relief significantly better than placebo or an equal dose of *d*-propoxyphene, but not better than 650 mg aspirin. The best performance was actually achieved with a combination of 32 mg codeine and 325 mg aspirin. Only one patient receiving codeine showed nausea and vomiting; "no other side effects were noted."

A study by Van Bergen *et al.* (154) examined the comparative efficacy of oral codeine (65 mg), meperidine (100 mg), *d*-propoxyphene (100 mg) and placebo. They concluded that all active drugs were better analgesics than placebo, but not significantly different from one another except in regard to side effects, codeine and meperidine having produced slightly more nausea and gastric distress than did *d*-propoxyphene. All 3 agents produced more drowsiness than did placebo. Incompleteness of crossover, dropouts, and analysis of doses only, rather than of patients, make it hard to evaluate these conclusions.

Prockop *et al.* (133) analyzed the responses of a large number of puerperal patients to oral analgesics. Most of these patients complained of uterine discomfort ("after-pains"), but others suffered from incisional pain (episiotomy or perineal tear). Thirty-two and one-half mg codeine provided complete or adequate relief of cramps for 55% of patients, as opposed to 36% of the placebo-treated group, 80% of the "ASA-compound"-treated group, and 80% who received both 32.5 mg codeine and ASA. (ASA compound = acetophenetidin 160 mg, acetylsalicylic acid 227 mg, and caffeine 32.4 mg.) Doubling the dose increased the placebo response to 43%, the codeine to 62%, and the codeine-ASA to 83%, while the ASA performance dropped to 61%. (These double-dose treatment groups were only ¼th as large as the single-dose groups, however, and were not studied contemporaneously with the latter.) The incisional pain study gave somewhat different results. The single dose phase showed only slight trends in favor of codeine and ASA compound, with no essential difference between them. A clear-cut superiority over placebo was seen only in the case of the codeine-ASA compound mixture. The double dose phase of the incisional study employed numbers of patients too small for analysis.

Side effects in this study were not impressive; codeine produced nausea, vomiting, and drowsiness somewhat more often than did placebo. A total of 28% of patients reported one or more side effects after 32.5 mg codeine, in contrast with 11% after placebo. Doubling the dose of codeine did not seem to increase the reporting of side effects, except in the case of codeine-ASA compound.

Sadove *et al.* (141) found 30 mg oral codeine better than placebo for relieving the pain of postoperative orthopedic patients.

Gruber and his colleagues (58, 59) studied two groups of patients similar to

that of Prockop *et al.* They found that ASA compound provided pain relief significantly greater than placebo, but 32 mg of codeine alone were ineffective, and when added to ASA compound yielded no additional analgesia.

Only two groups of investigators have published on the efficacy of parenteral codeine. Lasagna and Beecher (106) found 30 mg codeine considerably inferior to 10 mg morphine in treating postoperative pain. Sixty mg provided almost, but not quite as good a performance as 10 mg morphine, and 120 mg codeine also failed to equal the performance of the standard. Despite this inferior performance, codeine depressed the respiration and caused other undesirable morphine-like symptoms. [Bellville *et al.* (12) have shown that respiratory depression also occurs after codeine in healthy volunteers given 60 mg codeine by mouth.]

Houde and Wallenstein, while originally (72) suggesting that codeine and morphine had parallel dose-response curves, and that the "ceiling" for the two drugs was really not different, have indicated (65) that at high doses the curves diverge and that codeine is indeed an analgesic of lesser merit, in terms of peak or total performance, than is morphine. These high doses are, to be sure, well above the usual therapeutic doses of the two drugs, and the population studied is one with greater past exposure (and perhaps tolerance) to morphine or its substitutes than the patients studied by other groups. They found respiratory depression, nausea, vomiting, *etc.*, at least as frequent and severe after codeine as after morphine.

In summary, therefore, codeine by mouth appears to be a moderately effective analgesic, but one not superior, on the average, to aspirin when these drugs are given in usual doses. Indeed there is evidence suggesting that aspirin is a more reliable and effective agent for short-term use. Codeine plus aspirin, on the other hand, is worth trying in situations where either drug alone is ineffective. Codeine by injection, in 60-mg doses, approaches but does not equal 10 mg morphine as an analgesic. At these doses, however, codeine possesses most of the disadvantages of morphine. It would therefore seem that the use of codeine parenterally could be avoided by simply using doses of morphine smaller than 10 mg.

C. Dihydrocodeine (Paracodin)

Although dihydrocodeine has been in clinical use in Europe and Japan as an antitussive for half a century, its potential as an analgesic has been carefully scrutinized only during the last decade. Gravenstein *et al.* (54) compared the drug against morphine, giving both drugs subcutaneously, in doses calculated per 70 kg body weight, to patients suffering from postoperative pain. Fifteen mg of dihydrocodeine provided significant pain relief in 56% of patients, whereas 10 mg morphine did so in 89%. Doubling the dose of dihydrocodeine to 30 mg narrowed the difference between the drugs to 12%, but a further increase to 45 mg still left dihydrocodeine with an analgesic performance 13% less than that of 10 mg morphine. An extension of this work from the same laboratory (9) indicated that 60 mg dihydrocodeine were equal to 10 mg morphine as an analgesic at 45 minutes, but inferior 150 minutes after medication. Indeed at all dose levels studied, duration of pain relief was shorter after dihydrocodeine.

Keats *et al.* (90) also administered dihydrocodeine parenterally to postoperative patients, comparing it to morphine. Thirty mg dihydrocodeine were analgesic in 66% of doses, as opposed to 75% for morphine. At 60 mg, dihydrocodeine was indistinguishable from 10 mg morphine, but at 90 mg it was 5% less effective than the standard dose of morphine.

Seed *et al.* (143) studied dihydrocodeine in patients suffering from the pain of terminal cancer, most of whom had been on morphine-like drugs regularly, but all of whom had been receiving less than 16 mg morphine (or what the authors considered its equivalent) every 4 hours. Although these authors concluded that dihydrocodeine and morphine, given intramuscularly, yielded analgesic dose-response curves that were parallel, inspection of the data suggests another interpretation. The bulk of the pain scores in this paper is contained in their "second quartet" group, which totals 29 patients and actually includes 4 of the "remaining" 12 patients in the "first quartet" group. The mean 6-hour pain relief scores for morphine in the "second quartet" group are: 5 mg, 3.72; 10 mg, 6.06. The mean scores for dihydrocodeine in this group are: 30 mg, 4.23; 60 mg, 4.81. To this reviewer, the total impact of the data is to suggest that dihydrocodeine has a "ceiling" analgesic effect inferior to that of morphine, so that a potency ratio for the two drugs may be both pointless and invalid.

Cope and Jones (27), in an investigation not as well controlled as those already mentioned, studied patients who had undergone major gynecologic surgery or Caesarean section. They found only 35% of patients reporting "excellent" analgesia after 50 mg dihydrocodeine given subcutaneously, whereas 10 mg dextromoramide, 20 mg Pantopon, and 25 mg dipipanone provided such analgesia to 84%, 92%, and 91% of patients, respectively.

Lund (119) and Lund and Lind (121) compared dihydrocodeine, meperidine, morphine, and placebo in postoperative pain, and dihydrocodeine and meperidine in labor pain. In the former situation, 30 mg dihydrocodeine worked satisfactorily in 77% of the doses, as compared with 90% for 10 mg morphine, 87% for 100 mg meperidine, and 47% for saline placebo. In labor pain, 100 mg meperidine gave good relief in 64% of patients, whereas 30 mg dihydrocodeine worked well in only 41%.

The variable, but generally inferior, performance of dihydrocodeine makes it difficult to interpret the reported data on side effects. Gravenstein *et al.* (54) found 30 mg dihydrocodeine almost free of untoward subjective effects, as measured by spontaneous reports or questionnaires, and of respiratory depressant effect in healthy young male volunteers, but this dose is unquestionably inferior, for analgesic purposes, to the 10-mg dose of morphine used for comparison At 60 mg (9), dihydrocodeine depressed respiratory minute volume less than did 10 mg morphine, but increased the incidence of side effects, and of mood changes, over those seen with 30 mg dihydrocodeine.

Keats *et al.* (90) found that 30 mg dihydrocodeine depressed the respiration of healthy volunteers only slightly, but 60 mg produced effects comparable to those seen with 10 mg morphine. Using a check-list approach, these same authors found that a subcutaneous dose of 30 mg dihydrocodeine produced minimal

effects, whereas 60 mg clearly produced side effects, although they were in most respects less than were seen after 10 mg morphine.

Seed *et al.* (143), in an incomplete cross-over study of 2 healthy volunteers and 7 patients, concluded that the respiratory depressant effects of morphine and dihydrocodeine were roughly parallel to the analgesic potency of these drugs. These authors state that they observed drowsiness and grogginess "to roughly the same extent" following 10 mg morphine or 60 mg dihydrocodeine in their subjects, but give no actual data on this point.

In summary, dihydrocodeine provides analgesia, with a minimum of untoward effects, at parenteral doses of 30 mg. Higher doses provide some additional analgesia but substantial disadvantages in terms of side effects. The drug cannot be considered a complete substitute for morphine, and it is not clear that even the alleged advantages of the 30-mg dose cannot be readily achieved with doses of morphine smaller than the standard 10 mg.

D. Heroin (diacetylmorphine)

With few drugs is there a greater discrepancy between volume of published material and content of convincing and reliable information, than in the case of heroin. It was evident soon after the drug was placed on the market at the end of the 19th century that heroin possessed many, if not all, of the attributes of morphine, including the ability to relieve pain, suppress cough, depress respiration, and produce both euphoria and dysphoria (44).

It is unfortunate that so much emphasis has been placed on papers that are either insufficiently controlled or irrelevant. For example, one widely quoted article (144) compared heroin and morphine in trials on 8 healthy volunteers. The paper contained no placebo controls, was off in its estimate of the analgesic potency of heroin (by an experimental pain technique) by a factor of 2 to 5, and equated euphoria with "the opposite of narcosis . . . and stupefaction," although it admitted that the absence of unpleasant side effects after heroin (in retrospect, small doses were used, relative to all other drugs) may have accounted for "the pleasurable reaction to the drug." Yet the paper has become an important source of "evidence" of the high euphorigenicity and addiction potential of heroin.

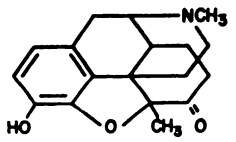
Lasagna, von Felsinger, and Beecher (115), on the other hand, employing 3 different experimental populations—healthy male volunteers, "postaddicts," and chronically ill patients—found a similarity in the responses to morphine and heroin, the prime differences being a greater euphoria after morphine in the postaddicts (in the 4:1 morphine-to-heroin ratio used) and a greater dysphoria after morphine in the healthy volunteers.

In 1962 a definitive set of experiments was published from Beecher's laboratory. First, Reichle *et al.* (136) showed that 2.3 to 5.2 mg heroin given parenterally were equal to 10 mg morphine in relieving postoperative pain. (Heroin's analgesic activity reached a peak earlier and was of shorter duration than that of morphine; this explains the range in ratios.) Next, Smith and Beecher (147), and Smith *et al.* (148) carefully compared heroin and morphine at equianalgesic doses,

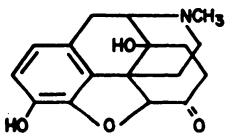
for subjective and objective effects in healthy volunteers. Again, the pattern was one of similarity between the two drugs, with heroin being, if anything, less pleasant than morphine. Work from this same laboratory suggests that heroin and morphine probably depress the respiration equally in equianalgesic doses (135). Finally, Martin and Fraser (123) have presented evidence in "postaddicts" that heroin and morphine are similar in their effects. They reported that their data did "not support the claim that addicts find heroin markedly superior to morphine" and also that "there was no indication that tolerance developed more rapidly to heroin than to morphine."

Although oral doses of heroin have not been subjected to controlled analgesic trials, early reports on this drug (122) indicated that 5 to 10 mg heroin by mouth provided little or no analgesia. This would suggest that heroin, like most other morphine-like compounds, is a considerably less effective analgesic by the oral route.

In summary, heroin seems little better or worse than morphine in its capacity to produce analgesia, respiratory depression, and other side actions, or in addiction potential. To quote from the recent report of the expert Ad Hoc Panel for the White House Conference on Narcotic and Drug Abuse: "There is a widespread misconception that heroin has effects significantly different from those of morphine. It does not, and this misconception should be dispelled permanently" (158).



METOPON



OXYMORPHONE
(DIHYDROHYDROXYMORPHINONE)

E. Metopon

In 1942, Lee reported on extensive clinical trials of metopon as an analgesic agent (116). Patients with acute pain on the emergency, medical, or surgical wards of a general hospital, and patients with chronic pain at a cancer hospital were given coded drugs (the former by injection, the latter either by injection or by mouth). Efficacy was gauged primarily by the evaluation of pain relief by nurses and physicians, rather than by the patients. It was concluded that 5 mg metopon were equivalent in pain-relieving power to 10 mg morphine, but that there was less nausea and vomiting after metopon. Although Lee reported that the mean individual oral doses for metopon and morphine were similar to those used by injection, relative efficacy of the two routes of administration cannot be assessed, since the patients on oral medication had less severe pain than those on parenteral drugs, and were also in "better general physical condition." The author himself points out that the total of 3 cases on morphine and 3 on metopon is too small to draw firm conclusions, but it seems relevant that 2 of the

patients on oral metopon and one on oral morphine had to be switched to hypodermic drug "as the pain became more severe."

In 1952, Keats and Beecher (83) subjected the same 2 drugs to comparison in a controlled trial in postoperative patients. Three-mg doses of metopon, given subcutaneously, gave adequate relief in 77% of instances, whereas 10-mg doses of morphine gave relief in 80% of cases. Six mg metopon, on the other hand, surpassed morphine by 14%. Keats and Beecher concluded that 3.5 mg metopon were equal, in analgesic efficacy, to 10 mg morphine. They also studied side-action liability in healthy male volunteers, finding that the 3-mg dose of metopon was as likely as, or more likely than, 10 mg morphine to affect respiration, pulse, temperature, and subjective responses.

Houde and Wallenstein (70) studied 42 patients with pain due to cancer, and estimated that 2.75 (95% confidence limits 2.1 to 3.6) mg metopon, intramuscularly administered, were equivalent in analgesic effect to 10 mg morphine. Raising the doses of both drugs to the level where undesirable side effects were produced showed no difference between the drugs in terms of side effects. The same investigators (71), studying the same type of patient, went on to compare the potency of metopon by the oral and parenteral routes. They found that doses of 15 mg metopon or greater were required by mouth to approach the analgesia conferred by 3 mg metopon given parenterally. Indeed, in terms of peak effects, the intramuscular form was over 11 times more potent.

In summary, 3 to 4 mg metopon are probably equivalent to 10 mg morphine when the drugs are given by injection. At these doses, the two drugs seem also equally likely, on the average, to produce untoward effects. The frequently made claim that metopon is as effective by mouth as by injection is unsupported by the available evidence.

F. Oxymorphone (dihydrohydroxymorphinone, Numorphan)

Oxymorphone was studied in a controlled trial by Eddy and Lee (45), who used subcutaneous medication in patients with chronic pain. This experiment indicated that 1 mg oxymorphone yielded pain relief similar to that provided by 10 mg morphine. Side effects after these two drugs, as reported by nurse observers, were not greatly different, although the authors suggested that perhaps oxymorphone might produce less nausea and vomiting, but more respiratory depression, than did morphine.

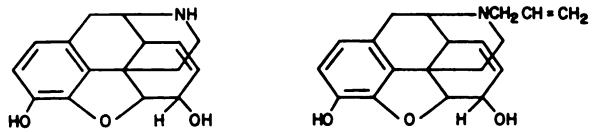
Wallenstein and Houde (157) had earlier come up with similar data in cancer patients with chronic pain. De Kornfeld (30) could detect no difference between 1 mg oxymorphone and 10 mg morphine given parenterally to patients with postoperative pain. This investigator believed that oxymorphone caused less sedation than morphine. In healthy volunteers, however, oxymorphone depressed respiration more than did morphine when both were given intravenously, and oxymorphone was said to produce more euphoria, nausea, and vomiting than did morphine.

Using the potency ratios estimated by the investigators mentioned above, Keats and Telford (88) studied the side effects of oxymorphone (1 mg per 70 kg)

and morphine (10 mg per 70 kg) in 60 female patients awaiting elective surgery. These authors found a higher incidence of most side effects after oxymorphone, including a statistically significant higher incidence of nausea and vomiting.

Resnick *et al.* (139) examined the respiratory depressant capacity of oxymorphone in healthy young subjects and in patients with cardiovascular, pulmonary, or hepatic disease. All subjects showed respiratory depression after 1.5 mg of the drug, with marked depression (including periodic breathing) in the older patients.

In summary, 1 mg oxymorphone given by injection is equal to 10 mg morphine as an analgesic, but at this ratio oxymorphone is at least as likely, and perhaps more likely, to produce untoward effects.



NORMORPHINE

NALORPHINE
(N-ALLYLNORMORPHINE)

G. Normorphine

Normorphine has been the subject of considerable speculation because of certain theoretical considerations regarding the metabolism of morphine. It has been suggested that N-demethylation of morphine to normorphine is a crucial step in the production of analgesia, a hypothesis particularly espoused by Beckett *et al.* (5).

In 1958, Lasagna and De Kornfeld (109) compared morphine and normorphine, given subcutaneously, in patients suffering from postoperative pain. They found that 40-mg doses of normorphine were required to equal the analgesia produced by 10 mg morphine. Keats *et al.* (92) also gave normorphine and morphine by injection to postoperative patients in pain. The percent of "analgesic doses" after normorphine was lower than that after 10 mg morphine at 16 mg (24% lower), 24 mg (6% lower) or 32 mg normorphine (6% lower). Houde and Wallenstein (72) attempted a similar comparison in cancer patients with chronic pain. Their data suggest that intramuscular normorphine may have a somewhat shorter duration than morphine, but in terms of total effect, morphine was 2.6 times more potent than normorphine (95% confidence limits 1.9 to 4.3).

Fraser *et al.* (50) administered normorphine subcutaneously to volunteers from a population imprisoned for narcotic offenses. They found 30-mg single doses of normorphine produced less sedation, miosis, vomiting, and depression of respiration and rectal temperature than did equal doses of morphine, but that repeated doses of normorphine led to marked cumulation of sedative effects, a finding opposite to the experience of Houde and Wallenstein in cancer patients (72).

Because of evidence suggesting that N-demethylation occurs chiefly or exclusively in the liver (3), the clinical assays described above seemed to rule out the theory that normorphine was the active metabolite of morphine. More recent

work by Milthers (125), however, indicates that N-dealkylation of morphine occurs *in vivo* in the rat brain. Although this has revived interest in Beckett's hypothesis, some of Milthers' data in rats are themselves inconsistent with the notion that the formation of *nor*-compounds is essential to analgesia, as is the work of Jóhannesson and Schou (81).

In summary, normorphine given subcutaneously or intramuscularly is considerably less active, milligram for milligram, than morphine as an analgesic in man. Although this finding does not eliminate the possibility that normorphine might be an important active metabolite of morphine, there seems little compelling evidence for the hypothesis. A comparison of the analgesic power of the two drugs in man when given by the intravenous route would be of interest to correlate with the data of Jóhannesson and Milthers in rats (80).

H. Nalorphine (N-allylnormorphine, Nalline)

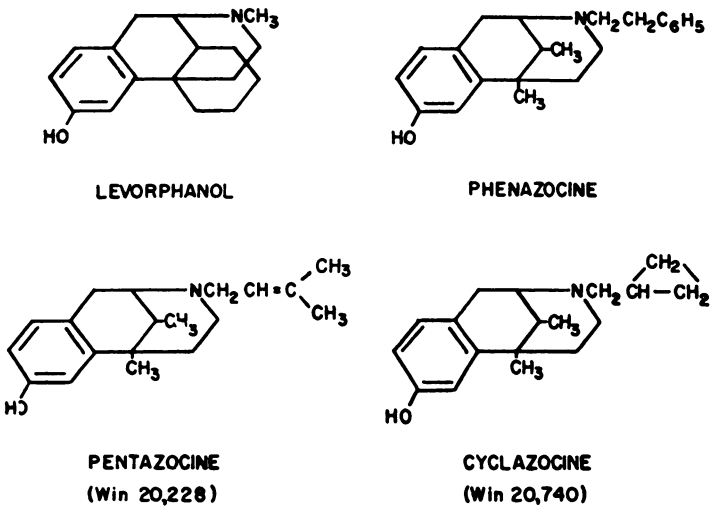
The analgesic powers of nalorphine were discovered by serendipity. Lasagna and Beecher (107) established in 1954 that the drug was, milligram for milligram, similar to morphine in relieving pain in man, despite the general impression from animal experiments that nalorphine was devoid of analgesic activity. This fact emerged accidentally during their unsuccessful attempts to find some "ideal" ratio of antagonist to analgesic which would preserve the desirable effects of morphine while decreasing the undesirable attributes. [Despite a considerable body of published opinion to the contrary, critical reviews (137, 150) suggest that this latter goal has still not been achieved.] To their surprise, nalorphine, which in most of the available animal work looked like a simple antagonist of morphine, was substantially less effective than 10 mg morphine only at doses of 5 mg (both drugs being given subcutaneously). At doses of 10 mg, nalorphine provided relief in 10% fewer postoperative patients, and at 15 mg, nalorphine was 5% more effective than 10 mg morphine.

These findings were confirmed by the work of Keats and Telford (86). Unfortunately, these latter investigators also substantiated (87) the findings of Wikler *et al.* (159) and of Lasagna and Beecher (107) that nalorphine could produce not only morphine-like subjective effects but also in some people a special type of dysphoric and hallucinatory reaction, which seems to qualify nalorphine as a depersonalizing and psychotomimetic drug. This propensity has been the chief reason why nalorphine, a nonaddicting analgesic, has never been introduced into clinical practice as a pain-reliever.

The similarity of nalorphine to morphine includes the ability to produce significant respiratory depression in both healthy volunteers and patients (42, 107, 152), a fact of considerable theoretical and practical interest in view of the drug's capacity to lighten respiratory depression in patients poisoned by large doses of narcotics. The dose-response curve for respiratory depression, however, seems to flatten out at a "ceiling" value considerably lower than that for morphine (151), and this may help to explain the paradox (104).

In summary, nalorphine is a nonaddicting analgesic in man with an unfortunate capacity for producing mental aberrations in some patients at dose levels re-

quired for pain relief. Its theoretical importance cannot be overstated, however: nalorphine has dramatically illustrated the limitations of animal testing in uncovering exciting new leads in the field of analgesics and has spurred the search for better pain-relieving drugs among compounds of the morphine-antagonist variety.



I. Racemorphan (Dromoran) and levorphanol (Levo-Dromoran)

Tidrick *et al.* (153) found 5 mg racemorphan and 10 mg morphine equally effective in relieving the pain of postoperative patients. Jaggard *et al.* (79) came to similar conclusions, giving the drugs subcutaneously to postoperative urologic patients. Keutmann and Foldes (97), giving racemorphan and morphine by the subcutaneous route in doses of 5 and 10 mg, respectively, presented evidence that racemorphan was somewhat more effective in the doses used.

Houde and Wallenstein (68) studied racemorphan, given by two routes of administration, in cancer patients. By mouth, racemorphan was a significantly less effective analgesic than when given intramuscularly.

There are a number of reports testifying to the ability of racemorphan to produce typical opiate side effects, such as nausea, itching, dizziness, and drowsiness in healthy volunteers in doses as low as 2 to 3 mg by injection or by mouth (117, 145, 160).

In patients, Tidrick *et al.* considered side effects to be as frequent after 5 mg racemorphan as after 10-mg doses of morphine. In general, Keutmann and Foldes came to the same conclusions, whereas Jaggard *et al.* thought that the overall incidence of side effects was greater after racemorphan.

There seems little reason for doubting that levorphanol, the levorotatory isomer, contributes the analgesic (and other morphine-like) activity present in the racemate (44, 76).

In summary, racemorphan in doses of 4 to 5 mg by injection is as effective as 10 mg morphine. The active levorotatory isomer, levorphanol, is effective in doses half as large as those of racemorphan. Although these drugs are said to be highly effective when given by mouth (53), the available evidence in controlled trials (68) suggests that they are probably similar to most morphine substitutes in this respect, *i.e.*, they must be given in oral doses several times larger than those given by injection to approach the efficacy of the latter. If so, then these agents possess no advantages over older morphine-like drugs.

J. Phenazocine (Prinadol)

This compound was at one time the subject of considerable publicity, when hopes were aroused that it might be relatively free of some of the disadvantages of morphine. Unfortunately, this temporary enthusiasm was founded on the optimistic "evidence" supplied by uncontrolled trials.

In properly designed experiments, the original estimate that 1 mg phenazocine was perhaps as analgesic as 10 mg morphine (41) was quickly modified. De Kornfeld and Lasagna (32), studying postoperative patients, found 0.5 and 2 mg phenazocine by injection decidedly inferior to 10 mg morphine, whereas 3 mg phenazocine gave results similar to those provided by 10 mg morphine. Houde *et al.* (75), studying cancer patients, collected data almost identical to those of De Kornfeld and Lasagna. They estimated that 2.3 to 3.1 mg phenazocine were equivalent, by injection, to 10 mg morphine, and that at equianalgesic doses the two drugs seemed to show similar incidence of untoward effects.

The claim that the drug is highly effective by mouth also seems unwarranted. Houde *et al.* (65) found that the chronic pain of cancer patients was poorly relieved by oral doses of phenazocine which were very effective by injection. The peak analgesic effects of 2 mg intramuscular phenazocine were considerably greater, for example, than those of 12 mg phenazocine by mouth.

Papadopoulos and Keats (129) examined the respiratory depressant capacity of 2.5 mg phenazocine (intramuscularly, per 70 kg body weight) in healthy volunteers. They concluded that phenazocine and morphine were equally depressant when given in equianalgesic doses. Greisheimer *et al.* (55), also using healthy subjects, found the respiratory effects of intravenous phenazocine more pronounced than those of meperidine, when the drugs were studied at a ratio of 1:40. Bellville *et al.* (11) concluded that 1.7 mg phenazocine depressed respiration as much as 10 mg morphine. This latter estimate is in line with the data of Berkowitz *et al.* (14), who studied respiratory depression in young and elderly "normals," and in patients with cardiovascular disease, emphysema, or cirrhosis. They concluded that 4 mg phenazocine depressed respiration more profoundly than did 15 mg morphine.

In summary, 3 mg phenazocine by injection can substitute for 10 mg morphine in the control of pain. By mouth, much higher doses of phenazocine are less effective than this standard dose given by injection. The drug possesses a capacity for depressing respiration which is at least as great as, and possibly greater than,

morphine, when both are given in equianalgesic dosage. Despite early hopes to the contrary, it is capable of causing addiction, being a "completely adequate" substitute for morphine in addicted persons (46a).

K. Pentazocine (Win 20,228)

This compound, 2-(3,3-dimethylallyl)-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan, has received only limited testing to date, but shows considerable promise in early trials. Keats and Telford (89) have presented evidence that postoperative pain is alleviated to a significant degree by parenteral doses of 10 mg or higher. The precise dose, equivalent to 10 mg morphine, is not yet defined, but is probably greater than 20 mg.

The side-action liability cannot, of course, be defined until more information is available on the doses required to produce analgesia of the degree produced by standard doses of morphine. At certain dose levels, the drug is capable of eliciting subjective reactions reminiscent of those produced by morphine, but is considered to have minimal addictive liability on the basis of studies on "postaddicts" (48). One instance of "nalorphine-like" symptomatology has been reported (82), but the incidence of this type of mental side effect seems low. It is said to depress respiration (in doses of 20 mg per 70 kg) to a degree similar to that seen after half this dose of morphine (2).

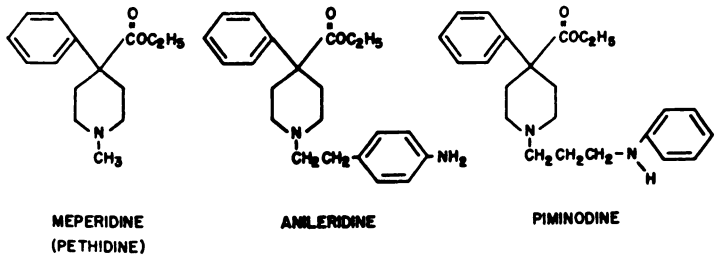
In summary, pentazocine, which in animals appears to be a weak antagonist of morphine and meperidine (2), is an analgesic in man. Further studies must corroborate early claims as to its analgesic efficacy, relative freedom from psychotomimetic effects, and minimal addiction risk, before it is known whether the drug represents an important advance, either in showing dissociation of morphine-like effects usually linked together or for clinical practice.

L. Cyclazocine (Win 20,740)

This drug, 2-cyclopropylmethyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan, is a potent antagonist of morphine and meperidine in animals (62). In man, however, the compound is an extraordinarily potent analgesic (112), being effective by mouth (against postpartum pain) and by injection (against postoperative pain) in doses as low as 0.25 mg. It depresses the respiration of volunteers (112), but the dose-response curve seems to flatten out at a lower "ceiling" than for morphine, in a manner reminiscent of other morphine antagonists (151). It is said to have little addiction liability (48), but in occasional patients produces confusion, depersonalization, and dysphoria (112). Such effects seem rare at low doses.

In summary, cyclazocine is another interesting development in the search for promising analgesics among compounds which appear to be antagonists of morphine and morphine substitutes in animals. It is very potent, on a weight basis, with 0.25 mg showing analgesic activity in man by oral and parenteral routes. Its

ultimate clinical potential remains in question until further experience is accumulated on both its pain-relieving capacity, and its side-action liability.



M. Meperidine (pethidine, Demerol, Dolantin)

Lasagna and Beecher (106) compared parenteral meperidine with morphine in patients with postoperative pain. Fifty mg meperidine were slightly less effective than 10 mg morphine, whereas 100 mg were 11% more effective. Houde and Wallenstein (71), studying the pain of cancer patients, concluded that 62 to 79 mg meperidine were equivalent to 10 mg morphine, depending on whether one focused on peak analgesic effect or total analgesic effect over 6 hours.

Masson (124), using a complex system of scoring involving elements of duration of effect, and both "subjective" and "objective" assessments, studied patients who had undergone major abdominal surgery, and came up with results similar to those described above. Although he had difficulty differentiating between saline and 10 mg morphine ($P = 0.13$ in favor of morphine) and between saline and 50 mg meperidine ($P = 0.17$ in favor of meperidine), Masson clearly showed activity with 100 mg meperidine, which was significantly better than either 10 mg morphine ($P = 0.04$) or saline ($P = 0.001$), and suggestively better than 50 mg meperidine ($P = 0.19$).

Keats *et al.* (94), in a beautifully designed comparison of meperidine, promethazine, and a mixture of the two, contributed data on the dose-response curve of meperidine. Their results indicate that 100 mg parenteral meperidine are considerably more effective than 25 mg meperidine and somewhat better (9 to 12%) than 50 mg meperidine.

Given by mouth, meperidine appears considerably less potent and reliable in its effects than meperidine by injection. This is apparent not only in controlled trials (72), but in the earlier uncontrolled trials of Batterman and others [see review by Eddy *et al.* (44)]. This is of some interest, in view of the studies of Burns *et al.* (21) suggesting that the drug is rapidly and completely absorbed in man.

Like other morphine substitutes, meperidine depresses respiration in man when given in therapeutic doses (16, 25, 91, 103, 118, 127, 132, 138). In equianalgesic doses, meperidine appears no better than morphine in this respect;

it is surprising that one continues to read statements to the contrary in textbooks and articles. (The fact that meperidine may have less effect than morphine on respiratory *rate* as opposed to tidal volume, and that rate is more readily and usually measured in the clinic may help to account for this widespread myth.) One point upon which there are few reliable data is the question of relative potential for respiratory depression in newborns delivered of mothers treated with meperidine. There is a general impression among obstetricians that meperidine carries less risk than would equianalgesic doses of morphine; but in a controlled trial by Campbell *et al.* (23a), a (mean) dose of 11 mg morphine administered to women in labor was not significantly different from a (mean) dose of 120 mg meperidine in its effect on the infant, as gauged by Apgar scores. Subjective side effects are similar to those produced by other morphine-like compounds (91), except that meperidine is, perhaps, more euphoriant than morphine (4, 77, 100).

The reports on the effects of meperidine on the gastrointestinal tract of man are conflicting [*cf.* review by Eddy *et al.* (44)]. Some authors claim that morphine increases intestinal tone whereas meperidine does not (98) or that both drugs increase tone (26) but that the effects of meperidine are less marked. It has been recently claimed again that morphine increases intraluminal gut pressure, whereas meperidine actually diminishes the number and dimensions of the pressure waves, both in healthy subjects and in patients with diverticulosis (128).

Meperidine seems to have a definite spasmogenic effect on the biliary tract (52), but it has been stated that occasional patients who have attacks of biliary colic precipitated by morphine do not do so after meperidine (28). These contradictions may be more apparent than real, however, since the work of Gaensler *et al.* (52) and that of Kjellgren and Löf (99) indicate that the rise in biliary pressure is probably somewhat greater and more prolonged, on the average, after morphine than after equianalgesic doses of meperidine. Nevertheless, Gaensler has noted that meperidine, like morphine, can precipitate typical biliary colic.

In summary, parenteral meperidine, in doses of 60 to 80 mg, can substitute for 10 mg morphine as an analgesic, but in equianalgesic doses produces many of the side effects seen with morphine, including respiratory depression. It is thought by some that it may have some advantage over morphine in regard to a decreased tendency to produce spasm of smooth muscle, but this is denied by others and is in any case counterbalanced by a risk of addiction which is substantial. [Meperidine is an extremely popular drug of addiction among doctors, nurses, and members of related professions (77, 134).] By mouth it is a relatively inefficient analgesic.

N. Anileridine (*Leritine*)

In 1957, Keats *et al.* measured the analgesic potency of parenteral anileridine in postoperative patients (91). Their data indicated that 20 mg anileridine were inferior to 50 mg meperidine but 40 mg anileridine were superior to 50 mg meperidine.

Houde and Wallenstein (71), studying cancer patients, estimated that in terms of total effect 39 mg (95% confidence limits 27 to 47) anileridine parenterally were equal to 100 mg meperidine, and that 31 mg anileridine were equivalent to 10 mg morphine. In terms of peak effect, 10 mg of morphine equalled 62 mg meperidine or 24 mg anileridine, suggesting that morphine had a somewhat longer duration of action.

Chang *et al.* (25), in a controlled trial on the efficacy of analgesic drugs in supplementing nitrous oxide anesthesia, estimated that 60 mg anileridine intravenously were approximately equivalent to 100 mg meperidine.

Keesling and Keats (96) studied the efficacy of anileridine and other drugs given by mouth to patients suffering from the pain of alveolar osteitis. Thirty mg anileridine were better than placebo but not significantly better than 0.6 gram aspirin, 30 mg dihydrocodeine, or a mixture of 2 mg methadone, 1 mg *d*-desoxyephedrine, and 30 mg pentobarbital sodium. Anileridine and dihydrocodeine produced more unpleasant side effects than did any of the other treatments.

Houde and Wallenstein (72) ran a comparison of oral and parenteral anileridine in cancer patients with chronic pain. Anileridine produced less peak analgesia but more prolonged pain relief when given by mouth, although it was more effective, milligram for milligram, and seemed less variable in its effects, than oral meperidine.

Keats *et al.* (91) found 40 mg anileridine as depressant to the respiration of healthy subjects as 100 mg meperidine, but the effects of anileridine were shorter lived. Chang *et al.* (25), studying similar subjects, concluded that parenteral anileridine was at least as depressant to the respiration as meperidine, when both drugs were given in equianalgesic doses.

Volunteers receiving anileridine report side effects similar to those reported after meperidine (25, 91). Chang *et al.* found nausea, vomiting, and dizziness more frequent after 60 mg anileridine than after 100 mg meperidine. Keats *et al.* found most symptoms to be reported as often after 50 mg anileridine as after 100 mg meperidine, although deep sedation was seen significantly more often, and nervousness, restlessness, and stimulation less frequently, after meperidine. In this study, both technicians and patients considered anileridine more unpleasant than meperidine.

In summary, 30 to 60 mg anileridine can probably be substituted for 100 mg meperidine (and presumably for equivalent doses of morphine and other standard morphine-like analgesics) in most clinical situations. Anileridine has only one real advantage: it is probably more efficacious by the oral route, relative to its parenteral potency, than morphine and many other morphine substitutes. It is not *as* good, milligram for milligram, by mouth as by injection, but has significant pain-relieving capacity at 30- to 60-mg doses by either route. In other respects, the drug has no superiority to older drugs, and side effects after it may possibly be greater than with equianalgesic doses of other agents.

O. Piminodine (Alvodine)

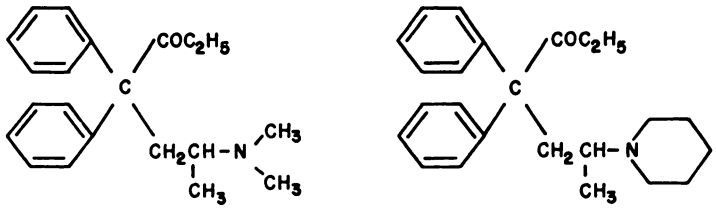
De Kornfeld and Lasagna (31) studied the efficacy of parenteral piminodine against postoperative pain. They found 5 mg piminodine inferior to 10 mg morphine, but 10 mg piminodine at least as effective as, and possibly more effective than, an equal dose of morphine. They estimated that 7.5 mg were perhaps equivalent to 10 mg morphine. There was no impressive incidence of untoward effects from piminodine, even at doses of 20 mg.

De Ciutiis (29) found that 10 to 20 mg piminodine provided pain relief that was "excellent and accompanied by minor change in vital signs" in 86% of postoperative patients, as compared with 43% for 50 to 100 mg meperidine. These doses of meperidine provided "good" pain relief in another 43% of patients, but at the cost of "significant" sedation and depression of blood pressure, pulse, and respiration. In the other 14% of patients, both drugs provided "moderate" pain relief and "moderate" change in vital signs. For preoperative sedation, piminodine was considered less effective than meperidine. In obstetrical patients, 100 mg meperidine were considered superior to 20 mg piminodine, perhaps because of the greater sedative qualities of the former. (Although this study is described as double blind, it is disturbing to read in the paper that all 4 recovery-room nurses were able to discriminate between saline, meperidine, and "new drug." Since the performance of the active drugs was such as to provide overlapping categories of response, one would at least have expected a certain confusion in deciding, for example, which drug had produced excellent pain relief and minor changes in vital signs.)

Betcher *et al.* (15) also compared piminodine and meperidine in postoperative patients, allowing nursing personnel a certain freedom in adjusting individual dosage of coded medication. Although this makes the paper a bit difficult to interpret, 10 mg piminodine appeared at least as good as, and possibly better than, 100 mg meperidine. The incidence of drowsiness was less after piminodine.

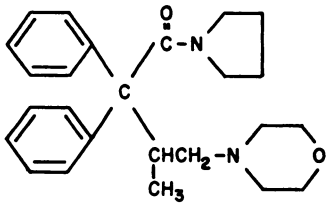
Groeber and Ziserman (56) found 10 to 20 mg piminodine given to women in labor to provide patients with as good analgesia as did 50 to 100 mg meperidine but to cause significantly less respiratory depression of newborns. The suggestion that piminodine may be intrinsically less depressing to the respiration than meperidine is supported by limited data in healthy volunteers on the respiratory effects of piminodine (66). Houde *et al.* found 5 mg piminodine as depressant, on the average, as 10 mg morphine, but 10 mg piminodine caused no further depression, whereas 20 mg morphine caused a considerably greater shift in P_{CO_2} response curves than did 10 mg morphine. These authors did not study the effects of higher doses of piminodine because of "pronounced sedation" with the 10-mg dose (66).

In summary, piminodine, when given by injection, is probably a somewhat more potent analgesic, milligram for milligram, than morphine. It is said by some to be less sedating, dose for dose, than morphine. There is suggestive evidence that the drug may be safer than morphine or meperidine in terms of respiratory depression.

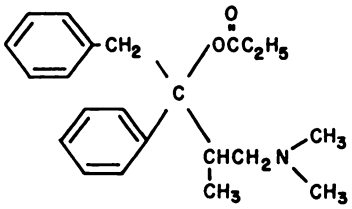


METHADONE

DIPIPANONE



DEXTROMORAMIDE



d-PROPOXYPHENE

P. Methadone (*Adanon, Amidon, Dolophin*)

Denton and Beecher (36) compared parenteral methadone with morphine (and other drugs) in patients with postoperative pain. They concluded that methadone was probably equivalent to morphine, milligram for milligram. These findings were confirmed by Beecher *et al.* (8) in postoperative and wounded patients, although there is a suggestion in their data that methadone may be slightly better than morphine on a weight basis, a finding which would be more in keeping with the bulk of the uncontrolled reports in the literature (44).

In healthy volunteers, Denton and Beecher (37) could see little difference between morphine and methadone in regard to side-action liability. Prescott *et al.* (132) found methadone as depressant to the respiration as morphine, milligram for milligram. Remy (138) showed depression of respiration after 10 mg methadone, to a degree similar to that caused by an equal dose of morphine or by 100 mg meperidine.

Gaensler and McGowan (51) presented evidence that methadone had spasmogenic effects on the human duodenum and could increase intrabiliary pressure, although Kewitz *et al.* (98) denied that methadone had morphine-like effects on the gut of man.

In summary, parenteral methadone is, milligram for milligram, as potent as, or slightly more potent than, morphine in most respects. There is a paucity of evidence on the oral efficacy of this drug, although in one trial (96) a mixture of 2 mg methadone with rather small doses of *d*-desoxyephedrine and pentobarbital was significantly better than a placebo in relieving dental pain. In addition, the drug is given orally at the United States Public Health Service Hospital in Lexington, Kentucky, during withdrawal of other narcotics, with satisfactory

effects. These facts suggest that oral methadone is deserving of more attention, although one should also anticipate cumulative effects if repeated doses are used.

Q. Dipipanone (Pipadone)

Houde, Seed, and Cochin, and Beecher and Gravenstein [results described by Eddy *et al.* (44)] have compared dipipanone and morphine by injection. Houde, Seed, and Cochin studied patients with chronic pain in 3 separate hospitals. The dose of dipipanone considered equivalent to 10 mg morphine was 20 mg, 22 mg, and 11 mg, respectively, for the 3 hospitals, with 19 mg being the best estimate from the combined data. Beecher and Gravenstein worked with patients suffering from postoperative pain. They found 15 mg dipipanone definitely inferior to 10 mg morphine, and 25 to 35 mg dipipanone essentially equal to 10 mg morphine.

Cope and Jones (27), studying women after gynecologic surgery, found 25 mg dipipanone given subcutaneously as good as 20 mg pantopon or 10 mg dextromoramide, and superior to 50 mg dihydrocodeine.

Cahal (22) evaluated the propensity of dipipanone for producing side effects in healthy volunteers. He found a steady increase in side effects as the subcutaneous dose was increased from 4 to 34 mg, with a sharp rise after 15 mg. The symptoms were those produced by most morphine-like compounds, and certain symptoms were less severe when subjects were in the recumbent position, as is the case with other morphine-like drugs.

In summary, 25 mg dipipanone, given parenterally, are probably equivalent to 10 mg morphine in most respects.

R. Dextromoramide (Dimorlin, Palfium)

Lasagna, De Kornfeld, and Safar (113) attempted to evaluate dextromoramide in patients with postpartum pain. The study had to be terminated prematurely because of a high incidence of dizziness, nausea, vomiting, drowsiness, sweating, feelings of warmth, and itching in the dextromoramide group. Enough data were collected, however, to indicate that the drug was an effective analgesic by mouth or injection in doses of 5 to 10 mg. There seemed to be no significant advantage of 10 mg over 5 mg.

Keats *et al.* (93), studying postoperative pain, also concluded that the dose-response curve for analgesia seemed to reach a plateau at 5 mg (per 70 kg in their study), and that this dose was for the most part the equivalent of 10 mg morphine, both in analgesia and in liability to produce side effects. The major difference between dextromoramide and morphine was a somewhat shorter duration of action for the former, evident in respiratory depression studies on healthy male subjects and in the 5- and 6-hour analgesia scores.

The results of Cope and Jones (27) referred to above (*cf.* sections on dihydrocodeine and dipipanone) are compatible with the estimate that dextromoramide and morphine are equianalgesic, milligram for milligram.

Houde and Wallenstein (72), studying cancer patients, estimated that 7 mg dextromoramide, given intramuscularly, were equivalent to 10 mg morphine,

and that the drug when given by mouth was approximately 90% as effective as when given by injection. Two sets of Scandinavian investigators, studying postoperative patients (40, 120) estimated that 7.5 mg dextromoramide were the analgesic equivalent of 10 mg morphine

The reports of Cahal (23), Peeters (131), and of Boudin and Barbizet (17), like those of Lasagna, De Kornfeld, and Safar (113) testify to the capacity of dextromoramide to produce nausea, vomiting, dizziness, somnolence, and other undesirable side effects. In addition, Keats *et al.* (93) observed apnea in 3 of 36 patients who received 5 mg per 70 kg dextromoramide, and Lund and Erikson (120) reported a similar experience after 10 mg of the drug.

In summary, 5 to 7.5 mg dextromoramide appear to be equal in analgesic activity to 10 mg morphine. The side-action liability of the drug, however, seems somewhat greater than that of morphine, when both drugs are given in equianalgesic doses, and the reported instances of serious respiratory depression after standard doses of the drug are somewhat disturbing. The compound has one interesting characteristic: by mouth it is almost as good as by injection, a characteristic not commonly seen in morphine-like compounds. The drug has been erroneously considered by some to be nonaddicting, but numerous cases of medical addiction to it have been seen in Europe (76a).

S. Propoxyphene and dextropropoxyphene (Darvon)

The *alpha*-racemate of 4-dimethylamino-1,2-diphenyl-3-methyl-2-propionoxybutane has been called propoxyphene. Its analgesic activity, however, appears to reside in the *alpha-d*-isomer, which is known as *d*-propoxyphene or dextropropoxyphene.

Gruber *et al.* (60) first studied the analgesic efficacy of propoxyphene in a small number of patients with chronic pain. The technique involved giving capsules routinely every 4 hours (except during hours of sleep) and then relying on the memory of the patients at the end of 24 hours to determine how many hours of pain they had suffered, and how bad each hour of pain had been. During the placebo periods, the patients averaged higher scores (*i.e.*, more pain) than when on doses of 32.5 mg codeine, 50 mg propoxyphene, or 325 mg aspirin, but there were no significant differences among the latter three treatments. No significant incidence of side effects was observed with any drug.

Gruber (57) then reported on *d*-propoxyphene, studying 32.5- and 65-mg doses of this drug, similar doses of codeine, and a placebo, all given by mouth. The order of administration of the active agents was counterbalanced, but the placebo was always given for 3 days in the middle of the trial. Again, Gruber used the anamnestic interview technique described above and a crossover design. The trial involved seven cooperating hospitals and a total of 101 patients. Codeine and *d*-propoxyphene both performed better than placebo, the higher doses performed in general better than the lower doses, and the two drugs appeared indistinguishable except for side effects. Codeine produced more nausea, anorexia, constipation, abdominal pain, and dizziness than did *d*-propoxyphene, the major differences being observed at the 65-mg level. The two drugs appeared equally

likely to cause drowsiness, and there were slightly more rashes with the 65-mg dose of *d*-propoxyphene than with any other treatment.

Van Bergen *et al.* (154) came to similar conclusions regarding 65 mg codeine and 100 mg *d*-propoxyphene given orally (*cf.* codeine section), with both agents performing better than placebo, but insignificantly different from each other as analgesics. There were more gastrointestinal complaints with codeine, but the drugs produced an equal incidence of drowsiness.

Boyle *et al.* (18) (*cf.* section on codeine), on the other hand, considered 65 mg codeine a better analgesic than a similar dose of *d*-propoxyphene, and observed 3 of their 4 cases of severe nausea and vomiting in patients receiving *d*-propoxyphene.

Sadove *et al.* (141) compared oral *d*-propoxyphene and codeine in patients on an orthopedic surgical ward. They found a 32-mg dose of dextropropoxyphene not significantly better than a placebo (whereas a 30-mg dose of codeine was), but that 65 mg dextropropoxyphene and 60 mg codeine did not differ significantly.

Prockop *et al.* (133) (*cf.* section on codeine) found *d*-propoxyphene to be not significantly better than a placebo in relieving after-pains or incisional pain in puerperal patients, despite the production of a certain amount of nausea, vomiting, and drowsiness.

Gruber *et al.* (58), studying postpartum pain (*cf.* section on codeine) also failed to detect analgesic activity with 32 or 65 mg *d*-propoxyphene.

Sahagian-Edwards (142) studied the oral efficacy of *d*-propoxyphene in patients with pain from carcinoma, myeloma, lymphosarcoma, or herpes zoster, using a "demand" technique wherein success of medication was judged by the time elapsing between requests for medication for pain. The mean pain relief interval was shorter following 100 mg *d*-propoxyphene (5.4 hours) than after 100 mg meperidine (6.4 hours). This difference was statistically significant at the 5% level.

Cass and Frederik (24) found *d*-propoxyphene substantially inferior to codeine in relieving chronic pain.

Burget and Greene (20) measured the effects of 130 mg *d*-propoxyphene given orally to five healthy male volunteers, and failed to demonstrate any changes in ventilation-response curves.

There are a few reports available on the parenteral use of *d*-propoxyphene. Stoelting *et al.* (149) gave the drug, as well as meperidine and placebo, to a group of patients who had undergone surgery "or who had organic pain from other causes." At 25-mg doses, neither parenteral meperidine nor parenteral *d*-propoxyphene was better than placebo. At 50 mg, both drugs were better than placebo, but indistinguishable from each other. At 100 mg, meperidine was significantly better than *d*-propoxyphene. It is stated by the authors that more central nervous system depression was noted after meperidine than after *d*-propoxyphene, but the details of the data are not presented, other than an uninformative analysis of covariance table.

Lasagna and De Kornfeld (111), in a study of postoperative patients, found

meperidine to be more potent than *d*-propoxyphene, when both were given by injection, at 50- or 100-mg doses. Houde *et al.* (66) agreed with these findings on the basis of a study of the two drugs in cancer patients. They estimated *d*-propoxyphene to be ⅓rd as potent an analgesic as meperidine. Nausea and drowsiness were seen after both drugs.

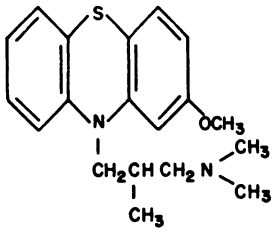
In summary, propoxyphene and *d*-propoxyphene appear to be mild analgesics when given by mouth, probably less effective than standard older oral analgesics, such as aspirin and codeine. As a compensating feature, the drugs may be less productive of side effects than more effective drugs. The parenteral form of *d*-propoxyphene would seem to have nothing to offer for clinical practice that is not already provided by other morphine-like drugs.

One is at first puzzled at the enormous popularity of oral *d*-propoxyphene in the United States, in view of its less than brilliant performance in controlled trials. This is less of a paradox than it seems, however. Like some compounds of even more dubious analgesic merit (ethoheptazine, carisoprodol), *d*-propoxyphene is sold not only alone but in combination with aspirin. Most *d*-propoxyphene is sold in combination with an "ASA" (*cf.* Section III B) preparation. Since aspirin is an excellent analgesic, and preparations containing *d*-propoxyphene can be obtained in the United States without a narcotic prescription, there are two obvious reasons for its popularity.

The narcotic status of *d*-propoxyphene is a muddled issue. The World Health Organization recommended to the Commission on Narcotic Drugs of the United Nations that governments control it as they do codeine. The U. S. Bureau of Narcotics, on the other hand, simply ruled that propoxyphene and *d*-propoxyphene did not have "addiction forming or addiction sustaining properties similar to morphine or cocaine," on the basis of comparative experiments at the U. S. Public Health Service Addiction Research Center and approximately 5 years of marketing experience on the part of the manufacturer. Propoxyphene in doses of 800 mg by mouth is considered by some postaddicts to produce effects resembling those of an opiate (47). Twelve to twenty-four hundred mg of oral propoxyphene daily suppress abstinence from morphine to a statistically significant but biologically slight degree. *d*-Propoxyphene, in doses of 355 to 600 mg, produces subjective effects termed pleasurable by postaddicts, who liken them to the effects of marihuana, heroin, morphine, and cocaine. It also reduces morphine abstinence significantly but slightly. *d*-Propoxyphene in doses of 800 mg per day does not suppress the morphine abstinence syndrome as well as 1500 mg of codeine, and attempts to use higher doses of *d*-propoxyphene have been limited by the production of toxic psychosis and other untoward effects.

There is, to be sure, little reported abuse of *d*-propoxyphene. There is also, however, essentially no abuse of codeine when it is prescribed in combination with aspirin-containing compounds (as *d*-propoxyphene usually is), probably in part because of the recognized low addiction liability of codeine, but also because abuse of aspirin or aspirin–phenacetin–caffeine preparations is likely to be limited, since toxicity from these drugs will occur before any substantial effects from overdose of codeine are manifest. One reasonably convincing case of abuse

of, and primary dependence on, *d*-propoxyphene itself has been reported (46), but the number of cases admitted to date at the U. S. Public Health Service Hospital at Lexington for abuse of *d*-propoxyphene has been small.



METHOTRIMEPRAZINE
(LEVOMEPROMAZINE)

T. Methotrimeprazine (*levomepromazine, Nozinan*)

There is considerable question as to whether most of the phenothiazine drugs now used in the clinic for one purpose or another are significant contributions to the management of pain except as adjuncts to control vomiting or provide sedation (69, 78, 94). Methotrimeprazine, however, seems to represent a distinct advance. Lasagna and De Kornfeld (110) demonstrated that 10 to 15 mg of this drug by injection were as effective as 10 mg morphine (in postoperative pain). De Kornfeld *et al.* (33) found 15 mg methotrimeprazine by injection indistinguishable from 75 mg meperidine in relieving labor pain.

Keats *et al.* (95), also studying postoperative pain, concluded that a 15-mg dose of methotrimeprazine by injection was definitely an analgesic, but somewhat less effective than 10 mg morphine. The data of Montilla *et al.* (126), on the other hand, from patients with a variety of types of pain, are in agreement, as are those of Houde and Wallenstein (working with cancer patients) (73), with the assessment of Lasagna and De Kornfeld (110).

By mouth, single 25-mg doses of methotrimeprazine were indistinguishable from a placebo in relieving postpartum pain (110).

The drug appears to lack morphine-like physical dependence properties (34, 48) and may have advantages over morphine in regard to respiratory depression. Pearson and De Kornfeld (130), studying healthy volunteers, found 15 mg methotrimeprazine to depress respiration when subjects were breathing room air, but not when they were breathing a CO_2-containing mixture, whereas 10 mg morphine depressed respiration under both sets of conditions.

In administering methotrimeprazine to ambulatory postpartum patients, Lasagna and De Kornfeld (110) observed symptoms of postural hypotension at doses that were not analgesic. Montilla *et al.* (126), and Houde and Wallenstein (73) were impressed by the considerably higher incidence and degree of sedation after this drug.

In summary, methotrimeprazine is a potent sedative and analgesic when given by injection in doses of 15 mg. The drug may be more sedative, and cause more

postural hypotension, dose for dose, than morphine, but its nonaddicting quality and its possible advantages in terms of decreased effect on respiration suggest that its clinical utility needs to be evaluated more fully. Its capacity to potentiate the analgesia of standard morphine-like compounds in man has not been tested adequately, although there was no evidence of synergistic effect on respiration when the two drugs were given together to healthy volunteers (130).

IV. ADDICTION LIABILITY

In the preceding discussion, reference to addiction liability has not been regularly made, in part because such information is available elsewhere (43, 44), and also because precise quantification of the addiction risk attendant on the *clinical* use of morphine or its substitutes is not at hand. It would seem, however, that morphine, heroin, metopon, oxymorphone, levorphanol, phenazocine, meperidine, anileridine, piminodine, methadone, dipipanone, dextromoramide, alphaprodine, and dihydromorphinone—all the compounds which are on the market and can more or less substitute for one another as analgesics—are substantially similar in their addiction liability. Analgesic drugs that appear less addicting than these—for example, codeine (63)—are also less effective as analgesics. Only in the case of nalorphine and of certain experimental drugs not yet freely available to physicians—pentazocine, cyclazocine, and methotrimeprazine —has there been claimed high-grade analgesic power and minimal addiction liability, and experience with the three latter compounds is inadequate to be sure of this point.

V. THE SEARCH FOR BETTER ANALGESICS

The large number of analgesic compounds now available has provided the physician with increased flexibility in his management of pain. Primarily, however, today's doctor is better off in possessing "backstop" drugs, *i.e.*, drugs which can be tried when standard, inexpensive, time-tested agents do not work well in individual patients. No new drug has come along which has made morphine obsolete. Most of the agents described above which can substitute for morphine as analgesic (and all such drugs now available on the market) are also addicting, and in some ways certain of the drugs that have been developed are perhaps more dangerous than morphine in this respect (*e.g.*, meperidine, which is so common a drug of addiction among physicians and nurses).

We must continue, therefore, to search for new agents. A truly nonaddicting morphine substitute would be a boon in a variety of ways. It would decrease the number of "medical addicts" (although addiction actually occurs infrequently when current drugs are properly utilized in the legitimate practice of medicine). It would decrease the problem (also minor) of diversion of medical stores of analgesics into illicit channels. Most important, perhaps, would be the increased comfort it would provide for patients in pain, who now suffer unnecessarily because of both legitimate and unreasonable apprehension among doctors and nurses that they will create addicts by using morphine or its substitutes as often as they are needed to control pain.

But there are other undesirable features of morphine: it can produce anorexia, nausea, vomiting, constipation, urinary retention, dizziness, sedation, respiratory depression, hypotension, and pruritus. Some of these "side effects" are, to be sure, put to good therapeutic use in certain situations—for example, the sedation is probably desirable in many cases of postoperative pain, labor pain, or pulmonary edema, and the constipating effect is used to control diarrhea. Yet a dissociation of these effects and analgesia would be highly desirable, and may indeed be seen more frequently in the future, in view of encouraging developments in the reports described above on nalorphine, pentazocine, cyclazocine, and methotrimeprazine. An achievement of great clinical importance would be the discovery of a morphine substitute to which significant tolerance did not develop on chronic use.

It would also be helpful to have additional analgesics which are truly as potent by mouth as by injection. Although a few of the current drugs are reasonably effective by mouth, many have to be given in much larger doses by this route, and the results even with these higher doses are sufficiently erratic and unpredictable as to be potentially dangerous.

VI. CONCLUDING REMARKS

In concluding this review, I should like to complement the quotations used at its beginning with the following remarks of Keats, Beecher, and Mosteller:

"... it is not so certain to what extent conclusions from experimentally produced pain apply to naturally occurring pain. In our practice this uncertainty is avoided by the use of clinical pain.

"... the subjectivity of the data is no serious limitation when adequate controls are used, both in the experimental design and in the collection of data. The individual variation in clinical pain is often larger, but not different in type from that found in most experimentation; this variation can be measured and accounted for ..." (85).

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Attachment-4

Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain (Review)

Moore RA, Collins SL, Rees JE, Derry S, McQuay HJ

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Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain (Review)

Moore RA, Collins SL, Rees JE, Derry S, McQuay HJ

This record should be cited as:
Moore RA, Collins SL, Rees JE, Derry S, McQuay HJ. Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. *Cochrane Database of Systematic Reviews* 1999, Issue 1. Art. No.: CD001440. DOI: 10.1002/14651858.CD001440.

This version first published online: 25 January 1999 in Issue 1, 1999.
Date of most recent substantive amendment: 16 October 1998

ABSTRACT

Background
This is an updated version of the original Cochrane review published in Issue 1, 1999. Patient surveys have shown that postoperative pain is often not managed well, and there is a need to assess the efficacy and safety of commonly used analgesics as newer treatments become available. Dextropropoxyphene is one example of an opioid analgesic that used to be widely prescribed for pain relief in combination with paracetamol under names such as Co-proxamol and Distalgesic. This drug is now only available on a named patient basis in the UK. For this group there is a provision for the supply of unlicensed co-proxamol on the responsibility of the prescriber.

Objectives
To determine the analgesic efficacy and adverse effects of single dose oral dextropropoxyphene alone and in combination with paracetamol (acetaminophen) for moderate to severe postoperative pain.

Search strategy
Published studies were identified from: MEDLINE, EMBASE, Cochrane CENTRAL up to December 2007, and the Oxford Pain Relief Database (1954 to 1994).

Selection criteria
The inclusion criteria used were: full journal publication, postoperative pain, postoperative oral administration, adult participants, baseline pain of moderate to severe intensity, double-blind design, and random allocation to treatment groups which included dextropropoxyphene and placebo or a combination of dextropropoxyphene plus paracetamol and placebo.

Data collection and analysis
Data were extracted by two review authors, and studies were quality scored.

Summed pain intensity and pain relief data were extracted and converted into dichotomous information to yield the number of participants with at least 50% pain relief. This was used to calculate the relative benefit and number-needed-to-treat-to-benefit (NNTB) for one participant to achieve at least 50% pain relief.

Main results
Eleven studies met the inclusion criteria. Six studies (440 participants) compared dextropropoxyphene with placebo, four studies (325 participants) and one individual patient meta-analysis (638 participant) compared dextropropoxyphene plus paracetamol 650 mg with placebo.

For a single dose of dextropropoxyphene 65 mg in postoperative pain the NNTB for at least 50% pain relief was 7.7 (95% confidence interval (CI) 4.6 to 22) when compared with placebo over four to six hours. There was no significant difference between the proportion of participants remedicating within four to eight hours with dextroporpoxyphene 65 mg (35%) and placebo (43%), relative risk 0.8 (0.7 to 1.03).

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For the equivalent dose of dextropropoxyphene combined with paracetamol 650 mg the NNTB was 4.4 (3.5 to 5.6) when compared with placebo. These results were compared with those for other analgesics obtained from equivalent systematic reviews. Significantly fewer participants remedicated within four to eight hours with dextropropoxyphene 65 mg combined with paracetamol 650 mg (34%) than with placebo (57%), relative risk 0.7 (0.5 to 0.8).

Pooled data showed increased incidence of central nervous system adverse effects for dextropropoxyphene plus paracetamol compared with placebo.

Authors' conclusions

Since the last version of this review no new relevant studies have been identified. The combination of dextropropoxyphene 65 mg with paracetamol 650 mg shows similar efficacy to tramadol 100 mg for single dose studies in postoperative pain but with a lower incidence of adverse effects. The same dose of paracetamol combined with 60 mg codeine appears more effective but, with the slight overlap in the 95% CI, this conclusion is not robust. Adverse effects of both combinations were similar.

Ibuprofen 400 mg has a lower (better) NNTB than both dextropropoxyphene 65 mg plus paracetamol 650 mg and tramadol 100 mg.

PLAIN LANGUAGE SUMMARY

Dextropropoxyphene in a single dose taken on its own and also with paracetamol to treat postoperative pain

This review assessed the analgesic efficacy and adverse effects that single dose oral dextropropoxyphene taken alone or in combination with paracetamol had in treating moderate to severe postoperative pain. The combination of dextropropoxyphene 65 mg with paracetamol 650 mg showed similar efficacy to that of tramadol 100 mg for single dose studies in postoperative pain but with a lower incidence of side effects. This review also highlighted that Ibuprofen 400 mg was yet more effective than both tramadol 100 mg and dextropropoxyphene 650 mg.

BACKGROUND

This is an update of a previously published review in the Cochrane Database of Systematic Reviews (Issue 1, 1999) on 'Single dose dextropropoxyphene for the treatment of acute postoperative pain'.

Dextropropoxyphene is an opioid analgesic which has been widely available since the 1950s. It used to be commonly available, particularly in combination with paracetamol under such names as Co-proxamol and Distalgesic. In 1996, there were ten million prescriptions in England for Co-proxamol alone, representing one fifth of all analgesics prescribed (opioid, non-opioid centrally acting, non-steroidal anti-inflammatory drugs (NSAIDS)) though it is not clear how much was used for postoperative pain (GSS 1996). There have been increasing limits on prescribing in recent years, especially in the UK, and to some extent in Australia. The reason for this was concern about intentional overdose in the community, and as many as 300 to 400 deaths per year were attributed to dextropropoxyphene combinations with paracetamol. The result is that the combination of dextropropoxyphene combined with paracetamol is much less prescribed in the UK with 2006 prescriptions down to 1.4 million of dextropropoxyphene plus paracetamol. This drug is now only available on a named patient basis in the UK. For this group there is a provision for the supply of unlicensed co-proxamol on the responsibility of the prescriber.

Patient surveys have shown that postoperative pain is often not managed well (Bruster 1994). There is no report of significant improvement in acute pain treatment in hospital in recent decades with the use of dextropropoxyphene, although individual units can often demonstrate excellent results. In part this is because of managerial problems rather than a lack of analgesic efficacy. The efficacy and safety of commonly used analgesics and newer treatments still require evaluation. Judging relative analgesic efficacy is difficult as clinical trials use a variety of comparators; more recent clinical trials tend to be better conducted and reported, and are larger than older ones. Efficacy can be determined indirectly by comparing analgesics with placebo in similar clinical circumstances to produce a common analgesic descriptor such as number-needed-to-treat-to-benefit (NNTB) to achieve at least 50% pain relief.

A reliable method has been developed to convert mean pain outcome values from categorical scales (percent of maximum possible pain intensity or pain relief; %maxSPID and %maxTOTPAR) into dichotomous information (number of participants with at least 50% pain relief) (Moore 1996; Moore 1997a; Moore 1997b). Other possible outcomes of interest include the requirement of patients to remedicate within a particular time window.

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OBJECTIVES

To quantitatively evaluate the analgesic efficacy and adverse effects of dextropropoxyphene, both with and without paracetamol, in postoperative pain. To compare the results with those for other analgesics assessed in the same way in order to provide evidence-based recommendations for clinical practice.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Studies were included if they were a full journal publication of single dose, randomised, double-blind, placebo controlled trials in postoperative pain. Multiple dose studies were included if the appropriate data from the first dose was available.

Studies were excluded if they did not clearly state that the interventions had been randomly allocated. Also excluded were studies of experimental pain, case reports and clinical observations. Abstracts and unpublished data were not included.

Types of participants

Only studies of adult participants with established postoperative pain of moderate to severe intensity were included.

Types of intervention

Studies were included if they contained a treatment group allocated to either dextropropoxyphene alone or a combination of dextropropoxyphene plus paracetamol. Treatments and placebo were administered orally.

Types of outcome measures

The derived pain relief outcomes used were TOTPAR (total pain relief) or SPID (summed pain intensity difference) over four to six hours or sufficient data provided to allow their calculation. The pain measures used for the calculation of TOTPAR or SPID were the five point pain relief (PR) scale with standard or comparable wording (none, slight, moderate, good, complete) or the four point pain intensity (PI) scale (none, mild, moderate, severe) or a visual analogue scale (VAS) for pain relief or pain intensity.

Also accepted were global evaluations of pain relief over four to six hours if measured on a five point scale by the participant and not the investigator. The data were extracted as dichotomous information (number of participants reporting good or excellent).

The number of participants who remedicated in the period of four to eight hours was also used, and the median time to remedication, if information was available was also assessed.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Pain, Palliative and Supportive Care Group methods used in reviews.

Electronic databases

The following electronic databases were searched:
Cochrane CENTRAL (Issue 2, 2004 for original review and Issue 4, 2007 for the update);
MEDLINE and Pre-MEDLINE from 1966 to July 1998 for the original review, and MEDLINE from January 1998 to December 2007 for the update;
EMBASE from 1980 to July 1998 for the original review and January 1998 to December 2007 for the update;
the Oxford Pain Relief database (handsearch records for the years 1954 to 1995 (Jadad 1996a).

Search strategy in MEDLINE

1. dextropropxyphene [single term MeSH]
2. dextropropoxyphene
3. OR/1-2
4. PAIN, POSTOPERATIVE [single term MeSH]
5. ((postoperative adj4 pain$) or (post-operative adj4 pain$) or post-operative-pain$ or (post$ NEAR pain$) or (postoperative adj4 analgesi$) or (post-operative adj4 analgesi$) or ("post-operative analgesi$")) [in title, abstract or keywords]
6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)) [in title, abstract or keywords]
7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")) [in title, abstract or keywords]
8. (("post surg$" or post-surg$) AND (pain$ or discomfort)) [in title, abstract or keywords]
9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 follow$ surg$")) [in title, abstract or keywords]
10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 follow$ surg$"))
11. OR/5-10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomized controlled trials.sh.
15. random allocation.sh.
16. double-blind method.sh.
17. single blind method.sh.
18. clinical trial.pt.
19. exp clinical trials/
20. (clin$ adj25 trial$).ti,ab.
21. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
22. placebos.sh.
23. placebo$.ti,ab.
24. random$.ti,ab.

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25. research design.sh.
26. OR/12-25
27. 3 AND 11 AND 26

Reference lists of retrieved reports were also manually searched. Unpublished data were not sought.

METHODS OF THE REVIEW

From each study we extracted: the number of participants treated, the mean TOTPAR or mean SPID, study duration, the dose of dextropropoxyphene and paracetamol where appropriate, and information on adverse effects. Mean TOTPAR and mean SPID values were converted to %maxTOTPAR or %maxSPID by division into the calculated maximum value (Cooper 1991). The following equations were used to estimate the proportion of participants achieving at least 50% maxTOTPAR (Moore 1997a; Moore 1997b):

Proportion with >50% maxTOTPAR = 1.33 x mean %maxTOTPAR - 11.5

Proportion with >50% maxTOTPAR = 1.36 x mean %maxSPID - 2.3

The proportions were converted to the number of participants achieving at least 50% maxTOTPAR by multiplying by the total number of participants in the treatment group. The number of participants with at least 50% maxTOTPAR was then used to calculate relative benefit and number-needed-to-treat-to-benefit (NNTB).

Relative benefit (RB) and relative risk (RR) estimates with 95% confidence intervals (CI) were calculated using the fixed-effect model (Gardner 1986). Homogeneity was assumed when P > 0.1. A statistically significant benefit of active treatment over placebo was assumed when the lower limit of the 95% CI of the RB was >1. A statistically significant benefit of placebo over active treatment was assumed when the upper limit of the 95% CI of the RB was <1. NNTB and number-needed-to-treat-to-harm (NNTH) with 95% CI were calculated (Cook 1995). The CI includes no benefit of one treatment over the other when the upper limit is represented as infinity. Calculations were performed using Excel v 5.0 on a Macintosh Performa 6320.

Dextropropoxyphene
is available as either a hydrochloride or napsylate salt. Equivalent molar doses are 65 mg of dextropropoxyphene hydrochloride and 100 mg of dextropropoxyphene napsylate. We did not distinguish between the different salts, other than to combine equivalent doses of dextropropoxyphene base.

DESCRIPTION OF STUDIES

One hundred and thirty two published studies were identified from the search as potential single dose RCTs. Two could not be obtained through either Oxford University Library or the British Library and attempts to contact the authors were unsuccessful. Five citations obtained from reference lists of the retrieved studies could not be traced by the British Library. Of the 125 retrieved studies 34 were not RCTs, 21 were not postoperative pain models or included other pain conditions, 27 were not placebo controlled, in five dextropropoxyphene was administered but was not the intervention being investigated, one was a preliminary report of a trial in progress which contained no data, one was an abstract and one was intra-muscular administration.

Of the 35 RCTs that were placebo controlled 23 were excluded. In 16 studies participants did not have baseline pain of at least moderate severity. This is methodologically important as testing the intervention on participants with established pain ensures adequate sensitivity (Lasagna 1962). In six studies pain outcome measurements other than those described in the selection criteria were used. As the method for generating dichotomous data has only been verified for the most commonly used pain scales (those described in the selection criteria) applied over four to six hours, other outcome measurements cannot be legitimately used with this technique. One study was not double-blind. The data from one study was duplicated and therefore added to the primary study which was Moore 1997. Eleven reports met our inclusion criteria and were included in the analysis.

METHODOLOGICAL QUALITY

Each report was independently scored for quality by two of the review authors using a three-item scale with a maximum score of five (see below) (Jadad 1996b); all of the review authors then met to agree upon a 'consensus' score for each report.

The quality scores for individual studies are reported in the notes section of the 'Characteristics of included studies' table. These scores were not used to weight the results in any way.

The scale used is as follows:
Is the study randomised ? If yes - 1 point
Is the randomisation procedure reported and is it appropriate ? If yes add 1 point, if no deduct 1 point
Is the study double blind ? If yes add 1 point
Is the double blind method reported and is it appropriate ? If yes add 1 point, if no deduct 1 point
Are the reasons for patient withdrawals and dropouts described ? If yes add 1 point

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RESULTS

Dextropropoxyphene versus placebo

Six studies compared dextropropoxyphene hydrochloride 65 mg (214 participants) with placebo (226 participants), and one study also compared a dose of 130 mg (25 participants) with placebo (25 participants). Two studies (Berry 1975; Bloomfield 1980) investigated postpartum pain (episiotomy), one pain following peridontal surgery (Cooper 1986), one post-urogenital surgery (Coutinho 1976), one post-gynaecological surgery (Van Staden 1971), and one after various surgical interventions (Trop 1979).

The placebo response rate (the proportion of participants experiencing at least 50% pain relief with placebo) varied between 4 and 76%. The dextropropoxyphene response rate (the proportion of participants experiencing at least 50% pain relief with dextropropoxyphene) varied between 19 and 84%. Dextropropoxyphene 65 mg was significantly different from placebo, RB 1.5 (1.2 to 1.9).

For a single dose of dextropropoxyphene 65 mg the NNTB was 7.7 (4.6 to 22) for at least 50% pain relief over a period of four to six hours compared with placebo for pain of moderate to severe intensity. One study (Trop 1979) used a dose of 130 mg of dextropropoxyphene (25 participants). The RB estimate for dextropropoxyphene 130 mg compared with placebo was 10 (1.4 to 72) and the NNTB was 2.8 (1.8 to 6.5) for at least 50% relief of pain of moderate to severe intensity over a period of five hours compared with placebo.

There was no significant difference between the proportion of participants remedicating within four to eight hours with dextroporpoxyphene 65 mg (35%) and placebo (43%), RR 0.8 (0.7 to 1.03).

Adverse effects:

Details of adverse effects are given in the notes section of the 'Characteristics of included studies' table. No participants withdrew as a result of adverse effects. All were reported as transient and of mild to moderate severity. One study reported no adverse effects with either placebo or active treatment (Berry 1975).

In one study the authors reported both dextropropoxyphene 65 mg and 130 mg to have a significantly higher incidence of 'grogginess', 'sleepiness', and 'light-headedness' than placebo (P = 0.05) (Trop 1979). However, pooled data from the four studies reporting either drowsiness, sleepiness or somnolence (Bloomfield 1980; Cooper 1986; Coutinho 1976; Trop 1979) showed no significant difference in incidence between dextropropoxyphene 65 mg (18/115) and placebo (15/121), with a RR of 1.3 (0.7 to 2.2). No other study reported light-headedness or 'grogginess' in the dextropropoxyphene group.

Dextropropoxyphene plus paracetamol versus placebo

Four studies compared dextropropoxyphene napsylate 100 mg plus paracetamol 650 mg with placebo, and one used dextropropoxyphene hydrochloride 65 mg plus paracetamol 650 mg. A total of 478 participants received dextropropoxyphene plus paracetamol, and 485 participants received placebo. Two studies (Cooper 1980; Cooper 1981) looked at pain following dental surgery (impacted third molar), two (Evans 1982; Honig 1981) post-orthopaedic surgery, and one (Moore 1997) pain following both dental and general surgery (abdominal, orthopaedic and gynaecological).

One study (Moore 1997) was a meta-analysis of individual patient data from 18 original studies providing dichotomous information (the number of participants achieving at least 50% maxTOTPAR). Eight of these studies investigated dextropropoxyphene napsylate 100 mg plus paracetamol 650 mg; one of these eight studies had been published separately by Sunshine et al and was added as a secondary study to Moore 1997.

The placebo response rate varied between 6% and 27%. The dextropropoxyphene plus paracetamol response rate varied between 25% and 57%. Dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate) plus paracetamol 650 mg was significantly superior to placebo, relative benefit 2.5 (2.0 to 3.2). For a single dose of dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate) plus paracetamol 650 mg the NNTB was 4.4 (3.5 to 5.6) for at least 50% pain relief over four to six hours compared with placebo for pain of moderate to severe intensity.

Significantly fewer participants remedicated within four to eight hours with dextropropoxyphene 65 mg combined with paracetamol 650 mg (34%) than with placebo (57%), RR 0.7 (0.5 to 0.8).

Adverse effects

Details of adverse effects are given in the notes section of the 'Characteristics of included studies' table. No participants withdrew as a result of adverse effects and all were reported as transient and of mild to moderate severity. One study (Honig 1981) did not give details of adverse effects but reported that there was no significant difference between active and placebo groups. The individual patient meta-analysis (Moore 1997) pooled data on adverse effects from all 18 placebo groups; 714 participants received placebo. Where possible the NNTH has been calculated. This is the number of participants who need to receive the treatment in order for one of them to suffer the adverse event.

Three studies reported the incidence of drowsiness or somnolence (Cooper 1980; Cooper 1981; Moore 1997). The pooled data indicated a significantly higher incidence of drowsiness and somnolence in the dextropropoxyphene combination group (57/405) than in the placebo group (55/799), with a RR of 2.1 (1.5 to 2.9) and a NNTH of 14 (9.1 to 30).

Four studies reported dizziness (Cooper 1980; Cooper 1981; Evans 1982; Moore 1997). Pooled data indicated a significantly higher incidence of dizziness with dextropropoxyphene plus paracetamol (17/428) compared with placebo (16/829), with a RR of 2.2 (1.1 to 4.3) and NNTH of 50 (24 to infinity).

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Four studies reported the incidence of headache (Cooper 1980; Cooper 1981; Evans 1982; Honig 1981). The pooled data showed dextropropoxyphene plus paracetamol (14/435) to have a significantly lower incidence of headache than placebo (51/829), with a RR of 0.5 (0.3 to 0.9) and number-needed-to-harm of -33 (-170 to -19).

Three studies reported the incidence of nausea (Cooper 1980; Cooper 1981; Moore 1997). Pooled data showed no significant difference with dextropropoxyphene plus paracetamol (12/405) than with placebo (33/799), RR 0.7 (0.4 to 1.4).

Vomiting was reported in one study (Moore 1997). The incidence of vomiting with dextropropoxyphene plus paracetamol (2/323) was not significantly different from placebo (6/714), RR 1.4 (0.3 to 6.7).

DISCUSSION

For a single dose of dextropropoxyphene 65 mg the NNTB was 7.7 (4.6 to 22) for at least 50% pain relief compared with placebo. This means that one in every eight participants with pain of moderate to severe intensity would experience at least 50% pain relief with dextropropoxyphene hydrochloride 65 mg who would not have done so with placebo. The equivalent NNTB for a single dose of dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate) plus paracetamol 650 mg was 4.4 (3.5 to 5.6), indicating higher efficacy. The CIs of the NNTB for dextropropoxyphene alone and for the combination with paracetamol overlapped.

For a single dose of dextropropoxyphene 130 mg the NNTB was 2.8 (1.8 to 6.5). This difference in NNTBs appears to show a dose response for dextropropoxyphene. However, given the overlapping CIs and the very small number of participants in the dextropropoxyphene 130 mg trial (50) this conclusion is not robust.

It was surprising that there were so few eligible randomised studies comparing either dextropropoxyphene alone or in combination with paracetamol against placebo considering the background of ten million prescriptions in 1996 in the UK for combinations with paracetamol. This probably reflects the fact that many of the studies were performed over 20 years ago when the now well established and validated methodology for single dose analgesic trials was still being developed.

A rank order of single dose analgesic efficacy in postoperative pain of moderate to severe intensity was presented previously (Collins 1998a). The additional information came from systematic reviews of single dose studies of a wide range of analgesics tested in postoperative pain which used a similar method (Collins 1998b; Moore 1997; Moore 1997c). The only analgesic whose 95% CIs does not overlap the lower limit CI for the dextropropoxyphene plus paracetamol combination was ibuprofen 400 mg (CI 2.5 to 3.0), which has a lower (better) NNTB of 2.7. However, as some patients cannot be prescribed NSAIDS it may be more appropriate to compare dextropropoxyphene with tramadol or a combination of paracetamol and codeine. The dextropropoxyphene plus paracetamol (65 mg/650 mg) combination has a slightly lower NNTB than that for tramadol 100 mg (NNTB 4.8 (3.8 to 6.1)), although the CIs overlap substantially. Paracetamol 650 mg with codeine 60 mg has a lower NNTB than both (NNTB 3.6 (2.9 to 4.5)) with less overlap of the CIs.

With dextropropoxyphene with and without paracetamol, about 35% of participants remedicated within four to eight hours. With placebo, the percentage remedicating was higher at 43% and 57% respectively. For the latter, but not the former, the difference achieved statistical significance. It is possible that, with more comparative information for other analgesics, and especially with reporting at the level of the individual patient, more and better outcomes can be found, one of which is likely to be remedication time or percentage (Moore 2005).

A single dose of dextropropoxyphene plus paracetamol (65 mg/650 mg) showed a significantly higher incidence of central nervous system adverse effects (somnolence, dizziness) than placebo. The same dose of paracetamol when combined with codeine 60 mg also showed a significantly higher incidence of dizziness and drowsiness than placebo, NNTH of 25 (7.7 to 257) and 10 (4.6 to 31) respectively. These adverse effects have also been shown for tramadol 100 mg with a lower (worse) NNTH for both dizziness (NNTH 13 (9 to 20)) and somnolence (NNTH 9 (6 to 13)) (Moore 1997). Tramadol 100 mg also showed a significantly higher incidence of nausea and vomiting than placebo. Nausea and vomiting were reported with both paracetamol combinations (dextropropoxyphene 65 mg or codeine 60 mg) but the incidence for either combination was not significantly different from placebo.

The combination of dextropropoxyphene 65 mg with paracetamol 650 mg showed similar efficacy to tramadol 100 mg for single dose studies in postoperative pain but the combination had a lower incidence of adverse effects. The same dose of paracetamol in combination with 60 mg codeine appears more effective, but with the slight overlap in the 95% CIs this conclusion is not robust. The two paracetamol combinations could not be separated for adverse effects as the NNTH CIs for both dizziness and drowsiness/somnolence overlap considerably.

AUTHORS' CONCLUSIONS

Implications for practice

Dextropropoxyphene is not particularly effective on its own in single dose postoperative use. It is far more commonly used in combination with paracetamol and our results support the assertion that this provides more effective analgesia. However, evidence

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produced by the same methodology suggests that ibuprofen 400 mg provides better analgesia for postoperative pain than the paracetamol/dextropropoxyphene combination. In some parts of the world limitations on prescribing make dextropropoxyphene increasingly difficult to obtain.

Implications for research

Dextropropoxyphene alone and in combination with paracetamol was previously extensively used. One of the major problems with reviewing such well established interventions is that the original studies may predate the development of validated analgesic trial methodology. However, a quantitative assessment of these interventions is required as a comparison for novel analgesics. Potentially more evidence may be produced by using the combination as the 'gold standard' analgesic in RCTs of new interventions. It is unlikely that new studies in acute pain will feature dextropropoxyphene alone or in combination with paracetamol, and there does not appear to be any pressing need for new studies because there are many alternative analgesics now available.

The combination of dextropropoxyphene with paracetamol has been widely used in chronic pain. Although results from single dose studies usually translate reasonably well to multiple dose situations, a method needs to be developed to quantitatively assess both efficacy and adverse effects in prolonged usage.

NOTES

The review authors consider that additional relevant studies are unlikely to be conducted, and that further updates of this review are unnecessary.

POTENTIAL CONFLICT OF INTEREST

SC and SD have no interests to declare. RAM has been a consultant for MSD. RAM and HJM have consulted for various pharmaceutical companies. RAM, HJM and JR have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. All authors have received research support from charities, government and industry sources at various times: no such support was received for this work.

ACKNOWLEDGEMENTS

We would like to thank Eija Kalso, Pascale Picard, Tomohide Suzuki and Martin Tramèr for translating studies.

SOURCES OF SUPPORT

External sources of support

- Biotechnology & Biological Sciences Research Council UK
- European Union Biomed 2 UK
- SmithKline Beecham Consumer Healthcare UK
- NHS Research and Development Health Technology Evaluation Programmes UK
- NHS Cochrane Collaboration Programme Grant Scheme UK

Internal sources of support

- Oxford Pain Research Funds UK

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* *Indicates the major publication for the study*

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TABLES

Characteristics of included studies

Study	Berry 1975
Methods	RCT, Double blind, single oral dose, parallel groups. Assessed by observer in hospital at 1/2, 1 hr, then hourly for 4 hrs. Medication taken when pain was of moderate to severe intensity.
Participants	Postpartum pain (episiotomy) n=225 Age: 15-39
Interventions	Dextropropoxyphene HCl 65 mg, n=73 Placebo, n=76
Outcomes	PI (4 point scale) standard PR (5 point scale) non-standard Global evaluation (good or excellent): Dextropropoxyphene 26/73 Placebo 18/76 r
Notes	Patients were allowed to remedicate "after a reasonable amount of time". No adverse effects were reported with either active treatment or placebo. 225 patients data analysed. No details given of withdrawals or dropouts. QS = 3
Allocation concealment	A – Adequate

Study	Bloomfield 1980
Methods	RCT, Double blind, single oral dose, parallel groups. Assessed, in hospital, by same nurse observer at 0, 1/2, 1 hr then hourly for 6 hours. Medication taken when pain of moderate to severe intensity.
Participants	Postpartum pain (episiotomy) n = 100 Age: adult
Interventions	Dextropropoxyphene HCl 65 mg, n = 25 Placebo, n = 25
Outcomes	PI (4 point scale) standard PR not measured Dextropropoxyphene was not significantly better than placebo at the 10% probability level SPID at 6 hours: Dextropropoxyphene = 9.32 Placebo = 8.12
Notes	If patients remedicated they were withdrawn from the study. Subsequent PR readings were set to the pre-treatment score. 100 patients data were analysed. 6 withdrew: either no pain relief or patients remedicated No serious adverse effects were reported & no patients withdrew as a result Dextropropoxyphene: 6/25 patients reported 12 adverse events Placebo: 9/25 patients reported 9 adverse events QS = 3
Allocation concealment	A – Adequate

Study	Cooper 1980
Methods	RCT, Double blind, single oral dose, parallel groups, mostly local anaesthetic. Self-assessed at 0, 1 hr then hourly for 4 hrs. Medication given when pain of moderate to severe intensity.

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Participants	Dental surgery n = 179 Age: Adult
Interventions	Dextropropoxyphene napsylate 100 mg + paracetamol 650 mg, n = 40 Placebo, n= 48
Outcomes	PI (4 point scale) standard PR (5 point scale) standard Global evaluation by patient (5 point scale) at 4 hrs Combination of dextropropoxyphene with paracetamol was significantly better than placebo for SPID and TOTPAR (P < 0.05). 4 hr TOTPAR: Dextropropoxyphene + paracetamol: 5.65 Placebo: 4.17
Notes	Did not state when remedication allowed. If remedicated last PR and PI score before remedication were used for all further time points. 179 patients data were analysed. No withdrawals were reported. No serious adverse events reported & no patients withdrew as a result. Dextropropoxyphene + paracetamol: 10/40 patients reported 13 adverse events. Placebo: 13/48 patients reported 17 adverse events. QS = 3
Allocation concealment	A – Adequate

Study	**Cooper 1981**
Methods	RCT, Double blind, single oral dose, parallel groups, general or local anaesthetic. Self-assessed at home at 0, 1 hr then hourly for 4 hours. Medication given when pain of moderate to severe intensity.
Participants	Dental surgery n = 248 Age: Adult
Interventions	Dextropropoxyphene napsylate100 mg + paracetamol 650 mg, n = 42 Placebo, n = 37
Outcomes	PI (4 point scale) standard PR (5 point scale) standard Global evaluation by patient (5 point scale) at 4 hrs Combination of dextropropoxyphene with paracetamol was significantly better than placebo for SPID and TOTPAR (P < 0.001). 4 hr TOTPAR: Dextropropoxyphene + paracetamol: 8.31 Placebo: 3.38
Notes	Remedication allowed at > 1 hr; if remedicated before patient withdrawn from study. If remedicated after PR recorded as 0, and last PI score prior to remedication taken for all further time points. 200 patients data were analysed. 48 excluded: 31 violated protocol, 17 did not take medication. No serious adverse events were reported & no patients withdrew as a result. Dextropropoxyphene + paracetamol: 5/42 patients reported 5 adverse events. Placebo: 4/37 patients reported 5 adverse events. QS = 4
Allocation concealment	A – Adequate

Study	**Cooper 1986**
Methods	RCT, Double blind, single oral dose, parallel groups, local anaesthetic. Self-assessed at 0, 1/2, 1 hr then hourly for 6 hours. Medication taken when pain of moderate to severe intensity.

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Characteristics of included studies (*Continued*)

Participants	Periodontal surgery n = 301 Age: adult
Interventions	Dextropropoxyphene HCl 65 mg, n = 50 Placebo, n = 56
Outcomes	PI (4 point scale) standard PR (5 point scale) standard Global evaluation by patient at 6 hrs (5 point) Dextropropoxyphene was significantly better than placebo (P < 0.1) TOTPAR at 6 hrs: Dextropropoxyphene: 7.7 Placebo: 5.2
Notes	Remedication allowed after 1 hour. Last score prior to remedication was used for the duration of the study. 212 patients data were analysed. 91 excluded: 48 did not medicate, 17 missed readings, 9 lost to follow-up, 4 remedicated at < 1 hour, 3 remedicated with slight pain, 4 uninterpretable data, 2 took other medication, 2 did not receive study medicine, 1 lost form. No serious adverse effects were reported & no patients withdrew as a result. Dextropropoxyphene: 10/50 patients reported 10 adverse effects Placebo: 5/56 patients reported 5 adverse events QS = 5
Allocation concealment	A – Adequate

Study	**Coutinho 1976**
Methods	RCT, Double blind, single oral dose, parallel groups, local anaesthetic. Assessed by observer at 0, 1/2, 1 hr then hourly for 5 hours. Medication taken when pain of moderate to severe intensity.
Participants	Urogenital surgery n = 90 (30 relevant patients) Age: adult
Interventions	Dextropropoxyphene HCl 65 mg, n = 15 Placebo, n = 15
Outcomes	PI (4 point scale) standard PR (5 point scale) nonstandard Dextropropoxyphene was not significantly better than placebo (P not given) Mean SPID @ 5 hrs: Dextropropoxyphene :4.5 Placebo: 3.3
Notes	Remedication allowed at 4 hours if no pain relief. If remedicated before 4 hours patients were withdrawn from the study. There were no exclusions or withdrawals. No serious adverse effects were reported & no patients withdrew as a result. Dextropropoxyphene: 1/15 patients reported 1 adverse event Placebo: 0/15 QS = 4
Allocation concealment	A – Adequate

Study	**Evans 1982**
Methods	RCT, Double blind, single oral dose, parallel groups, general anaesthetic. Assessed by same nurse observer at 0, 1/2, 1 hr then hourly for 4 hrs. Medication given when pain of moderate to severe intensity.
Participants	Minor orthopaedic surgery n = 120 Age: Adult
Interventions	Dextropropoxyphene HCl 65 mg + paracetamol 650 mg, n = 30

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	Placebo, n = 30
Outcomes	PI (4 point scale) standard PR (5 point scale) standard Dextropropoxyphene + paracetamol was significantly better than placebo (P < 0.05) for TOTPAR 4 hr TOTPAR: Dextropropoxyphene + paracetamol: 7.37 Placebo: 4.70
Notes	If remedicated before 4 hrs, last PI and PR score prior to remedication were used for all further time points. 120 participants data were analysed. No withdrawals were reported. No serious adverse events were reported & no patients withdrew as a result. Dextropropoxyphene + paracetamol: 16/30 patients reported 16 adverse events. Placebo: 13/30 patients reported 13 adverse events. QS = 3
Allocation concealment	A – Adequate

Study	**Honig 1981**
Methods	RCT, Double blind, single oral dose, parallel groups. Assessed by nurse observer at 0, 1/2, 1 hr then hourly for 6 hrs. Medication given when pain of moderate to severe intensity.
Participants	Postoperative - primarily orthopaedic surgery n = 196 Age: 19 - 74
Interventions	Dextropropoxyphene napsylate 100 mg + paracetamol 650 mg, n = 50 Placebo, n = 48
Outcomes	PI (4 point scale) standard PR (5 point scale) nonstandard Global evaluation by patient at 5 hrs (5 point) Combination of dextropropoxyphene with paracetamol was significantly better than placebo (P < 0.05) for SPID & TOTPAR. 6 hr TOTPAR: Dextropropoxyphene + paracetamol: 8.04 Placebo: 5.49
Notes	If patient remedicated within 6 hrs patient's overall rating of the drug was taken at time of remedication. 196 patients data were analysed. No withdrawals were reported. Authors did not give details of adverse events but reported that there was no significant difference between active and placebo groups. QS = 3
Allocation concealment	A – Adequate

Study	**Moore 1997**
Methods	Individual patient data from 18 Double blind, RCTs. Study duration 8 hrs. Single oral dose, parallel groups. Medication was given when pain of moderate to severe intensity.
Participants	Dental + general surgery n = 638 Age: Adult
Interventions	Dextropropoxyphene napsylate 100 mg + paracetamol 650 mg, n = 316 Placebo, n = 322
Outcomes	Number of patients with at least 50% of maxTOTPAR Dextropropoxyphene napsylate 100 mg + paracetamol 650 mg, n = 112/316 Placebo, n = 41/322
Notes	No remedication, withdrawals or exclusions were reported. No serious adverse events were reported & no patients withdrew as a result. Dextropropoxyphene + paracetamol: 88/316 patients reported adverse events.

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	Placebo: 66/322 patients reported adverse events. Significantly higher incidence of adverse events with active treatment than placebo for; Dizziness: RR 2.0 (1.1 - 4.0) Drowsiness/somnolence: RR 2.16 (1.5 - 3.2) QS = 4
Allocation concealment	A – Adequate

Study	**Trop 1979**
Methods	RCT, Double blind, single oral dose, parallel groups, local anaesthetic. Assessed by observer at 0, 1/2, 1 hr then hourly for 5 hours. Medication taken when pain of moderate to severe intensity.
Participants	Postoperative pain - various procedures n= 125 Age: 18 - 73
Interventions	Dextropropoxyphene HCl 65 mg, n = 25 Dextropropoxyphene HCl 130 mg, n = 25 Placebo, n = 25
Outcomes	PI (4 point scale) standard PR (5 point scale) standard Dextropropoxyphene 130 mg was significantly better than placebo (P < 0.01). SPID and TOTPAR given at 6 hours. TOTPAR: Dextropropoxyphene 65 mg: 8.54 Dextropropoxyphene 130 mg: 9.03 Placebo: 2.68
Notes	Did not state minimum time allowed for remedication. If remedicate last PR score before remedication was used for all further time points. 78 patients data were analysed. 47 were excluded due to “protocol violation”. Authors reported a significant difference from placebo for CNS AEs (P= 0.05). None serious & no withdrawals. Dextropropoxyphene HCl 65 mg: 19/25 patients reported 27 adverse events. Dextropropoxyphene HCl 130 mg:23/25 patients reported 34 adverse events. Placebo:10/25 patients reported 12 adverse events. QS = 3
Allocation concealment	A – Adequate

Study	**Van Staden 1971**
Methods	RCT, Double blind, crossover design, general anaesthetic. Self-assessed at 1 hour then hourly for 8 hrs. Medication given when pain of moderate to severe intensity.
Participants	Gynaecological surgery n = 91 Age: adult
Interventions	Dextropropoxyphene HCl 65 mg, n = 26 Placebo, n = 29
Outcomes	PI (4 point scale) standard PR measured as PID (pain intensity difference) Dextropropoxyphene was not significantly better than placebo (P not given). SPID at 4 hrs: Dextropropoxyphene HCl 65 mg: 1.64 Placebo: 1.57
Notes	Remedication allowed after 1 hour if no pain relief. PR scored as zero for all subsequent time points. 80 patients data were analysed. 11 excluded: 6 violated protocol, 2 vomited, 3 had insufficient pain. Authors reported a significant difference from placebo for CNS adverse events (P= 0.05). None serious & no withdrawals.

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	Dextropropoxyphene HCl 65 mg: 19/25 patients reported 27 adverse events. Dextropropoxyphene HCl 130 mg:23/25 patients reported 34 adverse events. Placebo:10/25 patients reported 12 adverse events. QS = 4
Allocation concealment	A – Adequate

QS = quality score
PR - pain relief
PI - pain intensity
CNS - central nervous system

Characteristics of excluded studies

Study	Reason for exclusion
Berdon 1964	Intervention given irrespective of baseline pain. Participants included children. Multiple dose regimen with no separate analysis of initial dose. 3 point pain and duration scales used after 48 hrs - not validated for the data extraction method used.
Chilton 1961	Baseline pain of moderate to severe intensity not established, multiple doses of intervention taken 4 hourly "when necessary". Global evaluation of efficacy of first and subsequent doses estimated by patient 48 hrs after surgery on a binary scale (analgesia or no analgesia).
Finch 1971	Included patients with mild baseline pain. Non standard pain scale and calculation of results.
Forbes 1982	Pain measured over 12 hours. Data presented as 12 hour SPID and TOTPAR. No other data given to allow calculation of values at 4 to 6 hours.
Gruber 1977	Does not report whether the patients had pain of at least moderate intensity on entering the trial or the pain scales used.
Hellem 1979	The first tablet was taken immediately after the dental surgery before the local anaesthetic had worn off. Therefore the included patients did not have established pain of at least moderate intensity.
Hopkinson 1973	5 point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient.
Hopkinson 1976	5 point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient.
Hopkinson 1980	5 point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient.
Liashek 1987	First dose was administered pre-operatively, data was provided for the second dose which was administered when pain was at least moderate but as a cumulative effect cannot be ruled out data from second doses was not included in the analysis.
Petti 1985	Only single blind
Prockop 1960	Analgesic regimen was prescribed as routine irrespective of baseline pain.
Reiss 1961	Interventions administered irrespective of patient's baseline pain; "469 capsules were given when patients were pain free".
Rejman 1967	Baseline pain levels were not defined, patient inclusion was based on the surgeon's preoperative judgement as to whether the patient would require postoperative analgesia.
Sadove 1961	Included patients with baseline pain defined as "slight".
Scopp 1967	Included patients with mild baseline pain.
Shiba 1972	Included patients with light (mild) baseline pain. Also assessed patients 1 week after the study medication had been administered.
Smith 1975	5 point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient.

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Characteristics of excluded studies (*Continued*)

Valentine 1959	Did not specify moderate to severe baseline pain. Used 3 point pain relief scales at unknown intervals to gauge outcome, therefore cannot extract any data.
Van Bergen 1960	"No attempt was made to determine hourly pain scores." Therefore no extractable data available. Also does not state the level of baseline pain.
Winter 1973	Included patients with baseline pain of mild intensity.
Winter 1978	Did not state patients had baseline pain of at least moderate intensity. Also used 3 point pain relief scale not validated for the data extraction method.
Young 1978	Included patients with mild to moderate baseline pain.

ANALYSES

Comparison 01. Dextropropoxyphene HCl 65mg Vs Placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)	6	440	Relative Risk (Fixed) 95% CI	1.48 [1.15, 1.90]
02 No. of patients requiring remedication within 4-8 hours	5	390	Relative Risk (Fixed) 95% CI	0.82 [0.66, 1.03]
03 No. patients reporting nausea as an adverse effect	3	211	Relative Risk (Fixed) 95% CI	1.88 [0.57, 6.16]
04 No. patients reporting headache as an adverse effect	2	156	Relative Risk (Fixed) 95% CI	1.76 [0.44, 6.99]
05 No. patients reporting drowsiness, sleepiness or somnolence as an adverse effect	4	236	Relative Risk (Fixed) 95% CI	1.22 [0.68, 2.20]

Comparison 02. Dextropropoxyphene HCl 130 mg Vs Placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)	1	50	Relative Risk (Fixed) 95% CI	10.00 [1.38, 72.39]

Comparison 03. Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)	5	963	Relative Risk (Fixed) 95% CI	2.52 [1.99, 3.20]
02 No. of patients requiring remedication within 4-8 hours	5	406	Relative Risk (Fixed) 95% CI	0.66 [0.54, 0.82]
03 No. patients reporting nausea as an adverse effect	3	1204	Relative Risk (Fixed) 95% CI	0.73 [0.37, 1.42]
04 No. patients reporting vomiting as an adverse effect	1	1037	Relative Risk (Fixed) 95% CI	0.74 [0.15, 3.63]
05 No. patients reporting dizziness as an adverse effect	4	1257	Relative Risk (Fixed) 95% CI	2.07 [1.06, 4.04]

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06 No. patients reporting headache as an adverse effect	4	1264	Relative Risk (Fixed) 95% CI	0.49 [0.27, 0.88]
07 No. patients reporting drowsiness or somnolence as an adverse effect	3	1204	Relative Risk (Fixed) 95% CI	2.06 [1.46, 2.93]

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [*therapeutic use]; Analgesics, Non-Narcotic [*therapeutic use]; Analgesics, Opioid [*therapeutic use]; Dextropropoxyphene [*therapeutic use]; Drug Therapy, Combination; Pain, Postoperative [*drug therapy]

MeSH check words

Humans

COVER SHEET

Title	Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain
Authors	Moore RA, Collins SL, Rees JE, Derry S, McQuay HJ
Contribution of author(s)	Original review SC: involved with searching, data extraction, analysis and writing. JR: involved with data extraction, analysis and writing. AM and HJM: involved with analysis and writing. Update 2008 SD and AM: carried out the searching, data extraction and analysis, and writing.
Issue protocol first published	/
Review first published	1998/4
Date of most recent amendment	18 February 2008
Date of most recent SUBSTANTIVE amendment	16 October 1998
What's New	Further studies satisfying our inclusion criteria were sought in MEDLINE (via Ovid), EMBASE (via Ovid) and Cochrane CENTRAL from January 2002 to December 2007. No further studies were identified, but some additional data was identified and included on remedication. The conclusions of the review are unchanged. There have been recent changes with regards to prescribing of the drug. The review authors consider that additional relevant studies are unlikely to be conducted, and that further updates of this review are unnecessary.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	25 January 2002
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author

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Contact address Dr Andrew Moore
Research Director
Pain Research Unit and Nuffield Department of Anaesthetics
University of Oxford
The Churchill Hospital
Old Road
Oxford
OX3 7LJ
UK
E-mail: andrew.moore@pru.ox.ac.uk
Tel: +44 1865 225674
Fax: +44 1865 226978

DOI 10.1002/14651858.CD001440

Cochrane Library number CD001440

Editorial group Cochrane Pain, Palliative and Supportive Care Group

Editorial group code HM-SYMPT

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Dextropropoxyphene HCl 65mg Vs Placebo, Outcome 01 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 01 Dextropropoxyphene HCl 65mg Vs Placebo

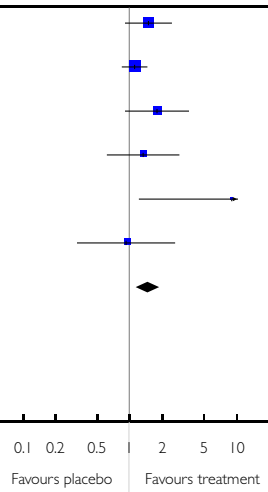
Outcome: 01 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Berry 1975	26/73	18/76		30.0	1.50 [0.90, 2.50]
Bloomfield 1980	21/25	19/25		32.3	1.11 [0.84, 1.46]
Cooper 1986	16/50	10/56		16.1	1.79 [0.90, 3.58]
Coutinho 1976	8/15	6/15		10.2	1.33 [0.61, 2.91]
Trop 1979	9/25	1/25		1.7	9.00 [1.23, 65.85]
Van Staden 1971	5/26	6/29		9.7	0.93 [0.32, 2.69]
Total (95% CI)	**214**	**226**		**100.0**	**1.48 [1.15, 1.90]**

Total events: 85 (Treatment), 60 (Placebo)

Test for heterogeneity chi-square=8.40 df=5 p=0.14 I^2 =40.5%

Test for overall effect z=3.01 p=0.003



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Analysis 01.02. Comparison 01 Dextropropoxyphene HCl 65mg Vs Placebo, Outcome 02 No. of patients requiring remedication within 4-8 hours

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 01 Dextropropoxyphene HCl 65mg Vs Placebo

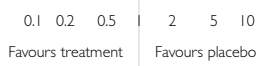
Outcome: 02 No. of patients requiring remedication within 4-8 hours

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Berry 1975	18/73	23/76		27.0	0.81 [0.48, 1.38]
Bloomfield 1980	1/25	3/25		3.6	0.33 [0.04, 2.99]
Cooper 1986	33/50	46/56		52.0	0.80 [0.64, 1.01]
Coutinho 1976	4/15	6/15		7.2	0.67 [0.23, 1.89]
Van Staden 1971	10/26	9/29		10.2	1.24 [0.60, 2.57]
Total (95% CI)	**189**	**201**		**100.0**	**0.82 [0.66, 1.03]**

Total events: 66 (Treatment), 87 (Placebo)

Test for heterogeneity chi-square=2.06 df=4 p=0.72 I² =0.0%

Test for overall effect z=1.70 p=0.09



Analysis 01.03. Comparison 01 Dextropropoxyphene HCl 65mg Vs Placebo, Outcome 03 No. patients reporting nausea as an adverse effect

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 01 Dextropropoxyphene HCl 65mg Vs Placebo

Outcome: 03 No. patients reporting nausea as an adverse effect

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bloomfield 1980	0/25	2/25		63.8	0.20 [0.01, 3.97]
Cooper 1986	3/50	0/56		12.1	7.82 [0.41, 147.84]
Van Staden 1971	3/26	1/29		24.1	3.35 [0.37, 30.21]
Total (95% CI)	**101**	**110**		**100.0**	**1.88 [0.57, 6.16]**

Total events: 6 (Treatment), 3 (Placebo)

Test for heterogeneity chi-square=3.33 df=2 p=0.19 I² =39.9%

Test for overall effect z=1.04 p=0.3

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Analysis 01.04. Comparison 01 Dextropropoxyphene HCl 65mg Vs Placebo, Outcome 04 No. patients reporting headache as an adverse effect

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 01 Dextropropoxyphene HCl 65mg Vs Placebo

Outcome: 04 No. patients reporting headache as an adverse effect

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bloomfield 1980	2/25	2/25		67.9	1.00 [0.15, 6.55]
Cooper 1986	3/50	1/56		32.1	3.36 [0.36, 31.27]
Total (95% CI)	**75**	**81**		**100.0**	**1.76 [0.44, 6.99]**

Total events: 5 (Treatment), 3 (Placebo)

Test for heterogeneity chi-square=0.67 df=1 p=0.41 I² =0.0%

Test for overall effect z=0.80 p=0.4

Analysis 01.05. Comparison 01 Dextropropoxyphene HCl 65mg Vs Placebo, Outcome 05 No. patients reporting drowsiness, sleepiness or somnolence as an adverse effect

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 01 Dextropropoxyphene HCl 65mg Vs Placebo

Outcome: 05 No. patients reporting drowsiness, sleepiness or somnolence as an adverse effect

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bloomfield 1980	2/25	4/25		26.1	0.50 [0.10, 2.49]
Cooper 1986	4/50	3/56		18.5	1.49 [0.35, 6.35]
Coutinho 1976	1/15	0/15		3.3	3.00 [0.13, 68.26]
Trop 1979	11/25	8/25		52.2	1.38 [0.67, 2.83]
Total (95% CI)	**115**	**121**		**100.0**	**1.22 [0.68, 2.20]**

Total events: 18 (Treatment), 15 (Placebo)

Test for heterogeneity chi-square=1.69 df=3 p=0.64 I² =0.0%

Test for overall effect z=0.67 p=0.5

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Analysis 02.01. Comparison 02 Dextropropoxyphene HCl 130 mg Vs Placebo, Outcome 01 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 02 Dextropropoxyphene HCl 130 mg Vs Placebo

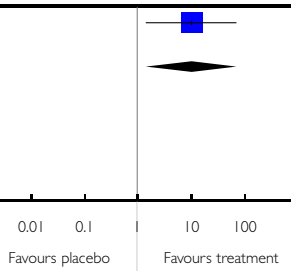
Outcome: 01 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Trop 1979	10/25	1/25		100.0	10.00 [1.38, 72.39]
Total (95% CI)	**25**	**25**		**100.0**	**10.00 [1.38, 72.39]**

Total events: 10 (Treatment), 1 (Placebo)

Test for heterogeneity: not applicable

Test for overall effect z=2.28 p=0.02



Analysis 03.01. Comparison 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo, Outcome 01 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo

Outcome: 01 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cooper 1980	14/40	11/48		13.7	1.53 [0.78, 2.98]
Cooper 1981	24/42	6/37		8.7	3.52 [1.62, 7.67]
Evans 1982	15/30	8/30		10.9	1.88 [0.94, 3.75]
Honig 1981	17/50	9/48		12.5	1.81 [0.90, 3.67]
Moore 1997	114/316	40/322		54.1	2.90 [2.10, 4.02]
Total (95% CI)	**478**	**485**		**100.0**	**2.52 [1.99, 3.20]**

Total events: 184 (Treatment), 74 (Placebo)

Test for heterogeneity chi-square=5.14 df=4 p=0.27 I^2 =22.1%

Test for overall effect z=7.59 p<0.00001

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Analysis 03.02. Comparison 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo, Outcome 02 No. of patients requiring remedication within 4-8 hours

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo

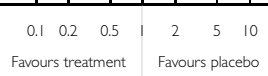
Outcome: 02 No. of patients requiring remedication within 4-8 hours

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cooper 1980	24/40	26/48		22.4	1.11 [0.77, 1.59]
Cooper 1981	7/42	20/37		20.1	0.31 [0.15, 0.65]
Evans 1982	12/30	20/30		18.9	0.60 [0.36, 1.00]
Honig 1981	24/50	37/48		35.7	0.62 [0.45, 0.86]
Moore 1997	2/41	3/40		2.9	0.65 [0.11, 3.69]
Total (95% CI)	**203**	**203**		**100.0**	**0.66 [0.54, 0.82]**

Total events: 69 (Treatment), 106 (Placebo)

Test for heterogeneity chi-square=12.08 df=4 p=0.02 I^2 =66.9%

Test for overall effect z=3.79 p=0.0002



Analysis 03.03. Comparison 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo, Outcome 03 No. patients reporting nausea as an adverse effect

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo

Outcome: 03 No. patients reporting nausea as an adverse effect

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cooper 1980	2/40	1/48		4.3	2.40 [0.23, 25.51]
Cooper 1981	1/42	1/37		5.0	0.88 [0.06, 13.59]
Moore 1997	9/323	31/714		90.7	0.64 [0.31, 1.33]
Total (95% CI)	**405**	**799**		**100.0**	**0.73 [0.37, 1.42]**

Total events: 12 (Treatment), 33 (Placebo)

Test for heterogeneity chi-square=1.11 df=2 p=0.57 I^2 =0.0%

Test for overall effect z=0.93 p=0.4

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Analysis 03.04. Comparison 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo, Outcome 04 No. patients reporting vomiting as an adverse effect

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo

Outcome: 04 No. patients reporting vomiting as an adverse effect

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Moore 1997	2/323	6/714		100.0	0.74 [0.15, 3.63]
Total (95% CI)	**323**	**714**		**100.0**	**0.74 [0.15, 3.63]**

Total events: 2 (Treatment), 6 (Placebo)

Test for heterogeneity: not applicable

Test for overall effect z=0.38 p=0.7

Analysis 03.05. Comparison 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo, Outcome 05 No. patients reporting dizziness as an adverse effect

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo

Outcome: 05 No. patients reporting dizziness as an adverse effect

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cooper 1980	2/40	1/48		8.2	2.40 [0.23, 25.51]
Cooper 1981	1/42	0/37		4.8	2.65 [0.11, 63.16]
Evans 1982	1/30	0/30		4.5	3.00 [0.13, 70.83]
Moore 1997	13/316	15/714		82.6	1.96 [0.94, 4.07]
Total (95% CI)	**428**	**829**		**100.0**	**2.07 [1.06, 4.04]**

Total events: 17 (Treatment), 16 (Placebo)

Test for heterogeneity chi-square=0.11 df=3 p=0.99 I^2 =0.0%

Test for overall effect z=2.14 p=0.03

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Analysis 03.06. Comparison 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo, Outcome 06 No. patients reporting headache as an adverse effect

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo

Outcome: 06 No. patients reporting headache as an adverse effect

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cooper 1980	0/40	3/48		8.9	0.17 [0.01, 3.21]
Cooper 1981	1/42	2/37		5.9	0.44 [0.04, 4.66]
Evans 1982	5/30	5/30		13.9	1.00 [0.32, 3.10]
Moore 1997	8/323	41/714		71.2	0.43 [0.20, 0.91]
Total (95% CI)	**435**	**829**		**100.0**	**0.49 [0.27, 0.88]**

Total events: 14 (Treatment), 51 (Placebo)

Test for heterogeneity chi-square=2.15 df=3 p=0.54 I² =0.0%

Test for overall effect z=2.40 p=0.02

Analysis 03.07. Comparison 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo, Outcome 07 No. patients reporting drowsiness or somnolence as an adverse effect

Review: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 03 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo

Outcome: 07 No. patients reporting drowsiness or somnolence as an adverse effect

Study	Treatment n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cooper 1980	9/40	5/48		12.4	2.16 [0.79, 5.93]
Cooper 1981	1/42	2/37		5.8	0.44 [0.04, 4.66]
Moore 1997	47/323	48/714		81.8	2.16 [1.48, 3.17]
Total (95% CI)	**405**	**799**		**100.0**	**2.06 [1.46, 2.93]**

Total events: 57 (Treatment), 55 (Placebo)

Test for heterogeneity chi-square=1.71 df=2 p=0.42 I² =0.0%

Test for overall effect z=4.07 p=0.00005

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Attachment-5

Eur J Clin Pharmacol (1998) 54: 107–112 © Springer-Verlag 1998

CLINICAL TRIALS

S. L. Collins · J. E. Edwards · R. A. Moore
H. J. McQuay

Single-dose dextropropoxyphene in post-operative pain: a quantitative systematic review

Received: 2 June 1997 / Accepted in revised form: 11 November 1997

Abstract *Objective*: To determine the analgesic efficacy and adverse effects of single-dose oral dextropropoxyphene alone and in combination with paracetamol for moderate to severe post-operative pain.
Methods: Published reports were identified from a variety of electronic databases including MEDLINE, Biological Abstracts, EMBASE, the Cochrane Library and the Oxford Pain Relief Database. Additional studies were identified from the reference lists of retrieved reports. Summed pain intensity and pain relief data were extracted and converted into dichotomous information to yield the number of patients with at least 50% pain relief. This was used to calculate the relative benefit and number-needed-to-treat for one patient to achieve at least 50% pain relief. Six reports (440 patients) compared dextropropoxyphene with placebo and five (963 patients) compared dextropropoxyphene plus paracetamol 650 mg with placebo.
Results: For a single dose of dextropropoxyphene 65 mg in post-operative pain the number-needed-to-treat for at least 50% pain relief was 7.7 (95% confidence interval 4.6 to 22) when compared with placebo over 4–6 h. For the equivalent dose of dextropropoxyphene in combination with paracetamol 650 mg the number-needed-to-treat was 4.4 (3.5 to 5.6) when compared with placebo. Pooled data showed increased incidence of central nervous system adverse effects for dextropropoxyphene plus paracetamol when compared with placebo. A rank order of single-dose analgesic effectiveness in post-operative pain of moderate to severe intensity obtained from similar systematic reviews is presented.
Conclusion: Dextropropoxyphene 65 mg plus paracetamol 650 mg has a similar analgesic efficacy to that of tramadol 100 mg but with a lower incidence of adverse effects. Ibuprofen 400 mg has a lower (better) number-needed-to-treat than both dextropropoxyphene 65 mg plus paracetamol 650 mg and tramadol 100 mg.

Key words Dextropropoxyphene, Post-operative pain

S.L. Collins · J.E. Edwards · R.A. Moore (✉) · H.J. McQuay
Pain Research and Nuffield Department of Anaesthetics,
University of Oxford, Oxford Radcliffe Hospital,
The Churchill, Headington, Oxford OX3 7LJ,
United Kingdom
Tel.: +44-1865 226161, Fax: +44-1865 226160,
e-mail: andrew.moore@pru.ox.ac.uk

Introduction

Dextropropoxyphene is an opioid analgesic which has been widely available since the 1950s. It is commonly found, particularly in combination with paracetamol, under such brand names as co-proxamol and distalgesic. In 1996, there were 10 million prescriptions in England for co-proxamol alone representing one-fifth of all analgesics prescribed (opioid, non-opioid and non-steroidal anti-inflammatory drugs) though it is not clear how much was used for post-operative pain [1].

Patient surveys have shown that post-operative pain is often not managed well [2] and there is a growing need to assess the efficacy and safety of commonly used analgesics as newer treatments become available. Judging relative analgesic efficacy is difficult as clinical trials use a variety of comparators. It can, however, be determined indirectly by comparing analgesics with placebo in similar clinical circumstances to produce a common analgesic descriptor, such as the number-needed-to-treat for at least 50% pain relief.

A reliable method has been developed to convert mean pain outcome values from categorical scales (percentage of maximum possible pain intensity or pain relief %maxSPID and%maxTOTPAR) into dichotomous information (number of patients with at least 50% pain relief) [3–5]. Using this method we have produced a quantitative systematic review of the analgesic efficacy of dextropropoxyphene, both with and without paracetamol, allowing comparison with other analgesics.

Methods

MEDLINE (1966 – November 1996), EMBASE (1980–1996), the Cochrane Library (November 1996), Biological Abstracts (1985–1996), and the Oxford Pain Relief Database (1950–1994) [6] were searched for randomised controlled trials of dextropropoxyphene, and its combinations in post-operative pain. The words 'dextropropoxyphene', 'd-propoxyphene', 'propoxyphene', 'random*', 'clinical trial', 'trial', 'study', 'analgesi*', 'pain' and 41 brand names (including distalgesic and co-proxamol) [7] were used in a broad free-text search without restriction to language. Additional reports were identified from reference lists of retrieved articles and reviews. Unpublished data were not sought.

The inclusion criteria used were: full journal publication, post-operative pain, post-operative oral administration, adult patients, baseline pain of moderate to severe intensity, double-blind design, and random allocation to treatment groups which included dextropropoxyphene and placebo or a combination of dextropropoxyphene plus paracetamol and placebo. Pain outcomes used were total pain relief (TOTPAR) or summed pain intensity difference (SPID) over 4–6 hours or sufficient data provided to allow their calculation. Pain measures which allowed for the calculation of TOTPAR or SPID were a standard five-point pain relief scale (none, slight, moderate, good, complete) or a standard four-point pain intensity scale (none, mild, moderate, severe).

From each study we extracted: the number of patients treated, the mean TOTPAR or mean SPID, study duration, the dose of dextropropoxyphene and paracetamol where appropriate, and information on adverse effects. Mean TOTPAR and mean SPID values were converted to %maxTOTPAR or %maxSPID by division into the calculated maximum value [8]. The following equations were used to estimate the proportion of patients achieving at least 50% maxTOTPAR [4, 5]:

$$\text{Proportion with} > 50\%\text{maxTOTPAR} = 1.33 \times \text{mean}\%\text{maxTOTPAR} - 11.5 \quad (1)$$

$$\text{Proportion with} > 50\%\text{maxTOTPAR} = 1.36 \times \text{mean}\%\text{maxSPID} - 2.3 \quad (2)$$

The proportions were converted to the number of patients achieving at least 50% maxTOTPAR by multiplying by the total number of patients in the treatment group. The number of patients with at least 50% maxTOTPAR was then used to calculate relative benefit and number-needed-to-treat.

Relative benefit and relative risk estimates with 95% confidence intervals were calculated using the fixed effects model [9]. Homogeneity was assumed at $P > 0.1$. A statistically significant benefit of active treatment over placebo was assumed when the lower limit of the 95% confidence interval (CI) of the relative benefit was >1. A statistically significant benefit of placebo over active treatment was assumed when the upper limit of the 95% CI of the relative benefit was <1. The number-needed-to-treat and the number-needed-to-harm with 95% CI were calculated [10]. CI includes no benefit of one treatment over the other when the upper limit is represented as infinity.

Dextropropoxyphene is available as either the hydrochloride or napsylate salt. Equivalent molar doses are 65 mg of dextropropoxyphene hydrochloride and 100 mg of dextropropoxyphene napsylate.

Results

A total of 130 published articles were identified. Two could not be obtained and attempts to contact the authors were unsuccessful. Five citations obtained from reference lists of retrieved reports could not be traced by the British Library. Of the 123 retrieved reports 33 were not randomised controlled trials, 24 were not post-operative pain models or included other pain conditions, 21 were not placebo controlled, and in five dextropropoxyphene was used as a rescue analgesic only.

Of the 40 randomised controlled trials that were placebo controlled, patients did not have baseline pain of at least moderate severity in 10 studies, in 16 there were no pain outcomes which were compatible with our inclusion criteria, and two trials were not double-blind. The data from one study was duplicated and therefore one of the duplicates [11] was excluded. Eleven reports met our inclusion criteria and were included in the analysis.

Details of the individual studies, including references for those we could not obtain, are available from the authors or on the World Wide Web (http://www.jr2.ox.ac.uk/Bandolier/painres/dextropr/dextropr.html).

Dextropropoxyphene versus placebo

Six reports compared dextropropoxyphene hydrochloride 65 mg (214 patients) with placebo (226 patients), and one trial also compared a dose of 130 mg (25 patients) with placebo (25 patients). Two trials [12, 13] investigated post-partum pain (episiotomy), one pain following peridontal surgery [14], one post-urogenital surgery [15], one post-gynaecological surgery [16], and one pain after various surgical interventions [17].

The placebo response rate (the proportion of patients experiencing at least 50% pain relief with placebo) varied between 4% and 76%. The dextropropoxyphene response rate (the proportion of patients experiencing at least 50% pain relief with dextropropoxyphene) varied between 19% and 84% (Fig. 1). Data were homogeneous, $P = 0.13$. Dextropropoxyphene 65 mg was significantly different from placebo, relative benefit 1.5 (1.2 to 1.9) (Table 1).

For a single dose of 65 mg dextropropoxyphene, the number-needed-to-treat was 7.7 (4.6 to 22) for at least 50% pain relief over a period of 4–6 h compared with placebo for pain of moderate to severe intensity. One trial [17] used a dose of 130 mg of dextropropoxyphene (25 patients). The relative benefit estimate for dextropropoxyphene 130 mg compared with placebo was 10 (1.4–73). The number-needed-to-treat was 2.8 (1.8–6.5) for at least 50% pain relief over a period of 5 h compared with placebo for pain of moderate to severe intensity.

Adverse effects

Details of adverse effects are given in Table 2. No patients withdrew from the trial as a result of adverse effects, which were all reported to be transient and of mild to moderate severity. One study reported no adverse effects with either placebo or active treatment [12].

In one study the authors reported both dextropropoxyphene 65 mg and 130 mg to have a signifi-

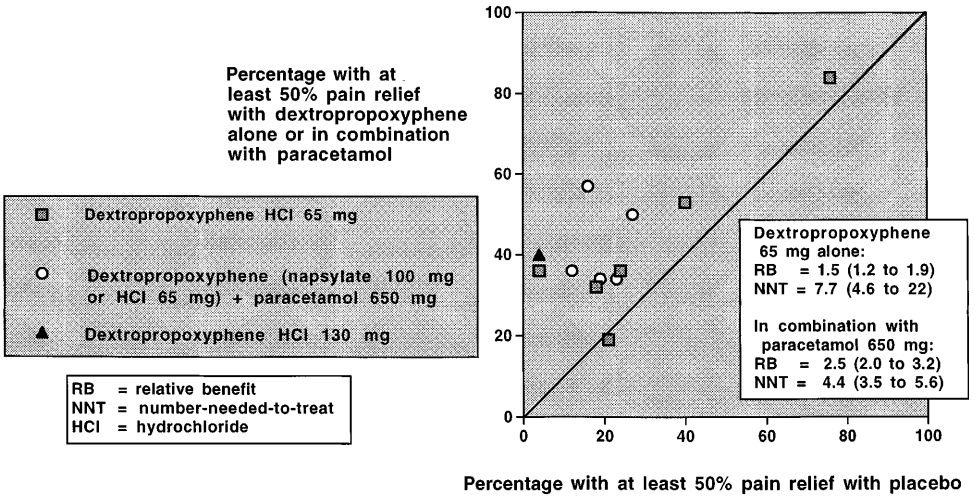

Fig. 1 Dextropropoxyphene or dextropropoxyphene plus paracetamol compared with placebo in randomised controlled trials of single oral doses in patients with moderate or severe postoperative pain for at least 50% pain relief

Table 1 Summary of relative benefit and number-needed-to-treat for trials of dextropropoxyphene and dextropropoxyphene plus paracetamol against placebo. Pooled relative benefit estimates were calculated using the fixed effects model [9]. (*CI* confidence interval)

Number of trials	Dose of dextropropoxyphene	No. of patients with >50% pain relief: dextropropoxyphene	No. of patients with >50% pain relief: placebo	Relative benefit (95% CI)	Number-needed-to-treat (95% CI)
6	65 mg	85/214	60/226	1.5 (1.2 to 1.9)	7.7 (4.6 to 22)
1	130 mg	10/25	1/25	10.0 (1.4 to 73)	2.8 (1.8 to 6.5)
Number of trials	**Dose of dextropropoxyphene (plus paracetamol 650 mg)**	**No. of patients with >50% pain relief: dextropropoxyphene plus paracetamol**	**No. of patients with >50% pain relief: placebo**	**Relative benefit (95% CI)**	**Number-needed-to-treat (95% CI)**
5	65 mg hydrochloride or 100 mg napsylate	184/478	74/485	2.5 (2.0 to 3.2)	4.4 (3.5 to 5.6)

cantly higher incidence of grogginess, sleepiness, and light-headedness than placebo ($P = 0.05$) [17]. However, pooled data from the four trials reporting either drowsiness, sleepiness or somnolence [13–15, 17] showed no significant difference in incidence between dextropropoxyphene 65 mg (18/115) and placebo (15/121), with a relative risk of 1.3 (0.7–2.2). No other trial reported light-headedness or grogginess in the dextropropoxyphene group.

Dextropropoxyphene plus paracetamol versus placebo

Four reports compared dextropropoxyphene napsylate 100 mg plus paracetamol 650 mg with placebo, and one used dextropropoxyphene hydrochloride 65 mg plus paracetamol 650 mg. A total of 478 patients received dextropropoxyphene plus paracetamol, and 485 patients received placebo. One report [18] was a meta-analysis of individual patient data from 18 studies with dichotomous information (the number of patients achieving at least 50% maxTOTPAR); eight investigated dextropropoxyphene napsylate 100 mg plus paracetamol 650 mg. Only one of the studies had been published and we excluded the duplicate publication [11]. Two reports [19, 20] studied pain following dental surgery (impacted third molar), two [21, 22] post-orthopaedic surgery, and one [18] pain following both dental and general surgery (abdominal, orthopaedic and gynaecological).

The placebo response rate varied between 6% and 27%. The dextropropoxyphene plus paracetamol response rate varied between 25% and 57% (Fig. 1). The trial results were homogeneous ($P = 0.35$). Dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate) plus paracetamol 650 mg was significantly superior to placebo, relative benefit 2.5 (2.0–3.2) (Table 1). For a single dose of dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate) plus paracetamol 650 mg the number-needed-to-treat was 4.4 (3.5–5.6) for at least 50% pain relief over 4–6 h compared with placebo for pain of moderate to severe intensity.

Adverse effects

Details of adverse effects are given in Table 2. No patients withdrew from the trial as a result of adverse effects, which were all reported to be transient and of mild to moderate severity. One trial [22] did not give details of adverse effects but reported that there was no significant

Table 2 Summary of adverse effects for trials of dextropropoxyphene and dextropropoxyphene plus paracetamol against placebo. Pooled relative risk estimates were calculated using the fixed effects model [9]. (*CI* confidence interval, *N/A* not calculated because no significant difference from placebo was shown for relative risk)

Number of trials	Adverse effect	No. of patients with adverse effects: dextropropoxyphene	No. of patients with adverse effects: placebo	Relative risk (95% CI)	Number-needed-to-harm (95% CI)
3	Nausea	6/101	3/110	2.1 (0.6 to 7.7)	N/A
3	Drowsiness/ sleepiness/ somnolence	18/115	15/121	1.2 (0.7 to 2.2)	N/A
2	Headache	5/75	3/81	1.8 (0.4 to 7.0)	N/A
Number of trials	**Adverse effect**	**No. of patients with adverse effects: dextropropoxyphene plus paracetamol**	**No. of patients with adverse effects: placebo**	**Relative risk (95% CI)**	**Number-needed-to-harm (95% CI)**
3	Nausea	12/405	33/799	0.7 (0.4 to 1.4)	N/A
1	Vomiting	2/323	6/714	1.4 (0.3 to 6.7)	N/A
4	Dizziness	17/428	16/829	2.2 (1.1 to 4.3)	50 (24 to ∞)
3	Drowsiness/ somnolence	57/405	55/799	2.1 (1.5 to 2.9)	14 (9.1 to 30)
4	Headache	14/435	51/829	0.5 (0.3 to 0.9)	−33 (−170 to −19)

difference between active and placebo groups. The individual patient meta-analysis [18] pooled data on adverse effects from all 18 placebo groups; 714 patients received placebo.

Three studies reported the incidence of drowsiness or somnolence [18–20]. The pooled data indicated a significantly higher incidence in the dextropropoxyphene combination group (57/405) than in the placebo group (55/799), with a relative risk of 2.1 (1.5–2.9) and a number-needed-to-harm of 14 (9.1–30).

Four trials reported dizziness [18–21]. Pooled data indicated a significantly higher incidence of dizziness with dextropropoxyphene plus paracetamol (17/428) compared with placebo (16/829), with a relative risk of 2.2 (1.1–4.3) and number-needed-to-harm of 50 (24–∞).

Four trials reported the incidence of headache [19–22]. The pooled data showed dextropropoxyphene plus paracetamol (14/435) to have a significantly lower incidence of headache than placebo (51/829), with a relative risk of 0.5 (0.3–0.9) and number-needed-to-harm of −33 (−170–−19).

Three trials reported the incidence of nausea [18–20]. Pooled data showed no significant difference with dextropropoxyphene plus paracetamol (12/405) than with placebo (33/799), relative risk 0.7 (0.4–1.4).

Vomiting was reported in one study [18]. The incidence of vomiting with dextropropoxyphene plus paracetamol (2/323) was not significantly different from placebo (6/714), relative risk 1.4 (0.3–6.7).

Discussion and conclusions

For a single dose of dextropropoxyphene 65 mg the number-needed-to-treat was 7.7 (4.6–22) for at least 50% pain relief compared with placebo. This means that one in every eight patients with pain of moderate to severe intensity would experience at least 50% pain relief with dextropropoxyphene hydrochloride 65 mg, who would not have done so with placebo. The equivalent number-needed-to-treat for a single dose of dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate) plus paracetamol 650 mg was 4.4 (3.5–5.6), indicating higher efficacy. The CIs of dextropropoxyphene alone and the combination with paracetamol overlapped.

For a single dose of dextropropoxyphene 130 mg, the number-needed-to-treat was 2.8 (1.8–6.5). This appears to show a dose response for dextropropoxyphene. However, given the overlapping CIs and the very small number of patients in the dextropropoxyphene 130 mg trial (50), this conclusion is not robust.

It was surprising that there were so few eligible randomised studies comparing either dextropropoxyphene alone or in combination with paracetamol against placebo, given the fact that 10 million prescriptions were made in 1996 in the UK for combinations with paracetamol. This probably reflects the fact that dextropropoxyphene has long been available, antedating the necessity for intense trial activity associated with the registration of a novel drug.

A rank order of single-dose analgesic efficacy in post-operative pain of moderate to severe intensity is presented in Fig. 2. The additional information came from systematic reviews of single-dose studies in post-operative pain which used a similar method. The only analgesic whose CIs did not overlap the lower limit CI for the dextropropoxyphene plus paracetamol combination was ibuprofen 400 mg, which has a lower (better) number-needed-to-treat. However, as some patients cannot be prescribed non-steroidal anti-inflammatory drugs, it may

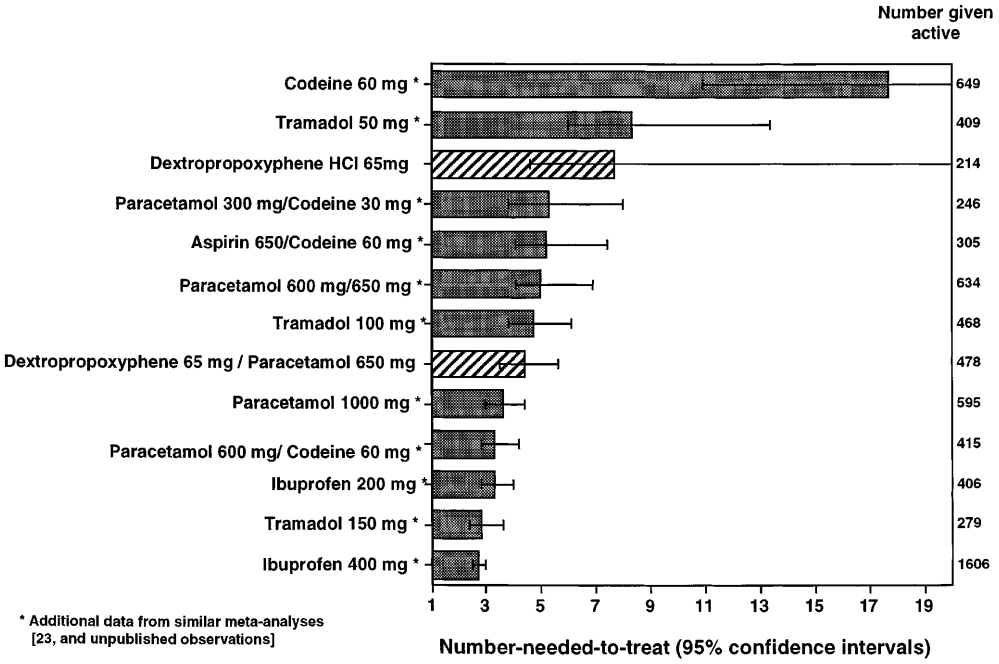

Fig. 2 Numbers-needed-to-treat for single oral doses of analgesics in moderate or severe postoperative pain compared with placebo for at least 50% pain relief

be more appropriate to compare dextropropoxyphene with tramadol. Figure 2 shows the dextropropoxyphene-plus-paracetamol combination to have a slightly lower number-needed-to-treat than tramadol 100 mg, although the CIs overlap substantially.

A single dose of dextropropoxyphene 65 mg plus paracetamol 650 mg showed a significantly higher incidence of central nervous system adverse effects (somnolence, dizziness) than placebo (Table 2). These adverse effects have also been shown for tramadol 100 mg with a lower (worse) number-needed-to-harm for both dizziness and somnolence [18]. Tramadol 100 mg also showed a significantly higher incidence of nausea and vomiting than placebo. These adverse effects were reported with dextropropoxyphene 65 mg plus paracetamol 650 mg but the incidence was not significantly different from placebo.

The combination of dextropropoxyphene 65 mg with paracetamol 650 mg showed similar efficacy to tramadol 100 mg for single-dose studies in post-operative pain with a lower incidence of adverse effects.

Acknowledgements This study was supported by grants from the Biotechnology & Biological Sciences Research Council, SmithKline Beecham Consumer Healthcare, European Union Biomed 2, NHS R and D Health Technology Evaluation Programmes, and Pain Research Funds. We would also like to thank Eija Kalso, Pascale Picard, Tomohide Suzuki and Martin Tramèr for translating reports.

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Attachment-6

Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol

A Li Wan Po, W Y Zhang

Abstract

Objective: To evaluate the comparative efficacy and tolerability of paracetamol-dextropropoxyphene combination and paracetamol through a systematic overview of randomised controlled trials.
Design: Systematic retrieval of trials of paracetamol-dextropropoxyphene, paracetamol, and placebo to allow pooling of results from head to head comparison trials and single active placebo controlled trials.
Subjects: 2231 patients with postsurgical pain, arthritis, and musculoskeletal pain reported in 26 randomised controlled trials.
Main outcome measures: Sum of difference in pain intensity; response rate ratio and difference in response rate with response defined as moderate to excellent pain relief; and rate ratio and rate difference of side effects.
Results: The difference in pain intensity between paracetamol-dextropropoxyphene and paracetamol was 7.3% (95% confidence interval −0.2 to 14.9). The response rate ratio for the combination and paracetamol was 1.05 (0.8 to 1.3) on the basis of the head to head trials. Indirect comparisons produced quantitatively consistent results. Compared with placebo, the combination produced more dizziness (3.1; 1.1 to 8.9) whereas paracetamol resulted in more drowsiness (1.8; 1.1 to 2.9).
Conclusion: On the basis of data on analgesic efficacy and acute safety in both head to head and indirect comparisons, there is little objective evidence to support prescribing a combination of paracetamol and dextropropoxyphene in preference to paracetamol alone in moderate pain such as that after surgery.

Introduction

Analgesic drug combinations are used widely both for self medication and as prescribed medication. In a recent survey of 30 teaching hospitals in the United Kingdom, combination products accounted for 73% of all paracetamol issues.[1] Co-proxamol, a combination product containing ~~650~~ 325 mg paracetamol and 32.5 mg dextropropoxyphene hydrochloride, was the most popular prescription, accounting for 35%.[1] Such widespread use has attracted considerable controversy. Surprisingly, the debate to date has been based on qualitative assessments of the literature. Haigh, for example, claims that the combination of 1 g paracetamol and 30-60 mg codeine, instead of dihydrocodeine, given as separate tablets gives greater analgesia in acute pain, but he provides no supporting data.[1] In response, Sykes et al said that co-proxamol has been popular "perhaps because the combination does indeed work well, because it is generally well tolerated and because patients like it."[2] Cynics would point out that similar claims can be made for the use of tiger bones in rheumatic pain. To help to enlighten the debate we conducted a systematic overview of the relevant literature. Earlier meta-analyses have shown that while codeine may add to the analgesic efficacy of paracetamol, the additive effect is probably of no clinical significance at the currently used doses.[3 4] We conducted a systematic review of the relevant randomised controlled trials to assess whether dextropropoxyphene adds to the analgesic effect of paracetamol.

Centre for Evidence Based Pharmacotherapy, Department of Pharmaceutical Sciences, University of Nottingham, Nottingham NG7 2RD

A Li Wan Po, *professor of clinical pharmaceutics*

W Y Zhang, *research fellow*

Correspondence to: Professor Li Wan Po

BMJ 1997;315:1565–71

Materials and methods

Retrieval of published studies

Reports of randomised controlled trials of paracetamol and dextropropoxyphene were identified through a systematic search consisting of electronic searching of Medline and BIDS (Embase and the Institute of Scientific Information (ISI) databases). The computerised searches covered the period 1966 to the end of March 1997. The same broad search strategy was used in both Medline and BIDS. A medical subject headings (MeSH) search in Medline was undertaken first, if possible, followed by a keyword search through both title and abstract. As Medline has standard terms (paracetamol entered as acetaminophen, dextropropoxyphene entered as propoxyphene) only one term was used. For BIDS, both terms were needed as keywords. We also conducted historical searches through the reference lists of reports retrieved through the electronic searches and review articles. Publications were retrieved as hard copies for subsequent study.

Inclusion and exclusion criteria

Only randomised controlled trials were included. Quality scoring of trials was restricted to this threshold criterion because of broad support on the critical importance of these items but less so on other items often included in quality scores. To facilitate interpretation, only studies including evaluations of

conventional oral formulations of paracetamol and dextropropoxyphene hydrochloride or dextropropoxyphene napsylate were included in the meta-analysis. Formulations intended for administration by non-oral routes were excluded from the meta-analysis. A randomised study was defined in our inclusion criteria as one in which the investigators reported it as being randomised without necessarily defining the randomisation method explicitly. If a clearly non-random method (for example, dates of birth or sequential assignment) was used, however, then our protocol would have led to rejection of the trial concerned for the main analysis, although it would have been included in our sensitivity analysis. No trial fell in this category.

Data extraction

Data extraction was undertaken by two authors independently. Any disagreement was solved by discussion. A customised form was used to record the authors of the study, the year of publication, study design (double blind or single blind, crossover or parallel), type of pain (dental, postpartum, other surgical), dose regimen, population characteristics (age, weight, baseline pain intensity, sample size, etc), and outcomes (pain relief, pain intensity, remedication). In addition, we recorded the proportion of patients reporting any side effect, nausea, vomiting, stomach ache, dizziness, drowsiness, and headache.

Statistical analysis

The sum of pain intensity difference is a widely used outcome in the assessment of analgesics. Patients are asked to grade their pain intensity on a scale such as 0 to 3 at time intervals, and the difference in pain intensity relative to time zero or immediately before drug administration is calculated. The differences in pain intensity so calculated at different time points are summed to give the sum of the pain intensity difference (SPID). We adjusted this figure as previously described to account for differences in the scale anchors by using the equation shown:

$$\text{SPID\%} = (\text{SPID}/(\text{maximum score} - \text{minimum score}) \times n) \times 100$$

where the maximum and minimum pain intensity scores are from the relevant scales.[4 5]

Standard errors were abstracted from the individual studies if provided. When the SEs or SDs and sample sizes were not provided or could not be calculated on the basis of the data reported, the pooled interstudy SE from studies reporting variances was used. All SEs were expressed in terms of units consistent with the outcome measures—that is, the percentage sum of the pain intensity difference.

The difference in effect (d_i) between the treatment and placebo or two treatments was derived as previously described.[4] Pooled SDs between the treatment and placebo or two treatments were calculated first, and the SE of the difference was obtained from this pooled estimate. The inverse of the squared SE (sampling variance) of the difference in response was used as the weight (w_i). For estimating the weighted pooled difference in effect (d), the method previously described was used.[4]

Efficacy was also estimated with the response rate ratio (ResRR), defined as the proportion of patients reporting moderate to excellent or greater than 50% pain relief during the observation period in the treatment group relative to the control group. Adverse effects were estimated with rate ratio (or relative risk) and rate difference in terms of any side effect, nausea, vomiting, dizziness, drowsiness, etc. In all cases, Rothman's method was used for interval estimation of the individual rate ratio and rate difference.[6]

In the pooling of relative risk and rate difference, the method of DerSimonian and Laird[7] as implemented by Whitehead and Whitehead[8] was used. The number needed to treat was estimated from the pooled rate difference.[9] A random effects model was used if trials were heterogeneous on the basis of the Q statistic for heterogeneity.[7 8] Results of both fixed and random effects modelling are shown when appropriate in the tables and graphs.

Paracetamol and the paracetamol-dextropropoxyphene combination were compared in two ways: firstly, indirectly, by estimating the pooled effects of paracetamol against placebo and the combination against placebo, and then comparing the two estimates; and, secondly, directly, by using the head to head comparisons without reference to the placebo group, even if provided.

In pooling the studies we considered the terms propoxyphene and dextropropoxyphene as equivalent, as only the dextro isomer of the analgesic is in clinical use. The salt forms, hydrochloride and napsylate, were assumed to have no effect on the systemic activity of the analgesic, and a dose of 65 mg of the hydrochloride was assumed to be equivalent to 100 mg of the napsylate, as previously described by Beaver.[10]

For each of the studies we calculated a standardised baseline pain score index (BPS%) to enable an comparison between trials of the mean severity of pain of the patients at entry. This was calculated by taking the mean baseline score reported in any given trial divided by the maximum score possible on the scale used. For example, if the scale used had a maximum score of 3 and the baseline score was 2 then the baseline score index was 67%. This adjusted for the different values used for anchoring the scales which were consistent at a descriptive level: no pain = 0% to severe pain = 100%.

Results

Characteristics of eligible trials

We retrieved 26 eligible trials.[11–36] Six trials were three-armed, head to head comparisons of paracetamol-dextropropoxyphene, paracetamol, and placebo (table 1)[11–16]; 21 trials were two-armed, placebo controlled trials, 15 of which compared paracetamol with placebo.[17–30] The six other trials compared the paracetamol-dextropropoxyphene combination against placebo (table 2).[31–36] One of the reports included two paracetamol versus placebo trials.[18] Two of the three-armed trials included 1000 mg paracetamol as a comparator.[13 14] That arm was excluded from both studies. Except for two trials[16 31] all trials were single dose comparisons (tables 1 and 2). Data from the two multidose trials were included in sensitivity analyses of adverse effects. One report included no quantitative efficacy data at all.[31] Another study reported efficacy in terms of pain score and pain relief in per cent per day, but in the author's description it was said

that patients were not instructed to keep track in any particular way.[16] Not all the trials reporting values for the sum of the pain intensity difference also reported response rates for efficacy. Therefore, to obtain the pooled estimates the trials included in the different analyses do not necessarily match.

Of the four abstracts identified,[37–40] three were from the same author. We did not pursue the authors for the raw data because all the reports were at least 10 years old. One trial published in German[41] and one published in French[42] were also identified. The German trial included paracetamol but only at a dose of 1000 mg, outside the focus of our study. The French trial evaluated efficacy of the analgesics in pain induced by voluntary interruption of pregnancy by mefepristone, and was considered not appropriate for combination with studies of the types of pain considered in this review.

Quality of trials

Our inclusion criteria ensured that all the trials included in our pooled estimates of effect were protected from the major threats to interval validity. The trials were all randomised, controlled, and double blinded, and we could not see any obvious threats to these in the reports, although we adopted a permissive stance with respect to randomisation by assuming efficient randomisation even if the authors did not describe the randomisation scheme in detail. Most trials failed to report variance of the sum of the differences in pain intensity associated with the responses

Table 1 Characteristics of randomised controlled trials: three-armed, head to head with active and placebo controls

First author of trial	Design	Type of pain	Par-dxp (mg)	Paracetamol (mg)	Period (hours)	Mean age (years)	Mean weight (kg)	BPS %	No of subjects: Par-dxp (n=232)	No of subjects: Paracetamol (n=229)	No of subjects: Placebo (n=229)	Sum of difference in pain intensity (SE): Par-dxp	Sum of difference in pain intensity (SE): Paracetamol	Sum of difference in pain intensity (SE): Placebo	No with moderate to excellent pain relief: Par-dxp	No with moderate to excellent pain relief: Paracetamol (n=237)	No with moderate to excellent pain relief: Placebo (n=77)
Cooper[11]	DB-P	3rd molar extraction	650+100	650	4	23.5	62.4	76	42	37	37	3.6	2.8	0.1	23	20	6
Hopkinson[12]	DB-P	Episiotomy	650+65	650	4	26.1	NR	58	50	50	50	5.4	4.4	3.1	36	34	21
Hopkinson[13]	DB-P	Postpartum	650+100	1000*	4	24.6	66.7	70	74	75	75	5.1	6.6	2.6	60	64	50
Huskisson[14]	DB-C	Arthritis	650+65F	1000*	6	NR	NR	NR	23	23	23	NR	NR	NR	NR	NR	NR
Liashek[15]	DB-P	3rd molar extraction	650+100	650	4	18.3	71.5	NR	11	12	12	3.1 (1.2)	−0.5 (1.4)	−2.3 (1.0)	NR	NR	NR
Messick[16]	DB-C	Musculoskeletal disorders	650+100	650	48†	NR	NR	NR	32	32	32	NR	NR	NR	NR	NR	NR

NR=not reported
Par-dxp=paracetamol-dextropropoxyphene; DB-P=double blind, parallel trial; DB-C=double blind, cross over trial; BPS%=percentage of baseline pain score relative to maximum pain score on scale 0%=no pain, 50%=moderate pain, 100%=severe pain.
*Excluded from analysis because of 1000 mg dose of paracetamol.
†Multidose studies excluded from pooling.

Table 2 Characteristics of randomised controlled trials: two-armed placebo controlled trials

First author of trial	Design	Type of pain	Paracetamol (mg)	Dxp (mg)	Period (hours)	Mean age (years)	Mean weight (kg)	BPS%	No of subjects: Treatment	No of subjects: Placebo	Sum of difference in pain intensity (SE): Treatment	Sum of difference in pain intensity (SE): Placebo	No with moderate to excellent pain relief: Treatment	No with moderate to excellent pain relief: Placebo
Paracetamol *v* placebo									(n=585)	(n=559)			(n=109)	(n=47)
Bloomfield[17]	DB-P	Postpartum	650	0	6	NR	NR	NR	22	26	10.8 (0.6)	8.4 (0.6)	NR	NR
Cooper[18]	DB-P	Tooth removal	650	0	6	23.7	62.5	77	39	35	2.4	0.3	NR	NR
Cooper[18]	DB-P	Tooth removal	650	0	4	31.9	70.7	73	49	43	3.4	2.1	NR	NR
Cooper[19]	DB-P	Tooth removal	650	0	6	23.6	64.6	87	37	44	2.4	1.9	12	6
Dionne[20]	DB-P	3rd Molar extraction	650	0	6	28.9	68.6	NR	27	25	NR	NR	NR	NR
Forbes[21]	DB-P	Postsurgical	650	0	6	39.2	74.5	83	31	33	4.9	2.4	17	11
Forbes[22]	DB-P	3rd Molar extraction	650	0	6	21.8	67.2	82	39	36	1.1	0.2	20	4
Hopkinson[23]	DB-P	Episiotomy	650	0	4	NR	NR	NR	88	88	5.2	2.1	51	16
Jain[24]	DB-P	Postsurgical	650	0	6	29.2	71.8	80	30	32	5.4 (0.8)	4.1 (0.7)	NR	NR
Melzack[25]	DB-P	Episiotomy	650	0	6	NR	NR	NR	29	29	6.7	5.8	9	10
Sunshine[26]	DB-P	3rd Molar extraction	650	0	6	22.5	60.6	67	30	30	4.2	1.7	NR	NR
Sunshine[27]	DB-P	Episiotomy	650	0	6	25.8	60.1	NR	75	50	4.4	1.5	NR	NR
Sunshine[28]	DB-P	Caesarean	650	0	6	26.1	60.3	NR	48	48	6.7	6.2	NR	NR
Terrence[29]	DB-P	3rd Molar	650	0	4	27.4	NR	85	11	11	4.3	1.9	NR	NR
Young[30]	DB-P	Postsurgical	650	0	4	46.0	68.5	NR	30	29	4.1 (0.6)	4.6 (1.0)	NR	NR
Paracetamol plus dextropropoxyphene *v* placebo									(n=200)	(n=45)			(n=45)	(n=26)
Buck[31]	DB-P	Episiotomy	650	65	48*	NR	NR	NR	19	19	NR	NR	NR	NR
Evans[32]	DB-P	Orthopaedic	650	65	4	42.2	67.8	NR	30	30	3.3 (0.6)	2.1 (0.4)	NR	NR
Forbes[33]	DB-P	Oral surgery	650	100	12	NR	NR	NR	29	28	4.9	1.4	NR	NR
Honig[34]	DB-P	Postsurgical	650	100	6	38.0	72.5	NR	50	48	3.4 (0.5)	1.4 (0.6)	28	17
Petti[35]	SB-P	Postsurgical	650	100	6	49.0	NR	NR	31	32	4.7 (0.7)	2.2 (0.6)	17	9
Sunshine[36]	DB-P	Caesarean	650	100	6	25.8	60.4	NR	41	40	6.7	4.2	NR	NR

NR=not reported
Dxp=dextropropoxyphene; DB-P=double blind, parallel trial; SB-P=single blind, parallel trial; BPS%=percentage of baseline pain score relative to maximum pain score on scale 0%=no pain, 50%=moderate pain, 100%=severe pain.
*Multidose studies excluded from pooling.

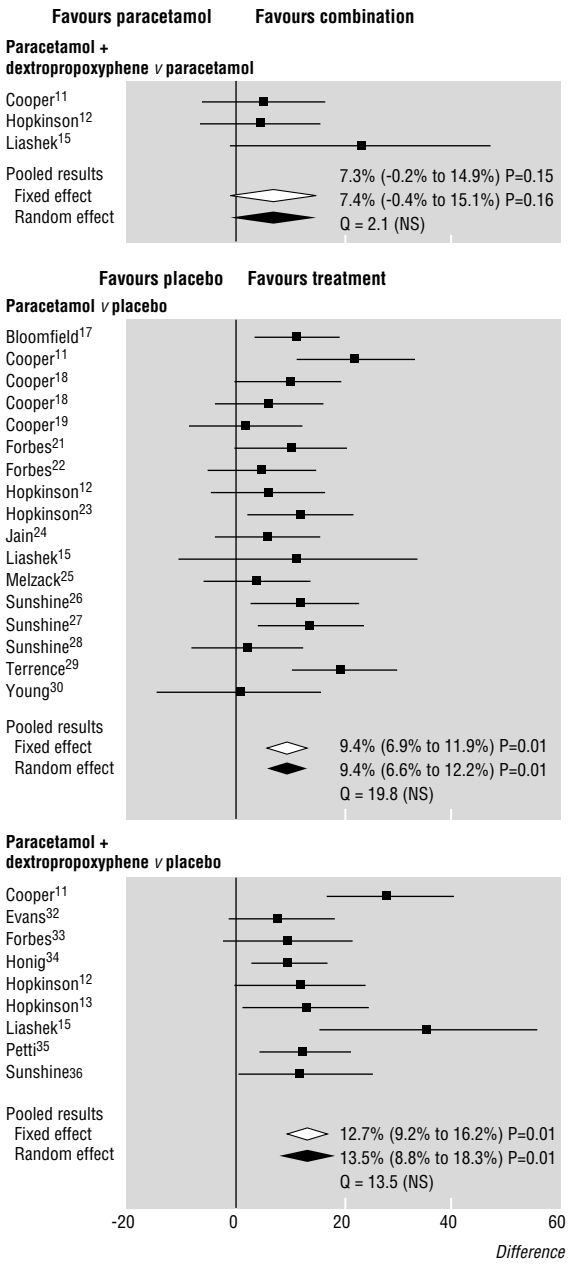


Fig 1 Mean (95% confidence interval) differences in percentage sum of differences in pain intensity between treatments

measured, necessitating variance imputation or sample size weighting when we pooled the data (see table 1).

Head to head comparisons

A total of 461 patients took part in six head to head, three armed trials with both active and placebo controls.[11–16] Two of these gave no data on the efficacy outcome measures in a form usable in our analysis.[14 16] Huskisson used pain relief scores and undertook multiple testing at six hourly time points over 6 hours and reported that at three of those time points co-proxamol was better than paracetamol 1000 mg but not at the other three.[14] No variance estimates were given. Messick on the other hand only reported mean pain score per hour, again without variance estimates.[16] The mean value reported (1.78 pain score units per hour for the combination, 1.89 for paracetamol 650 mg, and 1.81 for propoxyphene) suggested no sharp differences. The reported mean pain relief scores in per cent per day were 40.9, 39.5, and 39.0, respectively, again suggesting no obvious differences in efficacy. These two trials were the only two crossover trials retrieved by us. The results from the parallel group trials included in our meta-analysis indicate that both formulations were more effective than placebo, but there was no statistical difference in their efficacies on the basis of either the percentage sum of the pain intensity difference (see fig 1) or response rate ratio (see fig 2).

Indirect comparisons

A total of 397 patients participated in the paracetamol-dextropropoxyphene versus placebo trials. Figure 1 shows that the combination was effective, as shown by a pooled difference in sum of pain intensity difference of 12.7% (95% confidence interval 9.2 to 16.2%). Use of a random effects model led to the same conclusion (mean effect of 13.5%; 8.8% to 18.2%).

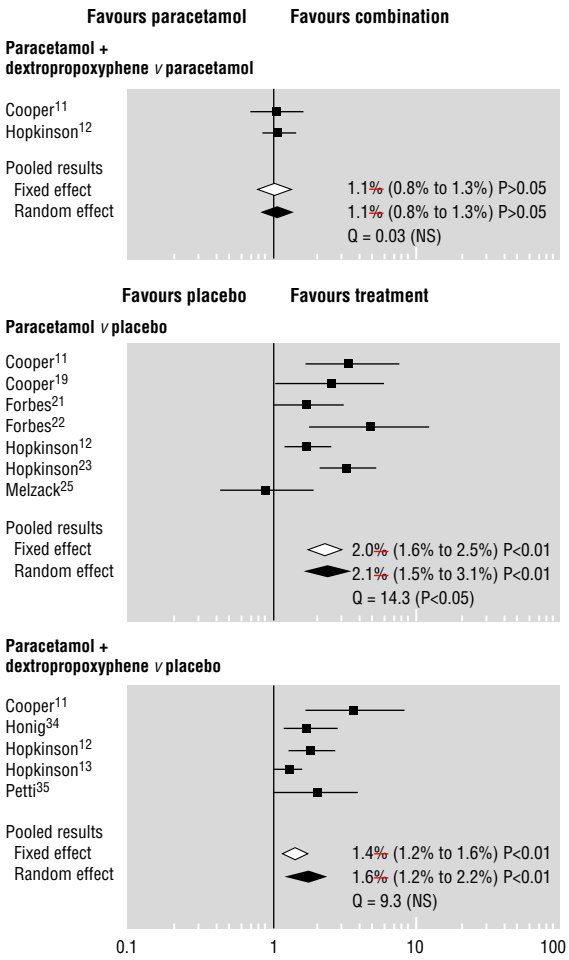
Overall, 1144 patients were included in the paracetamol versus placebo trials. These included patients from both the two-armed and three-armed studies. The pooled mean difference in the percentage sum of pain intensity difference was 9.4% (6.9% to 11.9%) with a fixed effects model and 9.4% (6.6% to 12.2%) with a random effects model, again indicating that paracetamol is an effective analgesic on the basis of this outcome measure.

Comparison of the effects estimated from the paracetamol-dextropropoxyphene versus placebo and the paracetamol versus placebo percentage sum of pain intensity difference (indirect estimation) failed to show any significant difference, as shown by the overlap of two sets of pooled confidence intervals (fig 1).

Use of the rate ratio of patients responding with moderate to excellent pain relief as a measure of efficacy yielded results consistent with the data on percentage sum of pain intensity difference. Both paracetamol and the paracetamol-dextropropoxyphene combination were more effective than placebo. There was no significant difference between the two paracetamol formulations, however, as shown by the overlap of two sets of pooled confidence intervals (fig 2). The random effects estimates should be used because of the heterogeneity of effects in the paracetamol versus placebo trials. Rate differences were 0.27 (0.17 to 0.38) for paracetamol and 0.24 (0.16 to 0.32) for paracetamol-dextropropoxyphene. A mean number needed to treat of 4 was obtained for both formulations by taking the inverse of rate difference in both cases. Compared with placebo, four subjects will on average require to be treated with either paracetamol or the combination for one more patient to obtain moderate to excellent pain relief.

Adverse effects

Comparison of side effect profiles showed that the combination of paracetamol and dextropropoxyphene caused more dizziness than placebo. On average, treating 42 patients will lead to one more patient complaining of dizziness than if they were receiving placebo. Surprisingly, paracetamol caused more drowsiness than placebo, an observation which clearly needs further confirmation because of its poor face validity. There was no difference in any of the reported side



(author corrected: % should be removed)

Fig 2 Mean (95% confidence interval) rate ratios for moderate to excellent pain relief between treatments

effects between paracetamol and its combination with dextropropoxyphene (table 3).

Sensitivity analysis for indirect comparison

Direct versus indirect comparisons—Two estimates of paracetamol-placebo effect were derived, one on the basis of the results of the head to head trials including a placebo arm and the other based on placebo controlled trials not including a paracetamol-dextropropoxyphene arm. This sensitivity analysis showed no difference in estimates of effect for placebo controlled trials in the two-armed studies (8.8%; 6.1% to 11.5%) when compared with the three-armed studies (14.1%; 6.9% to 21.4%). Similarly, for the combination product the estimated effect relative to placebo was no different in the two-armed studies (10.1%; 6.0% to 14.3%) than in the three-armed studies (19.3%; 12.8% to 25.9%). Both sets of trials therefore gave qualitatively consistent estimates (table 4), although the data suggest a more pronounced effect in the latter.

Method of analysis—Given that many of the studies considered in our meta-analysis failed to report on the variances associated with the estimates of effect, we undertook sensitivity analyses with respect to method of pooling. Firstly, we included only studies with variance estimates. Secondly, we used sample size weighting adopted by Eisenberg et al in their meta-analysis of non-steroidal anti-inflammatory drugs in cancer pain.[5] Thirdly, we used imputation of variance, whereby we assigned the pooled estimate of variance, calculated from studies reporting such values, to estimate variance for the 19 studies that had not done so (tables 1 and 2). Pooling only studies reporting variance showed that in the indirect comparisons the estimated effect size for paracetamol relative to placebo was 8.3% (2.7% to 13.9%) while for the combination analgesic the corresponding value was 9.4% (6.9% to 12.5%). These results show no difference in effect between paracetamol and the paracetamol-dextropropoxyphene combination. The head to head studies were not numerous enough for this sensitivity analysis. Use of sample size as weight provided pooled estimates of effect which were consistent with those seen when variance in studies not reporting them were imputed by using the pooled estimate of variance from studies that had, as shown in table 5. Irrespective of the method for imputing variance, paracetamol and paracetamol-dextropropoxyphene were both more effective than placebo, but there was no difference in their effectiveness.

Discussion

Our meta-analysis supports the claim of Sykes et al that paracetamol-dextropropoxyphene is effective as an analgesic.[2] Implicit in their response to Haigh's

Table 3 Comparison of risk of side effects (95% confidence intervals) with paracetamol, paracetamol plus dextropropoxyphene, and placebo

Comparisons	Any side effect	Nausea	Dizziness	Drowsiness	Headache
Paracetamol plus dextropropoxyphene *v* paracetamol					
Crude rate	16/117 *v* 25/112	10/234 *v* 8/229	7/234 *v* 6/229	10/229 *v* 12/229	1/234 *v* 5 / 229
Weighted relative risk	0.62 (0.35 to 1.10)	1.16 (0.47 to 2.85)	1.11 (0.37 to 3.36)	1.04 (0.40 to 2.69)	0.30 (0.05 to 1.93)
Weighted risk difference	–0.08 (–0.18 to 0.02)	0.007 (–0.03 to 0.04)	0.01 (–0.02 to 0.04)	–0.06 (–0.24 to 0.12)	–0.01 (–0.03 to 0.004)
Paracetamol *v* placebo					
Crude rate	64/345 *v* 48/355	16/355 *v* 14/362	11/364 *v* 9/372	43/ 378 *v* 24/389	13/427 *v* 17/431
Weighted relative risk	1.42 (1.01 to 2.02)*	1.14 (0.54 to 2.40)	1.24 (0.47 to 3.26)	1.77 (1.10 to 2.86*	0.79 (0.38 to 1.67)
Weighted risk difference	0.02 (–0.03 to 0.06)	0.003 (–0.03 to 0.03)	0.002 (–0.02 to 0.02)	0.02 (–0.01 to 0.05)	–0.01 (–0.03 to 0.01)
Paracetamol plus dextropropoxyphene *v* placebo					
Crude rate	24/167 *v* 28/239	13/295 *v* 10/367	14/316 *v* 5/388	15/279 *v* 10/356	7/295 *v* 18/367
Weighted relative risk	1.16 (0.69 to 1.97)	1.65 (0.73 to 3.69)	3.09 (1.07 to 8.87)*	1.69 (0.76 to 3.74)	0.70 (0.29 to 1.68)
Weighted risk difference	0.02 (–0.05 to 0.09)	0.02 (–0.01 to 0.05)	0.02 (0.0001 to 0.046)*†	0.02 (–0.01 to 0.05)	–0.03 (–0.06 to –0.01)*‡

*P≤0.05.
†Number needed to treat was 43 (21 to 6940).
‡Number needed to treat was –30 (–138 to –17) (favours paracetamol plus dextropropoxyphene—that is, fewer headaches in the active treatment group).

Table 4 Sensitivity analysis (95% confidence interval)with respect to type of placebo controlled trials

Type of trial	Difference in SPID%	Response rate ratio*
Paracetamol *v* placebo		
Placebo trials in two armed studies	8.8 (6.1 to 11.5)	2.2 (1.6 to 3.0)
Placebo trials in three armed studies	14.1 (6.9 to 21.4)	1.9 (1.3 to 2.6)
Overall	9.4 (6.9 to 11.9)	2.1 (1.5 to 3.1)
Paracetamol plus dextropropoxyphene *v* placebo		
Placebo trials in two armed studies	10.1 {96.0 to 14.3)	1.7 (1.2 to 2.5)
Placebo trials in three armed studies	19.3 (12.8 to 25.9)	1.7 (1.1 to 2.6)
Overall	12.7 (9.2 to 16.2)	1.4 (1.2 to 1.7)

SPID=sum of pain intensity difference.
*Response rate ratio for patients receiving treatment relative to placebo. Response rate is defined as proportion of patients reporting moderate to excellent or more than 50% pain relief during observation.

Table 5 Sensitivity analysis with respect to method of variance imputation for difference in SPID% (95% confidence interval)

Detail	Pooled estimate weighted for sample size*	Pooled estimate weighted for variance†
Paracetamol *v* placebo (n=17)	7.9 (4.2 to 11.7)	9.4 (6.9 to 11.9)
Paracetamol plus dextropropoxyphene *v* placebo (n=9)	11.4 (6.8 to 16.0)	12.7 (9.2 to 16.2)
Paracetamol plus dextropropoxyphene *v* paracetamol (n=3)	5.3 (–2.7 to 13.2)	7.3 (–0.2 to 14.9)

SPID=sum of pain intensity difference.
*Mean difference in SPID% weighted for sample size as described by Eisenberg et al.[5]
†Mean difference in SPID% weighted for variance, with variance in studies not reporting them imputed by using pooled estimate from studies reporting variance.

criticism of the widespread use of paracetamol-dextropropoxyphene[1] was the assumption that the combination was more effective than paracetamol alone. Our systematic overview shows that the current data do not support this view. Happily, though, the incidence of adverse effects is no higher with the combination than with paracetamol alone. Single dose randomised controlled trials cannot be expected to capture estimates of potential for abuse, however, and this is a subject of concern with combination products containing centrally acting analgesics.[43]

In undertaking our meta-analysis, we were hampered by the absence of variance estimates in many of the trials. This is a problem which should decrease with the wider adoption of the CONSORT statement on the quality of reporting of clinical trials.[44] The fact that irrespective of the method of variance imputation the same qualitative results were obtained gives us some confidence with respect to the robustness of our conclusion; on current evidence, the combination of dextropropoxyphene 65/100 mg with paracetamol 650 mg is no better than paracetamol 650 mg on its own for the type of pain considered in this meta-analysis.

There were relatively few studies, and it is possible that we could have missed small additive analgesic effects of dextropropoxyphene. Our 95% confidence interval estimates suggest that the magnitude of effect observed is neither statistically nor clinically meaningful. The differences in effect between the combination and paracetamol in the head to head studies were 7.3% (– 0.2% to 14.9%) on the basis of the percentage sum of differences in pain intensity and 1.1 (0.8 to 1.3) on the basis of response rate ratio. In an earlier communication we provided data to suggest that an analgesic effect, of 7 (3 to 10) assessed by using percentage sum of differences in pain intensity, was not translated into an increased number of patients who obtained at least moderate pain relief.[4] While that study assessed the possible additive effect of different drugs (codeine and caffeine rather than dextropropoxyphene), the fact that all three drugs are centrally active and that the same measure (percentage sum of pain intensity difference) was used suggests that comparison of the two sets of results is reasonable.

To explain why discordant conclusions may be obtained when relative efficacy and response rate ratio are used as outcomes, we propose that although a patient may well perceive a difference in pain intensity, this change may not be sufficient to be judged important. In other words, a decrease in pain intensity, reflected in the percentage sum of pain intensity difference, may not be sufficient for the patient to classify this change as a categorical change—for example, from severe to mild and reflected in response rate ratio as an outcome measure.

It has been suggested that as dextropropoxyphene is subject to a high first pass metabolism[45] single dose studies are inadequate to estimate the efficacy of the drug. In the only two multiple dose studies we could identify a beneficial effect over and above that of paracetamol was not detected.[16 31] We concur with the view of Miller et al that the popularity of the paracetamol combination does not lie in improved efficacy.[46]

Key messages

- Combinations of paracetamol with centrally acting analgesics are widely used, accounting for 73% of all prescriptions for paracetamol in a recent hospital survey in the United Kingdom
- The combination of paracetamol (650 mg) with dextropropoxyphene hydrochloride (32.5 mg) is particularly popular
- In both head to head and indirect comparisons of paracetamol and the combination, the combination was no better than paracetamol on its own
- Since the total number of patients in the few published head to head comparisons was modest, small differences in effect cannot be excluded but these are unlikely to be of clinical importance

Funding: No external funding.
Conflict of interest: ALWP has acted as a consultant to Boots, Zyma, and SmithKline Beecham, which market analgesic drugs, and is a member of the Chemistry, Pharmacy, and Standards Subcommittee of the Committee on Safety of Medicines. The views expressed in the paper are his personal views.

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(Accepted 5 August 1997)

Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review

P M Rothwell, J Slattery, C P Warlow

Abstract

Objective: To identify risk factors for operative stroke and death from carotid endarterectomy.
Design: Systematic review of all studies published since 1980 which related risk of stroke and death to various preoperative clinical and angiographic characteristics, including unpublished data on 1729 patients from the European carotid surgery trial.
Main outcome measure: Operative risk of stroke and death.
Results: Thirty six published studies fulfilled our criteria. The effect of 14 potential risk factors was examined. The odds of stroke and death were decreased in patients with ocular ischaemia alone (amaurosis fugax or retinal artery occlusion) compared with those with cerebral transient ischaemic attack or stroke (seven studies; odds ratio 0.49; 95% confidence interval 0.37 to 0.66; $P<0.00001$). The odds were increased in women (seven studies; 1.44; 1.14 to 1.83; $P<0.005$), subjects aged ≥75 years (10 studies; 1.36; 1.09 to 1.71; $P<0.01$), and with systolic blood pressure >180 mm Hg (four studies; 1.82; 1.37 to 2.41; $P<0.0001$), peripheral vascular disease (one study; 2.19; 1.40 to 3.60; $P<0.0005$), occlusion of the contralateral internal carotid artery (14 studies; 1.91; 1.35 to 2.69; $P<0.0001$), stenosis of the ipsilateral internal carotid siphon (five studies; 1.56; 1.03 to 2.36; $P=0.02$), and stenosis of the ipsilateral external carotid artery (one study; 1.61; 1.05 to 2.47; $P=0.03$). Operative risk was not significantly related to presentation with cerebral transient ischaemic attack versus stroke, diabetes, angina, recent myocardial infarction, current cigarette smoking, or plaque surface irregularity at angiography. Multiple regression analysis of data from the European carotid surgery trial identified cerebral versus ocular events at

Department of Clinical Neurosciences, Western General Hospital, Edinburgh, EH4 2XU

P M Rothwell, *research fellow*

J Slattery, *statistician*

C P Warlow, *professor of neurology*

Correspondence to: Dr P M Rothwell, Department of Clinical Neurology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE peter.rothwell@clneuro.ox.ac.uk

BMJ 1997;315:1571–7

Attachment-7

Single dose oral paracetamol (acetaminophen) for postoperative pain (Review)

Barden J, Edwards J, Moore A, McQuay H

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Single dose oral paracetamol (acetaminophen) for postoperative pain (Review)

Barden J, Edwards J, Moore A, McQuay H

This record should be cited as:
Barden J, Edwards J, Moore A, McQuay H. Single dose oral paracetamol (acetaminophen) for postoperative pain. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD004602. DOI: 10.1002/14651858.CD004602.

This version first published online: 26 January 2004 in Issue 1, 2004.
Date of most recent substantive amendment: 25 November 2003

ABSTRACT

Background
Paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the relief of mild and moderate pain arising from headache, musculoskeletal conditions and dysmenorrhoea. A prior Cochrane systematic review concluded that paracetamol is also effective for postoperative pain, but additional trials have since been published. This review sought to evaluate the efficacy and safety of paracetamol using current data, and to compare the findings with other analgesics evaluated in the same way.

Objectives
To assess the efficacy of single dose oral paracetamol for the treatment of acute postoperative pain.

Search strategy
We searched the Cochrane Library (Issue 3, 2002), the trials register of the Cochrane Pain, Palliative and Supportive Care group (November 2002); MEDLINE (1966 to May 1996); PubMed (1996 to August 2001); EMBASE (1980 to 1996); the Oxford Pain Relief Database (1950 to 1994); and reference lists of articles in order to update an existing version of the review.

Selection criteria
Randomised, double-blind, placebo-controlled clinical trials of paracetamol for acute postoperative pain in adults.

Data collection and analysis
Two reviewers independently assessed trial quality and extracted data. The area under the 'pain relief versus time' curve was used to derive the proportion of patients with paracetamol or placebo experiencing least 50% pain relief over four to six hours using validated equations. The number-needed-to-treat (NNT) was calculated using 95% confidence intervals. Information on adverse effects was also collected.

Main results
Forty-seven reports that enrolled 4186 patients (2561 patients were treated with a single oral dose of paracetamol and 1625 with placebo) met the inclusion criteria and were included in the analyses. The NNTs for at least 50% pain relief over four to six hours following a single dose of paracetamol were as follows: 325 mg NNT 3.8 (2.2 to 13.3); 500 mg NNT 3.5 (2.7 to 4.8); 600/650 mg NNT 4.6 (3.9 to 5.5); 975/1000 mg NNT 3.8 (3.4 to 4.4); and 1500 mg NNT 3.7 (2.3 to 9.5). Sub-group analysis showed no significant differences between smaller and larger trials, or lower and higher quality trials. Drug-related study withdrawals were rarely reported. Studies reported a variable incidence of adverse effects that were generally mild and transient. There were no statistically significant differences in the frequency of reported adverse effects between paracetamol 975/1000 mg and placebo.

Authors' conclusions
Single doses of paracetamol are effective analgesics for acute postoperative pain and give rise to few adverse effects.

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PLAIN LANGUAGE SUMMARY

Paracetamol is an effective pain killer for adults experiencing moderate to severe pain after surgery

Pain is commonly experienced after surgical procedures, and is not always well controlled. This review assessed data from forty-seven trials and found that paracetamol is an effective analgesic for patients experiencing moderate to severe pain after an operation, including dental surgery. There were no significant differences between doses of paracetamol. The trials included in the review did not associate paracetamol with any serious side effects.

BACKGROUND

Paracetamol (acetaminophen) was first identified as the active metabolite of two older antipyretic drugs, acetanilide and phenacetin in the late nineteenth century but the drug was not added to the British Pharmacopoeia until 1963 (PIC 2003). Since then it has become one of the most popular antipyretic and analgesic drugs worldwide, and is often also used in combination with other drugs.

The lack of significant anti-inflammatory activity for paracetamol implies a mode of action distinct to that of non-steroidal anti-inflammatory drugs (NSAIDs), yet despite years of use and research the mechanisms underlying the efficacy of paracetamol have yet to be identified. NSAIDs act by inhibiting the activity of cyclooxygenase (COX). COX (now recognised to consist of two isoforms, COX-1 and COX-2) catalyses the production of prostaglandins responsible for pain and inflammation. Paracetamol has no significant effects on COX-1 or COX-2 (Schwab 2003). Significant paracetamol-induced inhibition of prostaglandin production has been demonstrated in tissues in the brain, spleen, and lung (Flower 1972; Botting 2000). This is now emerging as a 'COX-3 hypothesis' wherein the efficacy of paracetamol is attributed to its specific inhibition of a third cyclooxygenase isoform enzyme, COX-3 (PIC 2003; Chandrasekharan 2002; Botting 2000).

Despite a low incidence of adverse effects, paracetamol has a recognised potential for hepatotoxicity and is thought to be responsible for approximately half of all cases of liver failure in the UK (Hawton 2001). Acute paracetamol hepatotoxicity at therapeutic doses is extremely unlikely despite reports of so-called therapeutic misadventure (Prescott 2000). In recent years legislative changes restricting pack sizes and the maximum number of tablets permitted in over-the-counter sales were introduced in the UK (CSM) on the basis of evidence that poisoning is lower in countries that restrict avaliability (Hawton 2001; Gunnell 1997). Such changes, whilst inconvenient and more costly (particularly to chronic pain sufferers), have resulted in small reductions in harm (Hawton 2001). There have been concerns over the safety of paracetamol in patients with compromised hepatic function (those with severe alcoholism, cirrhosis or hepatitis) but these have not been substantiated (PIC 2003; Dart 2000).

In 1997, the UK Audit Commission proposed that fewer than 20% of patients should experience severe pain after surgery, ideally declining to fewer than 5% by 2002 (Audit 1997). Recent reviews suggest that these goals are far from being met (Svensson 2000; Dolin 2002): 67% of patients treated with intramuscular analgesia; 36% with intravenous patient-controlled analgesia; and 21% with epidural analgesia still report moderate to severe pain (Dolin 2002). Despite high technology interventions, and the apparent efficacy of treatment options, acute pain is not being treated adequately (Moore 2003; Bruster 1994).

Paracetamol is the analgesic of choice for adult patients in whom salicylates or other NSAIDs are contraindicated. Such patients include asthmatics, those with salicylate allergies, and those with a history of peptic ulcer. Paracetamol is useful for children with febrile viral illnesses, in whom aspirin is contraindicated due to the risk of Reye's syndrome (swelling of the brain that may lead to coma and death).

Low technology interventions such as oral paracetamol administration, used appropriately, have the potential to reduce unnecessary pain.
A prior Cochrane systematic review (Collins 1998) concluded that paracetamol is also effective for postoperative pain, but additional trials have since been published. This review sought to evaluate the efficacy and safety of paracetamol using current data, and to compare the findings with other analgesics evaluated in the same way. This review aims to evaluate the efficacy and safety of single dose oral paracetamol when used to treat acute postoperative pain, and to compare these findings with those for NSAIDs, also commonly used in this context.

OBJECTIVES

To assess the efficacy and adverse effects of single dose paracetamol for acute postoperative pain using methods that permit comparison with other analgesics.

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CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Reports were included if they were double blind trials that compared single dose oral paracetamol and placebo for the treatment of moderate to severe postoperative pain in adults, and randomly allocated 10 patients or more patients to each treatment group. Multiple dose studies were included if evaluable data from the first dose were available, as were crossover studies if data from the first arm were presented separately. Postpartum pain trials were included if the pain investigated was due to episiotomy or Caesarean section irrespective of the presence of uterine cramps; trials investigating pain due to uterine cramps alone were excluded.

Reports were excluded if the trials:

- investigated pain other than postoperative pain (eg, experimental pain)
- assessed pain relief by clinician, nurse or carer report (ie, not patient report)
- lasted less than four hours or failed to present data over four to six hours post-dose
- included patients with only mild pain at baseline

Types of participants

Trials of adult patients (16 years and older) with postoperative pain of moderate to severe intensity following day surgery or inpatient surgery were included. For studies using a visual analogue scale (VAS), pain intensity was assumed to be of at least moderate intensity when the VAS score was greater than 30 mm (Collins 1997). When the baseline pain was only presented as a mean VAS score with the corresponding standard deviation (SD), the study was included only if the mean minus 1.96 times the SD was greater than 30 mm.

Types of intervention

Oral paracetamol or matched placebo administered as a single oral dose immediate-release formulation for postoperative pain.

Types of outcome measures

Data were collected on the following outcomes:

- Patient characteristics
- Patient-reported pain at baseline (physician-, nurse- or carer-reported pain assessments were not included in the analysis)
- Patient-reported pain relief, expressed hourly over 4 to 6 hours using validated pain scales (VAS and/or categorical scales)
- Use of rescue medication
- Withdrawals (discontinuation of treatment for any reason)
- Adverse effects - major and minor

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Pain, Palliative and Supportive Care Group methods used in reviews.

In the original review, sensitive search strategies were developed for the following electronic databases:

- The Cochrane Controlled Trials Register (CENTRAL) (Cochrane Library, Issue 2, 1996)
- MEDLINE (1966-May 1996)
- EMBASE (1980 to 1996)
- Oxford Pain database (Jadad 1996a)

To update this review the following databases were searched:

- PubMed (November 2002)
- The Specialised Register of the Cochrane Pain, Palliative and Supportive Care group (November 2002)
- The Cochrane Controlled Trials Register (CENTRAL) (Cochrane Library, Issue 3, 2002)
- Oxford Pain database (Jadad 1996a)

The same sensitive search strategy using the following free text terms was used for both the original review and this update:

'paracetamol' OR 'acetaminophen'
AND
'random*' OR 'trial' OR 'study'
AND
'analgesi*' OR 'pain'

Additional reports were identified from reference lists of retrieved articles, textbooks and reviews.

LANGUAGE
No language restriction was applied.

UNPUBLISHED STUDIES
Unpublished studies were not sought.

METHODS OF THE REVIEW

SELECTION OF STUDIES
Electronic searches were carried out by one reviewer (JE) to update searches conducted for the original review. Two reviewers (JE and JB) independently reassessed trials included in the original review, reviewed new titles and abstracts retrieved, and agreed upon the reports that would be retrieved in full for assessment for inclusion in the review. Disagreements were resolved by discussion.

QUALITY ASSESSMENT

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Each study that met the inclusion criteria was assessed independently for quality by two reviewers using a three-item scale (Jadad 1996b) and a consensus score out of a maximum of five points was agreed. These scores were not used to weight the results but were used for sensitivity analyses.

The scale used is as follows:

- Is the study randomised? If yes, add 1 point
- Is the randomisation procedure reported and is it appropriate? If yes, add 1 point, if no, deduct 1 point
- Is the study double blind? If yes, add 1 point
- Is the double blind method reported and is it appropriate? If yes, add 1 point, if no, deduct 1 point
- Are the reasons for patient withdrawals and dropouts described? If yes, add 1 point

The results of the quality assessment are described in the 'Methodological quality of included studies' section below.

DATA MANAGEMENT

Data were extracted by two reviewers (JE and JB) and recorded on a standard data extraction form. Data suitable for pooling were entered into RevMan 4.1 by JB.

DATA ANALYSIS

For each report, the mean TOTPAR, SPID, VAS TOTPAR or VAS SPID values for active and placebo were converted to %maxTOTPAR or %maxSPID by division into the estimated maximum value (Cooper 1991). The proportion of patients in each treatment group who achieved at least 50%maxTOTPAR was calculated using verified equations (Moore 1996; Moore 1997b; Moore 1997c). These proportions were then converted into the number of patients achieving at least 50%maxTOTPAR by multiplying by the total number of patients in the treatment group. Information on the number of patients with at least 50%maxTOTPAR for active and placebo was then used to calculate relative benefit (RB) and number needed to treat (NNT).

Pain measures accepted for the calculation of TOTPAR or SPID were:

- 5-point categorical pain relief (PR) scales with comparable wording to "none, slight, moderate, good or complete"
- 4-point categorical pain intensity (PI) scales with comparable wording to "none, mild, moderate, severe"
- Visual analogue scales (VAS) for pain relief
- VAS for pain intensity
- 5-point categorical global scale with the wording "poor, fair, good, very good, excellent" (Collins 2001)

Relative benefit/risk estimates were calculated with 95% confidence intervals (CI) using a fixed effects model (Morris 1995). Number-needed-to-treat and 95% confidence intervals were calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995). A statistically significant difference from control was assumed when the 95% confidence interval of the relative benefit did not include 1. Significant differences between doses were evaluated using the z test (Tramer 1997).

Heterogeneity tests were not used as they have previously been shown to be unhelpful (Gavaghan 2000; Higgins 2002) although homogeneity was examined visually (L'Abbe 1987). Publication bias was not assessed using funnel plots as these tests have been shown to be unhelpful (Tang 2000; Sterne 2000).

Sensitivity analyses were undertaken to explore the impact of pain model, trial size and quality score.

ADVERSE EFFECTS

The number of patients reporting treatment related adverse effects was extracted for each treatment group. Relative risk (RR) and number-needed-to-harm (NNH) estimates were calculated for a patient to report any adverse event and for particular adverse events.

DESCRIPTION OF STUDIES

One hundred and forty five trials were identified as potential double blind, randomised controlled trials (RCTs) of oral paracetamol against placebo in postoperative pain; 99 reports were excluded as they did not meet the inclusion criteria.

- Eleven reports did not state that they were randomised and double-blind (Cooper 1984; Daftary 1980; Davie 1978; Forbes 1981; Frerich 1981; Gallardo 1980; Parkhouse 1967; Petti 1985; Terrence 1983; Torabinejad 1994; Wojcicki 1977)
- Twenty did not include paracetamol administered alone (Babul 1993; Desjardins 1986; Forbes 1986; Forbes 1990; Forbes 1994; Fulkerson 1986; Gertzbein 1986; Heidrich 1985; Jacobson 1987; Mayer 1984; Ottinger 1990; Pande 1996a(study 1); Pande 1996a(study 2); Pande 1996b; Sagne 1987; Scoren 1987; Stubhaug 1995; Sunshine 1988; Turek 1988; Vangen 1988)
- Thirty four reports did not include a placebo control group (Breivik 1999; Bullingham 1981; De Santis 1993; Eskenazi 1976; Filtzer 1980; Gomez-Jimenez 1980; Gustafsson 1983; Haanaes 1986; Irvine 1982; Lataste 1981; Lecointre 1991; Marti 1993; McQuay 1986; Morrison 1994; Movilia 1989; Muckle 1984; Mugnier 1984; Nappi 1993; Nystrom 1988; Olstad 1986a; Olstad 1986b; Ouellette 1986; Quiding 1981; Quiding 1983; Quiding 1984; Ragot 1991; Reijntjes 1987; Veltmann 1980; Rodrigo 1989; Skjelbred 1977; Speranza 1992; Spivach 1984; Strom 1990; Yscla 1988)
- Sixteen reports failed to confirm initial pain at an intensity sufficient to ensure adequate baseline sensitivity or included

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mild pain (Ahlstrom 1985; Baer 1992; Cade 1993; Cheung 1992; Gillberg 1993; Huang 1986; Lokken 1980; Matthews 1984; Melzack 1985; Quiding 1982a; Sandhu 1996; Skjelbred 1979; Skjelbred 1982; Skoglund 1991; Skovlund 1991; Sveen 1975)

- Seven studies did not include standard pain measurement scales (Hopkinson 1973; Hopkinson 1974; Hopkinson 1976; Levin 1974; Liashek 1987; McMahon 1987; Smith 1975)
- Four studies did not provide data for at least four hours (Behotas 1992; Cooper 1976; Gallardo 1990; Rodrigo 1987)
- Two studies included children (McGaw 1987; Moore 1985)
- One study provided multiple dose data without analysing the first dose separately (Seymour 1983)
- One trial excluded all the data from patients taking rescue medication (Melzack 1983)
- One trial was a duplicate of a trial already included (Dolci 1993)
- The published systematic review (Collins 1998) included two reports of three trials which were excluded in this review as they included participants with postpartum uterine cramping without concurrent episiotomy (Laska 1983 (study 1); Laska 1983 (study 2); Beaver 1980).

METHODOLOGICAL QUALITY

The quality scores achieved by the included studies were as follows:

QUALITY SCORE 2 (low quality)
Two trials: Fassolt 1983; Sakata 1986; Winter 1979; .

QUALITY SCORE 3
Twelve trials: Bentley 1987; Berry 1975; Bhounsule 1990; Bjune 1996; Cooper 1986; Cooper 1991a; Dionne 1994; Forbes 1982; Honig 1984; Mehlisch 1995; Pinto 1984; Santos Pereira 1986.

QUALITY SCORE 4 (high quality)
Twenty-three trials: Cooper 1980; Cooper 1981; Cooper 1988; Cooper 1998; Dolci 1994; Forbes 1984b; Hersch 2000; Jain 1986; Kiersch 1994; Laska 1983 (Study 3); McQuay 1988; Mehlisch 1984; Mehlisch 1990; Moller 2000; Rubin 1984; Rubinstein 1986; Schachtel 1989; Seymour 1996; Sunshine 1989; Sunshine 1993; Winnem 1981; Winter 1983; Young 1979

QUALITY SCORE 5 (high quality - maximum score)
Eight trials: Cooper 1989; Forbes 1983; Forbes 1984a; Forbes 1989; Forbes 1990a; Forbes 1990b; Lehnert 1990; Sunshine 1986; Edwards 2002.

Overall methodological quality was acceptable signifiying minimal methodological bias within the included trial. Allocation concealment was generally poorly reported.

RESULTS

The previous review (Collins 1998) included data from 38 trials comprising a total of 2581 patients treated with paracetamol and 1643 patients treated with placebo. It should be noted that three studies included in the previous version of this review have been excluded in this update. In this updated version, forty-seven trials met inclusion criteria, and data from these are included in the analyses; a total of 2561 patients were treated with a single oral dose of paracetamol and 1625 with placebo.

- Twenty five trials investigated pain arising from dental surgery (third molar extraction with bone removal)
- Twelve trials investigated postsurgical pain (elective general, gynaecological, urological and orthopaedic surgery)
- Ten trials investigated postpartum pain (episiotomy and Caesarean section)

The doses of paracetamol investigated were 325 mg in one trial; 500 mg in six trials; 600/650 mg in nineteen trials; 975/1000 mg in twenty-three trials; and 1500 mg in one trial.

EFFICACY
Data from trials assessing doses of paracetamol 500 mg; 600/650 mg; and 975/1000 mg were extracted for meta-analysis. Efficacy data were used to compare each dose of paracetamol with placebo and are presented individually in MetaView 4.2 and summarised in Table 01. All doses of paracetamol were found to be statistically superior to placebo.

Comparison 01 01
PARACETAMOL 325 mg VERSUS PLACEBO
One trial (Winter 1983) of 100 patients undergoing various oral surgery procedures met inclusion criteria: 34/49 patients improved on treatment with paracetamol and 22/51 improved on placebo.

Comparison 02 01
PARACETAMOL 500 mg VERSUS PLACEBO
Data from six trials (561 patients) were meta-analysed to assess the efficacy of 500 mg paracetamol versus placebo (Cooper 1980; Laska 1983 (Study 3); Pinto 1984; Rubinstein 1986; Dolci 1994; Seymour 1996) giving a RR of 1.91 (95% CI 1.57 to 2.32).

Comparison 03 01
PARACETAMOL 600/650 mg VERSUS PLACEBO
Data from 19 trials (1886 patients) were meta-analysed to assess the efficacy of 600/650 mg paracetamol versus placebo (Bhounsule 1990; Cooper 1981; Cooper 1988; Cooper 1991a; Dionne 1994; Edwards 2002; Fassolt 1983; Forbes 1982; Forbes 1983; Forbes 1984a; Forbes 1984b; Forbes 1989; Forbes 1990b; Honig 1984; Jain 1986; Sunshine 1986; Sunshine 1989; Sunshine 1993; Young 1979) giving a RR of 2.42 (95% CI 2.05 to 2.84).

Comparison 04 01
PARACETAMOL 975/1000 mg VERSUS PLACEBO

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Data from 23 trials (2759 patients) were meta-analysed to assess the efficacy of 975/1000 mg paracetamol versus placebo (Bentley 1987; Berry 1975; Bjune 1996; Cooper 1986; Cooper 1989; Cooper 1998; Edwards 2002; Hersch 2000; Kiersch 1994; Laska 1983 (Study 3); Lehnert 1990; McQuay 1988; Mehlisch 1984; Mehlisch 1990; Mehlisch 1995; Moller 2000; Rubin 1984; Sakata 1986; Santos Pereira 1986; Schachtel 1989; Seymour 1996; Winnem 1981; Winter 1983) giving a RR of 2.47 (95% CI 2.18-2.81).

NUMBER NEEDED TO TREAT (NNT)
The NNTs for at least 50% pain relief over four to six hours following a single dose of paracetamol were calculated (Cook 1995) with the results as follows:

- 325 mg: 3.8 (95% CI 2.2 to 13.3)
- 500 mg: 3.5 (95% CI 2.7 to 4.8)
- 600/650 mg: 4.6 (95% CI 3.9 to 5.5)
- 975/1000 mg: 3.8 (95% CI 3.4 to 4.4)
- 1500 mg: 3.7 (95% CI 2.3 to 9.5)

There was no significant difference in NNT between paracetamol 600/650 mg and paracetamol 975/1000 mg.

The mean proportion of patients experiencing at least 50% pain relief with placebo ranged from 16% (145/932) to 46% (222/1132). The mean proportions of patients experiencing at least 50% pain relief over four to six hours following a single dose of paracetamol 325 mg, 500 mg, 600/650 mg, 975/1000 mg and 1500 mg were 69% (34/49), 61% (176/290), 38% (358/954), 46% (746/1627), and 65% (53/81) respectively.

ADVERSE EFFECTS
Drug-related study withdrawals occurred rarely: in total five patients were reported as withdrawing from studies, one on placebo and four on paracetamol (Dolci 1994; Kiersch 1994).

Where adverse events were reported, the incidence was variable and the adverse events were generally mild and transient. One participant vomited following medication with paracetamol but did not withdraw (Rubinstein 1986).

Relative risk estimates were calculated using MetaView 4.2 for paracetamol 975/1000 mg versus placebo for the most commonly reported adverse effects

1. 'Drowsiness/sleepiness/somnolence'
Six trials provided data for meta-analysis: Bentley 1987; Cooper 1989; Cooper 1991a; Kiersch 1994; Cooper 1998; Moller 2000. The RR was 0.93 (95% CI 0. 53 to 1.64).

2. 'Dizziness'
Seven trials provided data for meta-analysis: Berry 1975; Bentley 1987; McQuay 1988; Cooper 1991a; Kiersch 1994; Cooper 1998; Hersch 2000. The RR was 0.73 (95% CI 0.31 to 1.75).

3. 'Nausea',
Six trials provided data for meta-analysis: Bentley 1987; McQuay 1988; Cooper 1991a; Kiersch 1994; Hersch 2000; Moller 2000
The RR was 0.99 (95% CI 0.54 to 1.80).

4. 'Vomiting'
Four trials provided data for meta-analysis: Bentley 1987; McQuay 1988; Kiersch 1994; Hersch 2000
The RR was 1.34 (95% CI 0.57-3.17)

5. 'Headache'
Nine trials provided data for meta-analysis: Bentley 1987; McQuay 1988; Schachtel 1989; Cooper 1991a; Kiersch 1994; Mehlisch 1995; Cooper 1998; Hersch 2000; Moller 2000.
The RR was 0.90 (95% CI 0.59 to 1.37).

There were no statistically significant differences in the frequency of adverse effects between paracetamol 975/1000 mg and placebo, it was not appropriate to calculate the NNH (Table 02).

SENSITIVITY ANALYSIS
Sensitivity analyses were conducted to assess the effects of

- type of surgery
- trial size
- trial quality

on the estimates of treatment effect derived by meta-analysis.

PAIN MODEL (TYPE OF SURGERY)
Twenty-five of the forty-seven included studies used a dental pain model (postoperative pain following third molar surgery) to assess the effectiveness of paracetamol for postoperative pain. The remaining 22 trials used various postsurgical models (elective general, gynaecological, urological and orthopaedic surgery, episiotomy and Caesarean section). We pooled data for 600/650 mg and 975/1000 mg paracetamol from the trials of patients who had undergone third molar surgery and compared the results with the results from general postsurgical pain. The results were as follows:

- Paracetamol 600/650 mg

Comparison 03 02
POSTOPERATIVE PAIN FOLLOWING DENTAL SURGERY: PARACETAMOL 600/650 mg VERSUS PLACEBO
Data from ten trials (1265 patients) were meta-analysed to assess the efficacy of 600/650 mg paracetamol versus placebo in patients who experienced moderate to severe pain following dental surgery (Cooper 1981; Cooper 1988; Cooper 1991a; Dionne 1994; Edwards 2002; Forbes 1982; Forbes 1984a; Forbes 1989; Forbes 1990b; Sunshine 1986) giving a RR of 2.93 (95% CI 2.34 to 3.66).

Comparison 03 03

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POSTOPERATIVE PAIN FOLLOWING SURGERY OTHER THAN DENTAL: PARACETAMOL 600/650 mg VERSUS PLACEBO

Data from nine trials (621 patients) were meta-analysed to assess the efficacy of 600/650 mg paracetamol versus placebo in patients who experienced moderate to severe pain following surgery other than dental surgery (Bhounsule 1990; Fassolt 1983; Forbes 1983; Forbes 1984b; Honig 1984; Jain 1986; Sunshine 1989; Sunshine 1993; Young 1979) giving a RR of 1.86 (95% CI 1.46 to 2.36).

The NNT for at least 50% pain relief over four to six hours from postoperative dental surgery (1265 patients) was 4.2 (95% CI 3.6 to 5.2), compared to 5.5 (95% CI 33.9 to 9.1) for postsurgical pain (621 patients). (Combined NNT result 4.6).

There were no significant differences in NNT (4.2 and 5.5), RR (2.93 and 1.86) or absolute scores between dental and postsurgical pain relief with paracetamol 600/650 mg.

- Paracetamol 975/1000 mg

Comparison 04 02

POSTOPERATIVE

PAIN FOLLOWING DENTAL SURGERY: PARACETAMOL 975/1000 mg VERSUS PLACEBO

Data from nine trials (916 patients) were meta-analysed to assess the efficacy of 975/1000 mg paracetamol versus placebo in patients who experienced moderate to severe pain following dental surgery (Bentley 1987; Cooper 1989; Cooper 1998; Hersch 2000; Kiersch 1994; Lehnert 1990; Mehlisch 1995; Moller 2000; Seymour 1996) giving a RR of 3.50 (95% CI 2.57 to 4.77).

Comparison 04 03

POSTOPERATIVE PAIN FOLLOWING SURGERY OTHER THAN DENTAL: PARACETAMOL 975/1000 mg VERSUS PLACEBO

Data from 14 trials (1721) were meta-analysed to assess the efficacy of 600/650 mg paracetamol versus placebo in patients who experienced moderate to severe pain following surgery other than dental surgery (Berry 1975; Bjune 1996; Cooper 1986; Edwards 2002; Laska 1983 (Study 3); McQuay 1988; Mehlisch 1984; Mehlisch 1990; Rubin 1984; Sakata 1986; Santos Pereira 1986; Schachtel 1989; Winnem 1981; Winter 1983) giving a RR of 2.16 (95% CI 1.88 to 2.48).

The NNT for at least 50% pain relief over four to six hours from dental pain (1038 patients) was 3.7 (95% CI 3.1 to 4.7) and 3.9 (95% CI3.3 to 4.7) for postsurgical pain (1721 patients).

There was no significant difference in the NNT (3.7 and 3.9) between dental and postsurgical pain relief with paracetamol 975/1000 mg, but the difference between the RRs (3.5 and 2.16) was significant.

TRIAL SIZE

Across all trials of all doses, the overall mean number of patients included in paracetamol trial arms was 53 (range 20 to 306). The mean overall number of patients included placebo trial arms was 42 (range 17 to 109). Thirty seven patients was used as the cut-off in order to remain consistent with previous versions of the review.

- Paracetamol 600/650 mg

Twelve trials (680 patients) included treatment arms with 36 or fewer patients; 7 trials (1206 patients) included treatment arms with more than 36 patients. There was no significant difference in NNT between trials with 36 or fewer patients NNT 5.3 (3.8 to 8.4) and trials with more than 36 patients NNT 4.2 (3.6 to 5.2).

- Paracetamol 975/1000 mg

Four trials (214 patients) included treatment arms with 36 or fewer patients; 20 trials (2545 patients) included treatment arms with more than 36 patients. There was no significant difference in NNT between trials with 36 or fewer patients NNT 4.1 (2.7 to 8.6) and trials with more than 36 patients NNT 3.8 (3.3 to 4.3).

QUALITY SCORE

Across all trials, the mean overall quality score determined using the Oxford scale (Jadad 1996a) was 4, ranging between 2 and 5. 69% of trials scored 4 or 5. Three was chosen as the cut-off as it is signifies trials of acceptable quality and is consistent with analyses in previous versions of this review.

- Paracetamol 600/650 mg

Six trials (352 patients) were given a quality score of 3 or less; 13 trials (1534 patients) were given a quality score of 4 or 5.
There was no significant difference in NNT between trials with a quality score of 3 or less (NNT 4.9 (95% CI 3.3 to 9.7)) and trials with a quality score of 4 or 5 (NNT 4.5 (95% CI 3.8 to 5.4)).

- Paracetamol 975/1000 mg

Eight trials (831 patients) were given a quality score of 3 or less; 15 trials (1928 patients) were given a quality score of 4 or 5.
There was no significant difference in NNT between trials with a quality score of 3 or less (NNT 3.3 (95% CI 2.7 to 4.0) and trials with a quality score of 4 or 5 (NNT 4.1 (3.5 to 5.0)).

DISCUSSION

The NNT values for at least 50% pain relief over four to six hours with the two most common doses (600/650 mg and 975/1000 mg) compared against placebo, were 4.6 (3.9 to 5.5) and 3.8 (3.4 to 4.4). The NNTs for paracetamol 325 mg, 500 mg, and 1500 mg were 3.8 (2.2 to 13.3), 3.5 (2.7 to 4.8), and 3.7 (2.3 to 9.5) respectively.

Perhaps the greatest advantage of meta-analysis is that by combining appropriate data the threat of random chance associated with small patient numbers is reduced. Methodological research on analgesic trials has demonstrated that data from approximately

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200 patients is needed for credible estimates (ie, to be 95% confident that the NNT is true within 0.5 of the observed value) when the NNT is 2, and approximately 1000 patients when the NNT is 3 (Moore 1998). No dose was significantly more effective than any other, but if these criteria are applied then the comparisons for doses of 325 mg, 1500 mg, and probably 500 mg, are not persuasive.

Dose: 325 mg; 500 mg; 600/650 mg; 975/1000 mg;1500 mg
NNT: 3.8; 3.5; 4.6; 3.8; 3.7
Number of patients: 100; 561; 1886; 2759; 138

The sensitivity analyses did not show significant bias from small trials or trials judged to be of a lower quality (Khan 1996; Moore 1998). There was, however, a significant difference in relative risk between dental and postsurgical pain models for paracetamol 975/1000 mg although not for paracetamol 600/650 mg. This difference was found only for RR; the NNT and absolute event rates were not significantly different. Additional research using a substantial amount of data from systematic reviews of aspirin and ibuprofen found few statistically significant differences between dental and postsurgical trials; only in three out of 16 statistical comparisons (for relative risk with paracetamol 975/1000 mg as reported in this review, NNT with ibuprofen 400 mg, and the proportion of patients with 50% pain relief with aspirin 600/650 g) (Barden (in press)). The fact that differences between models were found so infrequently justifies pooling data (meta-analysis) from the retrieved trials. That differences between models were found at all necessitates that pooled analyses should be accompanied by sensitivity analyses wherever possible.

Paracetamol is one of several options for treating acute postoperative pain. Ibuprofen, aspirin and others have also been evaluated using the same methods. Paracetamol 975/1000 mg is as effective as aspirin 600/650 mg which has an NNT 4.4 (4.0 to 4.9) and ibuprofen 100 mg which has an NNT 4.3 (3.2 to 6.3) (Bandolier 2003). Paracetamol 975/1000 mg was less effective (had a higher NNT) than ibuprofen 400 mg with an NNT 2.4 (2.3 to 2.6) and diclofenac 50 mg with an NNT 2.3 (2.0 to 2.7) (Bandolier 2003). Adverse effects with paracetamol rarely occur more frequently than with placebo in acute pain trials. Consequently, significant differences in adverse effects are rarely found in systematic reviews. However, paracetamol is known to have fewer long term gastrointestinal adverse effects than other non-steroidal anti-inflammatory (NSAID) treatment options though is associated with renal and hepatic problems with long term use.

The efficacy results of this review are marginally better than those reported in the previous version however the place of paracetamol in clinical decision-makig remains unchanged.

AUTHORS' CONCLUSIONS

Implications for practice

Paracetamol is effective for postoperative pain after operations, including dental surgery, and has a low incidence of associated adverse effects.

Implications for research

Eleven reports of studies suspected to be RCTs were excluded from this review as the authors had failed to adequately describe their methods (CONSORT 2003). Unless methods are adequately described not only is meta-analysis unduly hampered but factors affecting quality and validity may be hidden and further methodological research hindered. The quality of reporting on adverse effects, withdrawals and exclusions was also poor with some reports failing to provide any useful information.

NOTES

This review is an update of a Cochrane systematic review by Collins S et al entitled: 'Single dose paracetamol (acetaminophen) with and without codeine for postoperative pain' , published in 1998. The original review has been split into two reviews: paracetamol alone, and paracetamol plus codeine.

POTENTIAL CONFLICT OF INTEREST

RAM & HJM have consulted for various pharmaceutical companies. RAM, HJM & JE have received lecture fees from pharmaceutical companies that market analgesics and other healthcare interventions. All authors have received research support from charities, government and industry sources at various times, but no such support was received for this work.

ACKNOWLEDGEMENTS

Sally Collins and Dawn Carroll were authors on the previously published version of this review (Collins 1998). Thanks to Martin Tramer, Marie Bisercic and Anna Oldman for translating reports, and Clare Abbott at the Cairns Library, The Churchill Hospital, for her help with obtaining papers.

SOURCES OF SUPPORT

External sources of support

- Anglia and Oxford RHA UK

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- NHS Research and Development Health Technology Evaluation Programmes UK
- European Union Biomed 2 Grant no. BMH4 CT95 0172 UK

Internal sources of support

- Oxford Pain Research funds UK

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TABLES

Characteristics of included studies

Study	Bentley 1987
Methods	RCT, DB, single oral dose, 4 parallel groups. No info on anaesthetic, no sedative or narcotic agents were used before, during or after surgery. Self assessed at home at 0,1, 2, 3, 4, 5 hrs then posted reports to investigator.
Participants	3rd Molar removal (Bony Impacted) n=128 Age - mean mid 20's
Interventions	Placebo n=17 Paracetamol(100 mg) n=41 Paracetamol (1000 mg) + Codeine (60 mg) n=41
Outcomes	PI (10pt scale) PR (5pt scale) Both paracetamol & the combination were significantly superior to placebo for all measures of efficacy, but the combination was not significantly different to paracetamol for any measure.
Notes	Patients who remed < 5hrs, last PI & PR scores carried on for all further timepoints. 120 analysed. Exclusions: 3 did not take the med, 1 took only a portion, 1 took no med until the day after surgery, 1 remed after 30 min, 1 vomited within 30mins of taking the med & 1 patient did not return the forms. 53 had 1 or more AE, 86 were reported in total, majority were dizziness, drowsiness, nausea & vomiting. There was no sig dif between treatment groups. # Patients with AE; Paracetamol 21/42 with 31 AE Para + cod 15/42 with 24 AE Placebo 9/19 with 16 AE QS 3
Allocation concealment	A – Adequate

Study	Berry 1975
Methods	RCT, DB, single oral dose, 3 parallel groups. 12 hr washout prior to start. Assessed by observer(s) in hospital at 0, 0.5, 1, 2, 3, 4 hrs.
Participants	Episiotomy n=225 Age15+
Interventions	Placebo n=76 Paracetamol(1000mg) n=76
Outcomes	PI (5pt scale) - non-standard scale PR (5pt scale) - non-standard scale Gastric discomfort (4pt scale) Global Rating (5 word scale) Total Pain Scores & Total Relief from pain scores showed Paracetamol to be significantly superior to Placebo. Global rating > good Placebo 18/76 Paracetamol 43/76

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Notes	After a reasonable period rescue analgesia could be prescribed at the investigator's discretion & the patient regarded as a treatment failure (no info on how data handled). No details on withdrawls or dropouts. "None of the patients experienced adverse drug reactions." QS 3
Allocation concealment	A – Adequate

Study	**Bhounsule 1990**
Methods	RCT, DB, single oral dose, 5 parallel groups. LA - lignocaine, 6 hr washout. Evaluated in hospital by observer at 0, 30 min, 1 hr then hourly for 6 hrs.
Participants	Post-episiotomy n = 100 Age: adult (not stated)
Interventions	Paracetamol (600 mg) n = 20 Placebo n = 20
Outcomes	PI (4 pt scale) PR (5 pt scale) Paracetamol was significantly superior to placebo across all time pointsexcept 1.5 hrs for PI and PR.
Notes	No patients remedicated, no other exclusion details given. No adverse effects were reported in either group. QS 3
Allocation concealment	A – Adequate

Study	**Bjune 1996**
Methods	RCT, DB, single oral dose, 3 parallel groups. 4hr washout prior to start. Baseline pain >40mm = moderate, >60mm = severe. Evaluated in hospital at 0, 0.5, 1hrs then hourly for 6 hrs.
Participants	Caesarean section n = 125 Age 27 - 37
Interventions	Placebo n = 21 Paracetamol (1000 mg) n = 43 Paracetamol (800 mg) + Codeine (60 mg) n = 44
Outcomes	PI VAS ("no pain" to "unbearable pain") PR (5pt scale) For the patients with moderate pain there were no differences between the groups for any measures of efficacy. For patients with severe pain the active groups were significantly superior to placebo for most measures of efficacy (p<0.005)
Notes	Remed after 1st hour (PI = 0 and PR last score used for all further time points). 108 analysed. Exclusions: 6 patients did not adhere to 4hr washout, 5 had PI<40 mm and 5 were excluded for other minor protocol violations. # Patients with AE;

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	Placebo 1/25 with 1 AE Paracetamol 10/50 with 14 AE Para + Cod 10/50 with 11 AE QS 3
Allocation concealment	A – Adequate

Study	**Cooper 1980**
Methods	RCT, DB, single oral dose, 6 parallel groups. No info on anaesthetic. Self assessed at home at 0,1,2,3,4 hrs (questionnaire) - majority collected 1 week later by observer, few returned by mail (patients telephoned if problems encountered)
Participants	Removal of impacted 3rd Molar n=298 Age - mean early 20's
Interventions	Placebo n=38 Paracetamol (500mg) n=37
Outcomes	PI (4pt scale) PR (5pt scale) Global Rating (5pt scale) 50% relief of baseline pain (y/n) Time to Remedication Paracetamol showed significant analgesic efficacy for all measures.
Notes	t>1hr before remed (unclear how data handled). 247 analysed. Exclusions: 21 were lost to follow up, 10 dropped out before ingesting med. (no details), 20 ingested med. but were excluded for protocol violations (no details). # Patients with AE; Placebo 6/38 with 7 AE Paracetamol 3/37 with 6 AE QS 4
Allocation concealment	A – Adequate

Study	**Cooper 1981**
Methods	RCT, DB, single oral dose, 5 parallel groups. Either GA or LA. Self assessed at home at 0,1,2,3,4 hrs (questionnaire).
Participants	Removal of impacted 3rd Molar n=248 Age - mean early 20's
Interventions	Placebo n=37 Paracetamol(650mg) n=37 Paracetamol (650mg) + Codeine (60mg) n=42
Outcomes	PI (4pt scale) PR (5pt scale) Global Rating (5pt scale) 50% relief of baseline pain (y/n) Time to Remedication

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	All active treatments were significantly superior to Placebo for all measures. The Combination was slightly more effective than the Paracetamol alone but the difference was not significant.
Notes	Remed after 1st hour if needed (last score used for all further time points). 200 analysed. Exclusions: 17 did not ingest med., 31 ingested med but violated protocol (remed before 1st hour obs, constant deviation of more than 15 min from evaluation times, not returning questionnaire & lost to follow up). No serious AE was reported. # Patients with AE; Placebo 4/37 with 5 AE Paracetamol 12/37 with 15 AE Para + cod 10/42 with 10 AE QS 4
Allocation concealment	A – Adequate

Study	**Cooper 1986**
Methods	RCT, DB, single oral dose, 3 parallel groups, single centre & 1 surgeon. No info on anaesthetic. Self assessed at home at 0,1,2,3,4,5,6 hrs (diary).
Participants	Oral surgery (involving bone removal) n=112 Age 16+
Interventions	PI (4 pt scale) PR (5 pt scale) Pain half gone? (y/n) Global rating (5 pt) Time to Remedication
Outcomes	Placebo n=22 Paracetamol (1000mg) n=38 For all measures Paracetamol was significantly superior to Placebo (P<0.05).
Notes	Remed after 1st hour if needed (last score used for all further time points). 99 analysed. Exclusions: 6 did not require analgesia, 3 fell asleep & the other 4 were "various protocol violations". No serious AE was reported. Over half reported were drowsiness & there were 2 reports of nausea. # of AE reported; Paracetamol 12 Placebo 0 QS 3
Allocation concealment	A – Adequate

Study	**Cooper 1988**
Methods	RCT, DB, single oral dose, 3 parallel groups, single centre & 1 surgeon. LA with sed &/or nitrous oxide. 4hr washout prior to start. Self assessed at home at 0,0.5,1,2,3,4,5,6 hrs (diary).
Participants	Removal of impacted 3rd Molar n=165 Age 18 - 57
Interventions	Placebo n=40 Paracetamol(600mg) n=36 Paracetamol(600mg) + Codeine(60mg)

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	n=31
Outcomes	PI (4 pt scale) PR (5 pt scale) Pain half gone? (y/n) Global rating (5 pt) Time to Remedication The Combination was significantly superior to Placebo for every measure & to Paracetamol for TOTPAR. Paracetamol appeared clinically more effective than Placebo but it was not significant. ($p < 0.05$).
Notes	Remed after 1st hour (last or baseline score used for all further time points). 143 analysed. Exclusions: 11 were lost to follow up, 8 did not require med. & 3 for "various protocol violations". No serious AE were reported. # of AE reported; Placebo 3 Para 8 Para + cod 4 QS 4
Allocation concealment	A – Adequate

Study	**Cooper 1989**
Methods	RCT, DB, single oral dose, 3 parallel groups. LA with iv sed., atropine &/or Nitrous oxide. 4hr washout prior to start. Self assessed at home at 0,0.5,1,2,3,4,5,6 hrs (diary).
Participants	Removal of impacted teeth n=194 Age 16+
Interventions	Placebo n=64 Paracetamol (1000mg) n=59
Outcomes	PI (4 pt scale) PR (5 pt scale) Pain half gone? (y/n) Global rating (5 pt) Time to Remedication Paracetamol was significantly superior to the Placebo ($P<0.05$ to $P<0.001$) for all measures.
Notes	Remed after 1st hour (last or baseline score used for all further time points). 184 analysed. Exclusions: 4 slept through more than 2 observations, 2 were lost to follow up, 2 did not need to medicate, 1 had inadequate baseline PI & 1 failed to complete the evaluations at the set times. 190 were evaluated for AE (all who ingested the medication). No serious AE were reported - drowsiness was the most common. # Patients with AE; Placebo 7/64 with 7 AE Paracetamol 11/63 with 13 AE QS 5
Allocation concealment	A – Adequate

Study	**Cooper 1991a**
Methods	RCT, DB, single oral dose, 6 parallel groups. LA. Self assessed at home at 0, 0.5hrs then hourly for 6hrs (diaries).
Participants	Removal of 1 or more impacted teeth

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	n=247 Age "Young Adults"
Interventions	Placebo n=44 Paracetamol(650mg) n=37 Paracetamol(650mg) + Codeine(60mg) n=39
Outcomes	PI (4pt scale) PR (5pt scale) Global Rating (5pt scale) Time to Remedication Paracetamol was the only active drug not to be significantly superior to Placebo for any measure. The combination was significantly superior to placebo for most measures & to Paracetamol for TOTPAR & the global rating.
Notes	t > 1hours before remed, data included & baseline or last score (most severe) used for all further time pts. 226 analysed. Exclusions; 13 did not require med. 3 were lost to follow up, 2 remed. with slight pain before the 2nd hour obs., 2 remed. before the 1st hr obs., 1 fell asleep for over 2 hrs. All AEs were mild; # Patients with AE; Placebo 7/44 with 9 AE Paracetamol 6/37 with 7AE Para + cod 8/39 with 11 AE QS 3
Allocation concealment	A – Adequate

Study	**Cooper 1998**
Methods	RCT, DB, single oral dose, 4 parallel groups, 4 hr washout. Self (patient) assessment at 0, 15, 30 & 45 min, 1 hr then hourly for 6 hours.
Participants	Dental (impacted third molar) n = 177 Age: 16+ (mean 23)
Interventions	PI (4 pt scale) VAS PI (100mm) PR (5 pt scale) Percent remedicated
Outcomes	Paracetamol (1000 mg) n = 50 Placebo n = 26 Paracetamol was significantly superior to placebo and equivalent to ketoprofen 100 mg.
Notes	All randomised patients were included in the analysis. Sleepiness was the most common adverse effect 50% following paracetamol and 15% with placebo. QS 4
Allocation concealment	A – Adequate

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Characteristics of included studies (*Continued*)

Study	**Dionne 1994**
Methods	RCT, DB, single oral dose, 5 parallel groups. GA & LA. 4hr washout prior to start. Self assessed at clinic for at least the first 2 hours then at home hourly for 6 hours.
Participants	Removal of impacted 3rd molar n=135 Age 16+
Interventions	Placebo n=25 Paracetamol(650mg) n=27 Paracetamol(650mg) + Codeine(60mg) n=24
Outcomes	PI (4pt scale) PR (5pt scale) Global Rating (5pt scale) Time to Remedication Neither Paracetamol nor the combination showed a significant difference to placebo for any measure of analgesia.
Notes	If t>2hrs before remed, data included & baseline used for all further timepoints. 124 analysed. Exclusions;4 previously enrolled in the study, 3 remed before t=2hrs, 2 were lost to follow up, 1 was ineligible because of codeine sensitivity. All AEs were mild; # Patients with AE; Placebo 5/25 with 5 AE Paracetamol 7/27 with 9AE Para + cod 9/24 with 10 AE QS 3
Allocation concealment	A – Adequate

Study	**Dolci 1994**
Methods	RCT, DB, single oral dose, 4 parallel groups. Multi-centre (11). No info on anaesthetic. 24hr washout prior to start. Evaluations made at 0, 0.5, 1, 1.5, 2 hours in the clinic then at 3 & 4 hours at home (diary).
Participants	Removal of single impacted 3rd Molar n=336 Age 18+
Interventions	Placebo n=76 Paracetamol(500mg) n=72
Outcomes	PI (4pt scale) PR (5pt scale) Global Rating (5pt scale) PID/PR: Paracetamol was significantly superior to Placebo ($p<0.01$) at t=30min & ($p<0.001$) from t=1 to t=4 hrs. SPID/TOTPAR: Paracetamol was significantly superior from t=1 to t=4.
Notes	Rescue analgesia was permitted after 90 min, no further eval. made post remed. 298 analysed. Exclusions: 15 were lost to follow up, 6 remed. before 1.5 hrs, 3 experienced an adverse event & did not complete the assessments & 14 did not experience > moderate baseline pain. 3 withdrew due to AE; Para, 1 for nausea & 1 for swelling Placebo, 1 for fever, nausea & diarrhoea. Total # of patients with AE;

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	Paracetamol 7/80 with 7 AE Placebo 8/82 with 12 AE QS 4
Allocation concealment	A – Adequate

Study	**Edwards 2002**
Methods	6 RCTs, DB, single oral dose, paralle group, multi-centre. Medication administered when baseline pain reached moderate to severe intensity.
Participants	Dental, gynaecologic and orthopaedic pain patients Age 16-83
Interventions	Trial 1(dental) paracetamol 650 mg n= 50 placebo n=50 Trial 2 (dental) paracetamol 650 mg n=50 placebo n=50 Trial 3 (dental) paracetamol 650 mg n=80 placebo n=79 Trial 4 (dental) paracetamol 650 mg n=80 placebo n=80 Trial 5 (gyne) paracetamol 975 mg n=50 placebo n=50 Trial 6 (ortho) paracetamol 975 mg n=50 placebo n=50
Outcomes	PI (5pt scale & VAS) PR (5pt scale) Global Rating (5pt scale) Time to Remedication All active drugs were significantly superior for all measures of efficacy.
Notes	No serious AE reported. QS 5
Allocation concealment	A – Adequate

Study	**Fassolt 1983**
Methods	RCT, DB, single oral dose. 5 parallel groups. GA used. 4hr washout prior to start. Evaluations made at 0, 30mins then hourly for 6 hrs by the same trained observer in hospital.
Participants	Post operative (“simple surgery” - 15+ named surgical interventions) n=146 Age 18+
Interventions	Placebo n=28 Paracetamol(650mg) n=29
Outcomes	PI (5pt scale & VAS)

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	PR (5pt scale) Global Rating (5pt scale) Time to Remedication All active drugs were significantly superior for all measures of efficacy.
Notes	Remed allowed after 2hrs (last score used for all further time points). No information given on withdrawls or dropouts. No serious AE reported - no further details given. QS 2
Allocation concealment	A – Adequate

Study	**Forbes 1982**
Methods	RCT, DB, single oral dose, 5 parallel groups. No info on anaesthetic. Self-assessed at home at 0,1 then hourly for 12hrs.
Participants	Removal of impacted 3rd Molar (1 or more) n=177 Age 15+
Interventions	Placebo n=30 Paracetamol(600mg) n=34 Paracetamol(600mg) + Codeine(60mg) n=31
Outcomes	PI (4pt scale) PR (5pt scale) 50% PR (y/n) Global Rating (5pt scale) Time to Remedication At 4hrs Paracetamol was significantly superior to Placebo for PR, Peak PR & 50% PR (p<0.01). The combination was significantly superior to Placebo for all measures.
Notes	If remed <2hrs excluded. If >2hrs <12hrs PR = 0 & PI baseline or last for all remaining timepoints. 159 analysed. Exclusions: 4 lost to follow up, 3 did not take med, 7 took remed < 2hrs, 1 med with mild pain & 3 did not complete the forms properly. None of the active treatments produced more AE than the Placebo. None were serious. QS 3
Allocation concealment	A – Adequate

Study	**Forbes 1983**
Methods	RCT, DB, single oral dose, 5 parallel groups. GA, given on request1st day able to take oral analgesia. Self-assessed in hospital at 0,0.5,1,1.5,2 then hourly for 12 hrs, Single nurse observer present for 1st 6 hrs, 2nd 6 hrs monitored by ward staff.
Participants	Postoperative (General, Gynaecological or orthopaedic surgery) n=132 Age 18 +
Interventions	Placebo n=26 Paracetamol(600mg) n=26 Paracetamol(600mg) + Codeine(60mg) n=26

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Outcomes	PI (4pt scale) PR (5pt scale) Pain half gone? (y/n) Global Rating (5pt scale) Time to Remedication For 6 hr data both Paracetamol & the combination were significantly superior to Placebo for all measures & for 12 hour data, all except SPID.
Notes	Patients were remed on demand if < 2hrs excluded. If remed < 12hrs PR=0, PI=baseline or last score for remaining time points. 132 analysed. There were no exclusions. No serious AE reported. Most common were drowsiness, dizziness & dry mouth. # Patients with AE; Placebo 4/26 with 5 AE Paracetamol 11/26 with 11 AE Para + cod 11/26 with 16 AE QS 5
Allocation concealment	A – Adequate

Study	**Forbes 1984a**
Methods	RCT, DB, single oral dose, 4 parallel groups. GA / LA - unclear. Self assess at home at 0,1 then hourly for 6 hours - returned 5 days later for review & debrief.
Participants	Removal of impacted 3rd molar (1 or more) n=191 Age 15 +
Interventions	Placebo n=36 Paracetamol(650mg) n=39
Outcomes	PI (4pt scale) PR (5pt scale) Pain half gone? (y/n) Global Rating (5pt scale) Time to Remedication Para significantly superior for all measures of total & peak analgesia.
Notes	Patients could remedicate after 2 hours but were asked to complete the next evaluation before doing so (PI last or baseline score, PR =0 for all further time points). 148 analysed. Exclusions: 1 did not return results, 1 was lost to follow up, 26 did not req. med, 8 did not follow the instructions & 7 remed < 2hrs. No sig dif in AE between treatments, none were serious. Most frequent was drowsiness. # patients with AE; Placebo 2/40 with 2 AE Paracetamol 1/43 with 2 AE QS 5
Allocation concealment	A – Adequate

Study	**Forbes 1984b**
Methods	RCT, DB, single oral dose, 5 parallel groups. GA, trial drug given on request 1st day after surgery. Assessed in hospital by single nurse-observer at 0, 15min, 30min then hourly for 6 hrs.
Participants	Postoperative (General, Gynaecological or orthopaedic surgery) n=132

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	Age 18 +
Interventions	Placebo n=33 Paracetamol(650mg) n=31
Outcomes	PI (4pt scale) PR (5pt scale) Pain half gone? (y/n) Acceptability (5pt scale - each hr) Time to Remedication Paracetamol was significantly superior for all measures of efficacy from t=1hr to t=4. But only marginally sig. for peakPID & peak PR.
Notes	If remed < 6 hrs PR=0, PI=baseline or last for all remaining time points. 129 analysed. Exclusions: 2 remed < 2hrs & 1 received an interferring med. No serious AE recorded. Sedation accounted for 2/3 of the AE's. # patients with AE; Placebo 8/33 with 9 AE Paracetamol 9/33 with 10 AE QS 4
Allocation concealment	A – Adequate

Study	**Forbes 1989**
Methods	RCT, DB, single oral dose, 4 parallel groups at 2 centres. GA & LA - unclear. Patients self-assessed at home at 0,1,2 then hourly for 12 hours or until remedication (diary) - returned 5 days later for review & debrief.
Participants	Removal of impacted 3rd molar (1 or more) n=107 Age 15 +
Interventions	Placebo n=23 Paracetamol(600mg) n=22 Paracetamol(600mg) + Codeine(60mg) n=17
Outcomes	PI (4pt scale) PR (5pt scale) Global Rating (5pt scale) Time to Remedication At 4hrs: Paracetamol & the Combination were significantly superior to Placebo. The combination was also significantly superior to Paracetamol for TOTPAR. (p<0.05).
Notes	Patients could remed after 2 hours but were asked to complete the next evaluation before doing so (PI last or baseline score, PR =0 for all further time points). 88 analysed. Exclusions: 9 did not take the med., 2 remedicated before the 2 hour point, 1 remedicated with slight pain, 4 did not complete their evaluation, 1 took only part of the med. & 2 remedicated despite of having some relief from the study med. No serious AE reported. # of patients with AE; Placebo 2/26 with 2 AE Paracetamol 3/26 with 3 AE Para + cod 1/17 with 1 AE NB includes AE reported post remed. QS 5

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Allocation concealment	A – Adequate

Study	**Forbes 1990a**
Methods	RCT, DB, single oral dose, 4 parallel groups, LA. Patients self-assessed at home at 0,1 then hourly til 6 hours (diary) - returned 5 days later for review & debrief.
Participants	Removal of impacted 3rd molar (1 or more) n=162 Age 15 +
Interventions	Placebo n=32 Paracetamol(600 mg) + Codeine(60 mg) n=27
Outcomes	PI (4pt scale) PR (5pt scale) Pain half gone? (y/n) Global Rating (5pt scale) Time to Remedication The combination was significantly superior to the placebo for all measures of efficacy.
Notes	If remed <2hrs excluded. If >2hrs <6hrs PR = 0 & PI baseline or last which ever was greater. 128 analysed. Exclusions: 1 failed to return the form, 19 did not require analgesia & 14 had invalid data. No serious AE reported. # of patients with AE; Placebo 5/34 with 6 AE Para + cod 9/31 with 12 AE QS 5
Allocation concealment	A – Adequate

Study	**Forbes 1990b**
Methods	RCT, DB, single then multiple oral dose, 6 parallel groups. GA / LA - unclear. Self assess at home at 0,1 then hourly for 6 hours - returned 5 days later for review & debrief.
Participants	Removal of impacted 3rd molar (1 or more) n=269 Age 15 +
Interventions	Placebo n=34 Paracetamol(600mg) n=36 Paracetamol(600mg) + Codeine(60mg) n=38
Outcomes	PI (4pt scale) PR (5pt scale) Pain half gone? (y/n) Global Rating (5pt scale) Time to Remedication All active medications were significantly superior for all measures of total & peak analgesia.
Notes	Remed allowed after 2 hrs but asked to complete the next eval (PI last or baseline score, PR =0 used for all remaining time points). 206 analysed. Exclusions; 3 lost to follow up, 1 lost report card, 22 did not req med, 8 remed despite having relief from study med, 6 remed with only slight pain, 13 remed < 2hrs, 7 failed to follow instructions , 3 did not complete the forms. No AE was serious.

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	# patients reporting AE; Placebo 0/38 Paracetamol 5/41 with 5 AE Para + cod 8/40 with 9 AE QS 5
Allocation concealment	A – Adequate

Study	**Hersch 2000**
Methods	RCT, DB, single oral dose, 4 parallel groups, 4 hr washout. Self (patient) assessment at 0, 15, 30, 45, 60 & 90 mins then hourly for 12 hours. Six hour data extracted.
Participants	Dental (impacted third molar) n = 210 Age: 16+
Interventions	Paracetamol (1000 mg) n = 63 Placebo n = 27
Outcomes	PI (4 pt scale) VAS PI (100mm) PR (5 pt scale) Global rating (5 pt scale) Percent remedicated Paracetamol was significantly superior to placebo, but significantly less effective than ibuprofen 400 mg.
Notes	Remedication allowed after 1 hr. PI was set to baseline or last value (most severe) and PR was set to zero for all further assessments. All randomised patients were included in the analysis. All reported adverse effects were mild or moderate. QS 4
Allocation concealment	A – Adequate

Study	**Honig 1984**
Methods	RCT, single oral dose, 4 parallel groups. No info on anaes, 4hr washout prior to start. Interviewed in hospital by nurse observer at 0, 0.5, 1hrs then hourly for 6hrs.
Participants	Post elective surgery (abdominal, orthopaedic, rectal, thoracic & vascular) n=116 Age 19-87
Interventions	Placebo n=30 Paracetamol(600mg) n=28 Paracetamol(600mg) + Codeine(60mg) n=30
Outcomes	PI (4pt scale) PR (5pt scale) 50% PR (y/n)

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	Global Rating (5pt scale) TOTPAR & Global Rating; Both Paracetamol & the Combination were significantly superior to Placebo (p<0.05). The combination was also significantly superior for SPID & no. remedicating before 6hrs.
Notes	If remed last score was used for all further timepoints. No details given on withdrawls or dropouts. None severe except 1 severe dry mouth. Reported in all groups & were primarily CNS & gastrointestinal effects. QS 3
Allocation concealment	A – Adequate

Study	**Jain 1986**
Methods	RCT, DB, single oral dose, 4 parallel groups. GA, trial drug given within 72 hours of surgery on request for analgesia. 4hr washout prior to start. Assessed in hospital by nurse-observer at 0, 15min, 30min then hourly for 6 hrs.
Participants	General, Gynaecological or orthopaedic surgery n=128 Age 18 - 70
Interventions	Placebo n=32 Paracetamol(650mg) n=30
Outcomes	PI (4pt scale) PR (5pt scale) Paracetamol was only significantly superior for one measure of analgesia.
Notes	Remed < 2hrs data excluded. If > 2hrs last measure used for all remaining time points. 122 analysed. Exclusions: 2 had improperly blinded drugs, 2 remed < 2 hrs & 2 received concomitant medication. No serious AE reported. No sig dif in occurrence between groups. Total # patients with AE; Placebo 6/32 with 8 AE Paracetamol 9/30 with 9 AE QS 4
Allocation concealment	A – Adequate

Study	**Kiersch 1994**
Methods	RCT, DB, single oral dose, 3 parallel groups. LA, 48 hr washout prior to start. Self-assessed in clinic for first 2 hrs then at home. Assessed at 0, 20mins, 30mins, 40mins, 1 hr then hourly for 12hrs.
Participants	Removal of impacted 3rd molar n=232 Age 14 +
Interventions	Placebo n=30 Paracetamol(1000mg) n=30
Outcomes	PI (4pt scale) PR (5pt scale) Pain half gone? (y/n) Global Rating (5pt scale) Time to Remedication PI VAS (100mm) Paracetamol was significantly superior to Placebo for most efficacy measures in the first 6 hours.

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Notes	"Patients were asked to allow 2 hours.....before taking alternate medication." 226 analysed. Exclusions: 1 experienced nausea & vomiting so did not ingest the treatment, 2 did not require analgesia, 1 failed to follow the instructions & 2 vomited within 10 mins of taking the trial drug. None serious. # patients reporting AE; Placebo 13/45 with 18 AE Paracetamol 31/92 with 35 AE QS 4
Allocation concealment	A – Adequate

Study	**Laska 1983 (Study 3)**
Methods	RCT, DB, single oral dose, 7 parallel groups. 4hr washout prior to start. Evaluated by same nurse observer in hospital at 0, 0.5, 1hrs then hourly for 4 hrs.
Participants	Post partum (post episiotomy and post-surgical) n = 552 Age - did not say
Interventions	Placebo n=57 Paracetamol(500mg) n=81 Paracetamol(1000mg) n=81 Paracetamol(1500mg) n= 81
Outcomes	PI (4pt scale) PR (5pt scale) - NB non-standard scale (% pain relief) All doses of paracetamol were significantly superior to placebo for SPID, TOTPAR, %SPiD and ONSET ($p<0.05$).
Notes	Remed after 1st hour (PI = 0 and PR last score used for all further time points). 358 analysed. Exclusions: 14 for protocol violations. No AE were reported. QS 4
Allocation concealment	A – Adequate

Study	**Lehnert 1990**
Methods	RCT, DB, single oral dose, 3 parallel groups. 4hr washout prior to start. Self assesed at 0, 0.5, 1hrs then hourly for 6 hrs.
Participants	Removal of 3rd molar n= 150 Age - did not say
Interventions	Placebo n=40 Paracetamol(1000mg) n=49
Outcomes	PI (4pt scale) PR (5pt scale) Global Rating (4pt scale) Paracetamol was significantly superior to Placebo for all measures of efficacy.
Notes	If remed <6 hrs patient was considered a dropout, no data on how data was handled. 133 analysed. Exclusions: 11 did not take the medication, 3 were lost to follow up and 3 for various protocol violations.

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	# patients reporting AE; Placebo 4/40 with ? AE Paracetamol 5/49 with ? AE QS 5
Allocation concealment	A – Adequate

Study	**McQuay 1988**
Methods	RCT, DB, single oral dose, 5 parallel groups. GA, trial drug given 1/2 days after surgery. 3hr washout prior to start. Assessed in hospital by nurse-observer at 0, 0.5,1 & 1.5hrs then hrly for 6 hrs.
Participants	Postelective orthopaedic surgery n=158 Age 18 - 70
Interventions	Placebo n=30 Paracetamol(1000mg) n=30 NB these are the numbers after exclusions
Outcomes	PI (4pt scale, VAS & 8 word verbal rating) PR (5pt scale & VAS) Pain half gone? (y/n) Global Rating (5pt scale - both patient & observer) Time to Remedication Paracetamol was significantly superior to Placebo for all integrated measures of efficacy.
Notes	If remed after 1hr PI scored at baseline & PR = 0. 150 analysed. Exclusions: 2 were discharged before the end, 3 received drugs prohibited by protocol, 1 vomited intact med. within 15min & 2 patients pain assessments were not adequately completed. None serious & no sig dif between groups. # patients reporting AE; Placebo 6/30 with 8 AE Paracetamol 6/30 with 10 AE QS 4
Allocation concealment	A – Adequate

Study	**Mehlisch 1984**
Methods	RCT, DB, single oral dose, 3 parallel groups. No info on anaesthetic except no long acting im or iv anaesthetics were used, 4hr washout period prior to start. Assessed in clinic by nurse-observer at 30min then hourly for 6 hrs.
Participants	Oral surgery (involving bone removal) n=174 Age 16+
Interventions	Placebo n=55 Paracetamol(1000mg) n=58
Outcomes	PI (4pt scale) PR (5pt scale) Pain half gone? (y/n) Global Rating (5pt scale) Time to Remedication

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	Paracetamol was significantly superior (p<0.05) to Placebo for all measures.
Notes	Remed if req after 1 hr - If remed patient considered treatment failure (no details on how data was handled). 162 analysed. Exclusions: 9 failed to comply with protocol & 3 were lost to follow up. No sig dif between # of AE for Paracetamol & placebo - no other details given. QS 4
Allocation concealment	A – Adequate

Study	**Mehlisch 1990**
Methods	RCT, DB, single oral dose, 3 parallel groups. LA, 6 hr washout prior to start. Self-assessed at 0, 0.5, 1 hrs then hourly for 6hrs. Multi-centre (7 investigators).
Participants	Oral surgery (various procedures) n=706 Age 17 - 64
Interventions	Placebo n=85 Paracetamol (1000 mg) n=309
Outcomes	PI (4pt scale) PR (5pt scale) Both active treatments were significantly superior to placebo.
Notes	If remedicated PI = baseline and PR = 0. 697 analysed. Exclusions: 4 lost to follow up, 4 entered in trial twice and 1 failed to meet inclusion criteria. # patients reporting AE; Placebo 12/85 with ? AE Paracetamol 32/307 with ? AE QS 4
Allocation concealment	A – Adequate

Study	**Mehlisch 1995**
Methods	RCT, DB, single oral dose, 3 parallel groups. LA, 12 hr washout prior to start. Self-assessed at 0, 15mins, 45mins, 1 hr & 90mins then hourly for 6hrs.
Participants	3rd molar removal (at least 1 embedded) n=240 Age 15 +
Interventions	Placebo n=40 Paracetamol(1000mg) n=101
Outcomes	PI (4pt scale) PR (5pt scale) Global Rating (5pt scale) Paracetamol was significantly superior to Placebo for all measures of efficacy.
Notes	If remed before 1 hour, data was excluded from the analysis. A value of 0 was assigned for PID & PR at all timepoints after remedication. 399 analysed. Exclusions: 1 patient failed to complete the diary. No serious AE reported. # patients reporting AE; Placebo 4/40 with ? AE

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	Paracetamol 17/101 with ? AE QS 3
Allocation concealment	A – Adequate

Study	**Moller 2000**
Methods	RCT, DB, single oral dose, 4 parallel groups, 12 hr washout. Self (pateint) assessment at 0, 10, 20, 30, 45 min, 1 hr then hourly for 4 hrs.
Participants	Dental (impacted third molar) n = 315 Age: 18-50 years
Interventions	Paracetamol tablet (1000 mg) n = 60 Placebo n = 60 Paracetamol effervescent n = 60 Placebo n = 62
Outcomes	PI (4 pt scale) VAS PI (100mm) PR (5 pt) Global rating (4 pt, nonstandard) Time to remedication Time to onset of meaningful oain relief Both paracetamol preparations were significantly superior to placebo
Notes	Exclusions: not stated. Most adverse effects were mild or moderate in severity. QS 4
Allocation concealment	A – Adequate

Study	**Pinto 1984**
Methods	RCT, DB, single oral dose, 3 parallel groups, 4 hr washout. Evaluated in hospital by patient at 0, 30 min, then hourly for 4 hr.
Participants	Tonsillectomy n = 85 Age: 14+ (mean 23 years)
Interventions	Paracetamol (500 mg) n = 29 Placebo n = 29
Outcomes	PI (4 pt scale) PR (5 pt scale)

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	Global rating (4 pt nonstandard scale) Paracetamol was significantly superior to placebo.
Notes	Remedication allowed after 2 hr and patients were withdrawn from the study. Withdrawals and exclusions were not stated. Only one patient reported adverse effects (dipyrone group). QS 3
Allocation concealment	A – Adequate

Study	**Rubin 1984**
Methods	RCT, DB, single oral dose, 4 parallel groups. 6hr washout prior to start. Evaluated at 0, 0.5,1 then hrly for 4 hrs by the same observer.
Participants	Episiotomy (Post uncomplicated delivery) n=500 Age 13 - 40
Interventions	Placebo n=125 Paracetamol(1000mg) n=125
Outcomes	PI (4pt scale] All active groups produced significantly superior pain relief to placebo from t=0.5 hrs to the end of the study.
Notes	If remed < 2hrs excluded. If remed > 2hrs PI last or baseline was allocated for remaining timepoints. 476 analysed. Exclusions: 5 withdrew without taking the medication and 19 remedicated before 2 hours. None serious. # patients reporting AE; Placebo 6/109 with 6 AE Paracetamol 6/123 with 6 AE QS 4
Allocation concealment	A – Adequate

Study	**Rubinstein 1986**
Methods	RCT, DB, single oral dose, 3 parallel groups, 4 hr washout. Patient (self) evaluation at 0, 30 min, 1 hr then hourly for 4 hrs.
Participants	Postoperative (urological) n = 90 Age: 18-94 years
Interventions	Paracetamol (500 mg) n = 30 Placebo n = 30
Outcomes	PI (4 pt scale) PR (5 pt scale) Global rating (5 pt scale) Paracetamol was signifiacntly superior to placebo.
Notes	Eight pateints were withdrawn as they remedicated within the study period. One patient in the paracetamol group vomited however no other adverse effects were reported.

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	QS 4
Allocation concealment	A – Adequate

Study	**Sakata 1986**
Methods	RCT, DB, single oral dose, 3 parallel groups, 4 hr washout. Self (patient) evaluation in hospital at 0, 30 min, then hourly for 4 hrs.
Participants	Postoperative (mainly orthopaedic) n = 86 Age: 14-63 (mean 32 years)
Interventions	Paracetamol (1000 mg) n = 30 Placebo n = 27
Outcomes	PI (4 pt scale) PR (5 pt scale) Global rating (nonstandard) Paracetamol was significantly superior to placebo and equivalent to dipyrone 1000 mg.
Notes	Not stated how many remedicated or how the data handled. Withdrawals and exclusions not stated. No information on adverse effects. QS 2
Allocation concealment	A – Adequate

Study	**Santos Pereira 1986**
Methods	RCT, DB, single oral dose, 3 parallel groups, 4 hr washout. Self (patient) evaluation in hospital at 0, 15 & 30 min, 1 hr then hourly for 4 hrs.
Participants	Orthopaedic surgery n = 85 Age: mean 37-40 years
Interventions	Paracetamol (1000 mg) n = 28 Placebo n = 29
Outcomes	PI (4 pt scale) PR (5 pt scale) Global rating (4pt nonstandard scale) Paracetamol was significantly superior to placebo.
Notes	Remedication allowe and patients withdrawn from the study. No details given on withdrawals and exclusions or adverse effects. QS 3
Allocation concealment	A – Adequate

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Characteristics of included studies (*Continued*)

Study	**Schachtel 1989**
Methods	RCT, DB, single oral dose, 3 parallel groups. 4hr washout prior to start. Assessed (where & by who not clear) at 0, 0.5,1 then hrly for 4 hrs.
Participants	Episiotomy (Post uncomplicated delivery) n=115 Age 16 - 37
Interventions	Placebo n=38 Paracetamol(1000mg) n=37
Outcomes	PI (4pt scale) PR (5pt scale) Global rating (5pt scale) Paracetamol was significantly superior (p<0.05) to Placebo for TOTPAR, Global & # remed.
Notes	Remed after 1 hr - if did considered treatment failures, last/baseline PI & PR=0 scored for the remaining time points. 111 analysed. Exclusions: 4 patients remed but did not record at what time. No AE were reported. QS 4
Allocation concealment	A – Adequate

Study	**Seymour 1996**
Methods	RCT, DB, single oral dose, 5 parallel groups. 12hr washout prior to start. Evaluated at 0, 0.25, 0.5, 0.75, 1, 1.5, 2hrs then hrly for 6 hrs. Baseline pain >30mm.
Participants	Third Molar Extraction n= 206 Age - Adults
Interventions	Placebo n=41 Paracetamol (500 mg) n=41 Paracetamol(1000mg) n=41
Outcomes	PI VAS ('no pain" to "unbearable pain") Global rating (5pt by patient) All active treatments resulted in significantly less pain than placebo (p<0.01)
Notes	If remedicate< 1hr excluded. If > 1hr last PI value was allocated for all remaining timepoints. 200 analysed. EXclusions: 6 for remedicating in the first hour. No patients reported any AE's. QS 4
Allocation concealment	A – Adequate

Study	**Sunshine 1986**
Methods	RCT, DB, single oral dose, 6 parallel groups. LA (lidocaine/epinephrine). 4hr washout prior to start. Evaluations at 0, 0.5, 1, 2 & 3hrs in clinic by single observer. At 4, 5 & 6hrs self-assessed. 1 week later met with observer & reviewed the forms.
Participants	Removal of impacted 3rd Molar n=182 Age 16+
Interventions	Placebo n=30

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	Paracetamol(650mg) n=30 Paracetamol(650mg) + Codeine(60mg) n=31
Outcomes	PI (4pt scale) PR (5pt scale) Global rating (4pt scale) Overall improvement (7pt scale) Time to remedication Both Paracetamol & the Combination were significantly superior (p<0.05) to Placebo for; PID 1-3 hrs, SUMPID at 4 hrs, PR at 2hrs & t to Peak effect. The combination was also significantly superior for TOTPAR.
Notes	If < 1hr excluded. If > 1hr use last PI or baseline & PR = 0. 182 analysed. No exclusions. No serious AE, no sig dif between groups. # patients reporting AE; Placebo 1/30 Para 1/30 Para + cod 3/31 QS 5
Allocation concealment	A – Adequate

Study	**Sunshine 1989**
Methods	RCT, DB, single oral dose, 3 parallel groups. Only inc patients with severe pain. 4hr washout prior to start. Evaluations in hosp by nurse observer at 0, 0.5, 1 then hrly for 6 hrs (if asleep - woken). Interviewed in patients 1st language (Spanish).
Participants	Episiotomy (multiparous inpatients) n=200 Age 18+
Interventions	Placebo n=50 Paracetamol(650mg) n=75
Outcomes	PI (4pt scale) PR (5pt scale) Global rating (4pt scale) Overall improvement (7pt scale) Time to remedication Paracetamol was significantly superior (p<0.05) to Placebo for all measures of efficacy.
Notes	If remed < 2hrs excluded. If remed > 2hrs PI last or baseline & PR = 0 for remaining timepoints. No remeds < 2hrs. 200 analysed. No exclusions. Only 2 patients with AE neither were in the Paracetamol nor Placebo groups. AE were mild dizziness, sleepiness & sweating. QS 4
Allocation concealment	A – Adequate

Study	**Sunshine 1993**
Methods	RCT, DB, single oral dose then multi-dose, 5 parallel groups. Only inc. patients with severe pain, 4hr washout prior to start. Eval carried out by same nurse observer at 0, 0.5, 1 then hourly for 8hrs. Interviewed in patients 1st language (Spanish).
Participants	Postoperative (Caesarean Section)

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	n=240 18+
Interventions	Placebo n=48 Paracetamol(650mg) n=48
Outcomes	PI (4pt scale) PR (5pt scale) Global rating (5pt scale) Time to meaningful relief Paracetamol was not significantly superior (p<0.05) to placebo for any measure.
Notes	If remed < 1hr after 1st dose, dropped & replaced. If remed> 1hr after 1st dose eligible for the repeat dose phase. All 240 enroled were analysed. No details on AEs for single dose phase. QS 4
Allocation concealment	A – Adequate

Study	**Winnem 1981**
Methods	RCT, DB, single oral dose, 4 parallel groups. 4hr washout period prior to start. Evaluated by nurse observer at 0, 0.5, 1 hrs then hourly for 6 hrs.
Participants	Post orthopaedic surgery n = 80 Age 17 - 63
Interventions	Placebo n=20 Paracetamol(1000mg) n=20
Outcomes	PI (4pt scale) PI VAS (“no pain” to “unbearable pain”) Paracetamol was significantly superior to placebo for all measures of pain relief. (p<0.05)
Notes	If remed after 2 hrs withdrawn and all subsequent scores were assumed to be baseline. 79 analysed. Exclusions:1 for vomiting medication. No AE were observed. QS 4
Allocation concealment	A – Adequate

Study	**Winter 1979**
Methods	RCT, DB, single oral blind, 4 parallel groups, 3 hr washout period prior to start.GA &/or LA. Self (patient) assessment at 0, 0.5, 1, 2, 4 and 6 hours.
Participants	Oral surgery (various procedures) n = 231 age: 18-65
Interventions	Paracetamol (325 mg) n = 49 Placebo n = 51
Outcomes	PI (4 pt scale) Paracetamol was significantly better than placebo.

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Notes	Remedication was allowed. No info provided on how the data was then handled. None remedicated before two hours. 31 particpants were excluded but no reasons given. No serious AE reported. QS 2
Allocation concealment	A – Adequate

Study	**Winter 1983**
Methods	RCT, DB, single oral dose, 4 parallel groups. 4hr washout period prior to start. GA &/or LA. Self-assessed at 0, 0.5, 1, 2, 3 & 4hrs.
Participants	Oral Surgery (various procedures) n=168 Age 16 - 75
Interventions	Placebo n=41 Paracetamol(1000mg) n=41
Outcomes	PI (4pt scale) PR (5pt scale) 50% PR Global Rating (5pt scale) Paracetamol was significantly superior to placebo for all measures of analgesic efficacy. Both produced sig analgesia as early as t=0.5hrs.
Notes	Remed was allowed after 2 hrs or if pain returned to pre-medication levels. 2 patients remed ?2hrs (1 placebo + 1 Paracetamol). 164 analysed. Exclusions: 3 Protocol violations & 1 did not received study med. No serious AE were reported. # Patients with AE; Placebo 1/41 (severe headache) Paracetamol 0/41 QS 4
Allocation concealment	A – Adequate

Study	**Young 1979**
Methods	RCT, DB, single oral dose, 4 parallel groups. GA, 4hr washout prior to start. Evaluated in hospital by single observer at 0, 0.5, 1, 2, 3 & 4 hrs.
Participants	Post various elective procedures n=120 Age 12 - 83
Interventions	Study 1: Placebo n=29 Paracetamol(650mg) n=30
Outcomes	PI (4pt scale) PR (5pt scale) 2 Global Ratings (5pt scale) - Both Pat & obs opinion Paracetamol was only significantly superior ($p<0.05$) to placebo at t=2hrs PR score.
Notes	"Any concomitant or additional medication given was duly noted". No details given on this data or how it was handled. 119 analysed. Exclusion: 1 patient had received analgesia within 2hrs of the study. No serious AE reported.

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	# Patients reporting AE; Placebo 1/30 (sedation) Paracetamol 3/30 (nausea) QS 4
Allocation concealment	A – Adequate

Characteristics of excluded studies

Study	Reason for exclusion
Ahlstrom 1985	Intervention administered immediately after surgery before anasthetic wore off. Therefore inadequate baseline pain.
Babul 1993	Did not include paracetamol alone.
Baer 1992	Intervention administered preoperatively. Therefore inadequate baseline pain.
Beaver 1980	Assessed women with postpartum uterine cramps, without any surgical procedure.
Becker 1990	Pain only assessed for 2 hours after administration of the interventions.
Behotas 1992	Interventions were given when pain was "of sufficient intensity that analgesia would normally be given" and data was only presented for pain relief over the first hour.
Breivik 1999	No placebo control.
Bullingham 1981	No placebo control (paracetamol v a paracetamol/buprenorphine combination).
Cade 1993	Intervention administered preoperatively. Therefore inadequate baseline pain.
Cheung 1992	Intervention administered preoperatively. Therefore inadequate baseline pain.
Cooper 1976	Data only collected over 3 hours.
Cooper 1984	Inadaquate description of method. Excluded as did not state whether allocation was randomised or if the studies (summary of five trials) were double blind.
Daftary 1980	Inadaquate description of method. Excluded as did not state whether allocation was randomised.
Davie 1978	Inadaquate description of method. Excluded as did not state whether allocation was randomised.
De Santis 1993	No placebo control (paracetamol v ST679).
Desjardins 1986	Did not include paracetamol alone.
Dolci 1993	Contains a subset of patients from another included report [Dolci 1994]. Confirmed by author as duplication.
Eskenazi 1976	No placebo control (paracetamol v Mephenoxalone v a combination of both).
Filtzer 1980	No placebo control (paracetamol v naproxen v pentazocine).
Forbes 1981	Inadaquate description of method. Excluded as did not state whether allocation was randomised.
Forbes 1986	Did not include paracetamol alone.
Forbes 1990	Did not include paracetamol alone.
Forbes 1994	Did not include paracetamol alone.
Frerich 1981	Inadaquate description of method. Excluded as did not state whether allocation was randomised.
Fulkerson 1986	Did not include paracetamol alone.
Gallardo 1980	Inadaquate description of method. Excluded as did not state whether allocation was randomised.
Gallardo 1990	Pain only assessed for 3 hours after administration of the interventions.
Gertzbein 1986	Did not include paracetamol alone.
Gillberg 1993	Intervention administered preoperatively. Therefore inadequate baseline pain.

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Gomez-Jimenez 1980	Dental study; no placebo control. Episiotomy study; pain scale used was 5 point - therefore not validated for the data extraction method used.
Gustafsson 1983	No placebo control (pre-operative paracetamol v post-operative paracetamol).
Haanaes 1986	No placebo control (paracetamol v fluproquazone).
Heidrich 1985	Did not include paracetamol alone.
Hopkinson 1973	5 point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient.
Hopkinson 1974	5 point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient.
Hopkinson 1976	5 point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient.
Huang 1986	Intervention administered preoperatively. Therefore inadequate baseline pain.
Irvine 1982	No placebo control (paracetamol v diflunisal).
Jacobson 1987	Did not include paracetamol alone..
Lasagna 1967	Analysis presented does not provide SPID or TOTPAR or sufficient data to allow their calculation. Therefore there is no data presented which is validated for the data extraction method used.
Laska 1983 (study 1)	Assessed women with postpartum uterine cramps, without any surgical procedure.
Laska 1983 (study 2)	Assessed women with postpartum uterine cramps, without any surgical procedure.
Lataste 1981	No placebo control (paracetamol v fluproquazone).
Lecointre 1991	No placebo control (paracetamol v tiaprofenic acid).
Levin 1974	PI scale was 5 point and therefore not validated for the data extraction method. No results for pain relief which would allow the calculation of TOTPAR were presented. Global evaluation was in the opinion of the investigator and not the patient.
Liashek 1987	First dose was administered pre-operatively, data was provided for the second dose which was administered when pain was at least moderate but as a cummulative effect cannot be ruled out data from second doses was not included in the analysis.
Lokken 1980	Intervention given 4 times a day postoperatively irrespective of baseline pain.
Marti 1993	No placebo control (paracetamol v lysine clonixinate).
Matthews 1984	Intervention administered immediately after surgery before anasthetic wore off. Therefore inadequate baseline pain.
Mayer 1984	Did not include paracetamol alone.
McGaw 1987	Participants were children (7 to 16 years old).
McMahon 1987	Used a 4 point pain relief scale which is not validated for the data extraction method used. No information was provided about the pain intensity scale used.
McQuay 1986	No placebo control (paracetamol v ketorolac).
Melzack 1983	All patients requesting another medication during the study were excluded from the analysis. Therefore the derived outcomes (SPID/TOTPAR) calculated from this data is probably not comparable with those calculated the standard way. The standard practice is to exclude patients remedicating in the first hour to hour and a half. Those taking alternative medication after that are included in the analysis, allocating the pain intensity score at time of remedication for all remaining time points to calculate SPID, or a pain relief score of "none" for all further timepoints in the calculation of TOTPAR.
Melzack 1985	Intervention given 3- to 45 mins after surgery, irrespective of baseline pain.

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Moore 1985	Participants were children (5 to 12 years old).
Morrison 1994	No placebo control (paracetamol v ibuprofen v ketorolac).
Movilia 1989	No placebo control (paracetamol v aceclofenac).
Muckle 1984	No placebo control (paracetamol v flurbiprofen). Also is a multiple dose trial which does not provide separate data for the first dose.
Mugnier 1984	No placebo control (paracetamol v naproxen).
Nappi 1993	No placebo control (paracetamol v ST-697).
Nystrom 1988	No placebo control (paracetamol v difluisal).
Olstad 1986a	No placebo control (paracetamol v methylprednisolone).
Olstad 1986b	No placebo control (paracetamol v indoprofen).
Ottinger 1990	Did not include paracetamol alone.
Ouellette 1986	No placebo control (paracetamol plus codeine v naproxen).
Pande 1996a(study 1)	Did not include paracetamol alone.
Pande 1996a(study 2)	Did not include paracetamol alone.
Pande 1996b	Did not include paracetamol alone.
Parkhouse 1967	Inadaquate description of method. Report did not state whether allocation was randomised. Also there was no description of the scales used. Hourly pain relief data provided was in the opinion of the investigator no the patient.
Petti 1985	Single blind study.
Quiding 1981	No placebo control (paracetamol v a dextropropoxyphene combination v a codeine preparation).
Quiding 1982a	Patients instructed to take tablets “when pain relief was needed”. Mean baseline pain minus 2 standard deviations was less than 30mm for all interventions (>30 mm equates to at least moderate pain), therefore it is probable that paitients with mild pain were included.
Quiding 1982b	No placebo control (paracetamol v phenazone v phenazone plus dextropropoxyphene).
Quiding 1983	Patients instructed to take tablets “when pain relief was needed”. Mean baseline pain minus 2 standard deviations was less than 30mm for all interventions (>30 mm equates to at least moderate pain), therefore it is probable that paitients with mild pain were included.
Quiding 1984	No placebo control (paracetamol v codeine).
Ragot 1991	No placebo control (paracetamol v mefenamic acid).
Reijntjes 1987	No placebo control (paracetamol v suprofen).
Rodrigo 1987	Two dose study. Second dose was permitted two hours after the first. No data was provided to allow the calculation of SPID over 4 to 6 hours for the first dose.
Rodrigo 1989	No placebo control (paracetamol v diflunisal).
Sagne 1987	Did not include paracetamol alone.
Sandhu 1996	Intervention administered preoperatively. Therefore inadequate baseline pain.
Scoren 1987	Did not include paracetamol alone.
Seymour 1983	Multiple dose trial. No data gathered on the first dose.
Skjelbred 1977	No placebo control (paracetamol v aspirin).
Skjelbred 1979	Intervention “commenced on the day of surgery”. Baseline pain does not appear to have been measured. Also only one reading taken during the first 4 hours on a 5 point pain intensity scale, therefore SPID cannot be calculated.
Skjelbred 1982	Interventions administered 3 hours after surgery irrespective of baseline pain.
Skoglund 1991	Interventions administered 3 hours after surgery irrespective of baseline pain.

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Characteristics of excluded studies (*Continued*)

Skovlund 1991	Patients were included if they asked for an analgesic. There is no further information provided on the baseline pain level except in figure 3 which shows pain recorded at t=0 of less than 30 mm. Therefore it must be excluded as some included patients did not experience at least moderate baseline pain.
Smith 1975	5 point pain intensity scale and 5 point pain relief scale (including "worse") neither of which are validated for the data extraction method used. Global evaluation was the opinion of the investigators rather than the patient.
Speranza 1992	No placebo control (paracetamol v oxycodone). Also the doses were administered pre-operatively, therefore would not have met the baseline pain criteria.
Spivach 1984	No placebo control (paracetamol v aspirin v caffeine v a combination of the three).
Strom 1990	No placebo control (varyious doses and formulations of paracetamol only).
Stubhaug 1995	Did not include paracetamol alone.
Sunshine 1988	Outline of 5 studies. Study 3 and 4 compare paracetamol plus codeine to placebo. Study 4 is a duplicate of an included RCT. Study 3 cannot be included as the report fails to state whether the allocation to each intervention was randomised.
Sveen 1975	Intervention administered immediately after surgery before anasthetic wore off. Therefore inadequate baseline pain.
Terrence 1983	Inadaquate description of method. Report did not state whether allocation was randomised.
Torabinejad 1994	Intervention administered immediately after surgery before anasthetic wore off. Therefore inadequate baseline pain.
Turek 1988	Did not include paracetamol alone.
Vangen 1988	Did not include paracetamol alone.
Veltmann 1980	No placebo control (paracetamol v paracetamol plus phenylephrine).
Wittenberg 1984	Did not include paracetamol alone.
Wojcicki 1977	Inadaquate description of method. Excluded as did not state whether allocation was randomised. Also inadequate assesment of baseline pain (analgesic taken when required) and only a vague description of the pain scales used.
Yscla 1988	No placebo control (paracetamol v aceclofenac).

ADDITIONAL TABLES

Table 01. Efficacy summary

Dose	No of trials	50% PR paracetamol	50% PR placebo	RB (95% CI)	NNT (95% CI)
325 mg	1	34/49 (69)	22/51 (43)	1.6 (1.1 to 2.3)	3.8 (2.2 to 13.3)
500 mg	6	176/290 (61)	86/271 (32)	1.9 (1.6 to 2.3)	3.5 (2.7 to 4.8)
600/650 mg	19	358/954 (38)	145/932 (16)	2.4 (2.0 to 2.8)	4.6 (3.9 to 5.5)
975/1000 mg	23	746/1627 (46)	222/1132 (20)	2.5 (2.2 to 2.8)	3.8 (3.4 to 4.4)
1500 mg	1	53/81 (65)	22/57 (39)	1.7 (1.2 to 2.4)	3.7 (2.3 to 2.9)

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Table 02. Adverse effects with paracetamol 975/1000 mg

Adverse effect	No of trials	AE with paracetamol	AE with placebo	RR (95% CI)	NNH (95% CI)
Drowsiness/ sleepiness/ somnolence	6	28/342 (8)	22/378 (6)	1.1 (0.6 to 2.0)	Not calculated
Dizziness	6	10/315 (3)	8/192 (4)	0.7 (0.3 to 1.8)	Not calculated
Nausea	6	26/384 (7)	15/287 (5)	1.0 (0.5 to 1.8)	Not calculated
Vomiting	4	17/227 (7)	6/121 (5)	1.3 (0.6 to 3.2)	Not calculated
Headache	9	40/572 (7)	31/389 (8)	0.9 (0.6 to 1.4)	Not calculated

ANALYSES

Comparison 01. Paracetamol 325 mg versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 No. patients with >50% pain relief			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 02. Paracetamol 500 mg versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 No. patients with >50% pain relief	6	561	Relative Risk (Fixed) 95% CI	1.91 [1.57, 2.32]

Comparison 03. Paracetamol 600/650 mg versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 No. patients with >50% pain relief	19	1886	Relative Risk (Fixed) 95% CI	2.42 [2.05, 2.84]
02 3rd molar surgery: no. patients >50% pain relief	10	1265	Relative Risk (Fixed) 95% CI	2.93 [2.34, 3.66]
03 Other surgery: no. patients >50% pain relief	9	621	Relative Risk (Fixed) 95% CI	1.86 [1.46, 2.36]

Comparison 04. Paracetamol 975/1000 mg versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 No. patients with >50% pain relief	23	2759	Relative Risk (Fixed) 95% CI	2.47 [2.18, 2.81]
02 3rd molar surgery: no. patients >50% pain relief	9	916	Relative Risk (Fixed) 95% CI	3.50 [2.57, 4.77]
03 Other surgery: no. patients >50% pain relief	14	1721	Relative Risk (Fixed) 95% CI	2.16 [1.88, 2.48]
04 No. patients with drowsiness / sleepiness / somnolence	6	720	Relative Risk (Fixed) 95% CI	0.93 [0.53, 1.64]
05 No. patients with dizziness	7	507	Relative Risk (Fixed) 95% CI	0.73 [0.31, 1.75]
06 No. patients with nausea	6	671	Relative Risk (Fixed) 95% CI	0.99 [0.54, 1.80]

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07 No. patients with vomiting	4	348	Relative Risk (Fixed) 95% CI	1.34 [0.57, 3.17]
08 No. patients with headache	9	961	Relative Risk (Fixed) 95% CI	0.90 [0.59, 1.37]

Comparison 05. Paracetamol 1500 mg versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 No. patients with >50% pain relief			Relative Risk (Fixed) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [*administration & dosage; adverse effects]; Analgesics, Non-Narcotic [*administration & dosage; adverse effects]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans

COVER SHEET

Title	Single dose oral paracetamol (acetaminophen) for postoperative pain
Authors	Barden J, Edwards J, Moore A, McQuay H
Contribution of author(s)	Information not supplied by author
Issue protocol first published	2004/1
Review first published	2004/1
Date of most recent amendment	21 October 2004
Date of most recent SUBSTANTIVE amendment	25 November 2003
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	25 September 2003
Date authors' conclusions section amended	25 September 2003
Contact address	Miss Jodie Barden Research Associate c/o Pain Research Unit Churchill Hospital Old Road Headington Oxford OX3 7LJ

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UK
E-mail: jodie.barden@pfizer.com
Tel: +44 1865 225775
Fax: +44 1865 226978

DOI 10.1002/14651858.CD004602

Cochrane Library number CD004602

Editorial group Cochrane Pain, Palliative and Supportive Care Group

Editorial group code HM-SYMPT

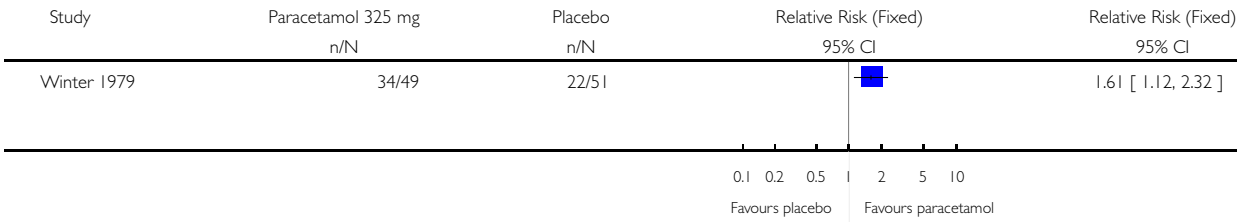
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Paracetamol 325 mg versus placebo, Outcome 01 No. patients with >50% pain relief

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 01 Paracetamol 325 mg versus placebo

Outcome: 01 No. patients with >50% pain relief



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Analysis 02.01. Comparison 02 Paracetamol 500 mg versus placebo, Outcome 01 No. patients with >50% pain relief

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 02 Paracetamol 500 mg versus placebo

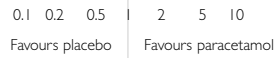
Outcome: 01 No. patients with >50% pain relief

Study	Paracetamol 500 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cooper 1980	11/37	11/38		12.2	1.03 [0.51, 2.07]
Dolci 1994	54/72	25/76		27.3	2.28 [1.61, 3.23]
Laska 1983 (Study 3)	46/81	22/57		29.0	1.47 [1.01, 2.15]
Pinto 1984	24/29	10/29		11.2	2.40 [1.41, 4.07]
Rubinstein 1986	22/30	8/30		9.0	2.75 [1.46, 5.17]
Seymour 1996	19/41	10/41		11.2	1.90 [1.01, 3.57]
Total (95% CI)	**290**	**271**		**100.0**	**1.91 [1.57, 2.32]**

Total events: 176 (Paracetamol 500 mg), 86 (Placebo)

Test for heterogeneity chi-square=7.82 df=5 p=0.17 I^2 =36.0%

Test for overall effect z=6.47 p<0.00001



Analysis 03.01. Comparison 03 Paracetamol 600/650 mg versus placebo, Outcome 01 No. patients with >50% pain relief

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 03 Paracetamol 600/650 mg versus placebo

Outcome: 01 No. patients with >50% pain relief

Study	Para. 600/650 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bhounsule 1990	7/20	6/20		4.1	1.17 [0.48, 2.86]
Cooper 1981	21/37	6/37		4.1	3.50 [1.60, 7.67]
Cooper 1988	12/36	9/40		5.8	1.48 [0.71, 3.10]
Cooper 1991a	10/37	9/44		5.6	1.32 [0.60, 2.90]
Dionne 1994	24/27	18/25		12.7	1.23 [0.93, 1.63]
Edwards 2002	108/340	14/339		9.5	7.69 [4.50, 13.15]
Fassolt 1983	21/29	8/28		5.5	2.53 [1.35, 4.75]
Forbes 1982	15/34	6/30		4.3	2.21 [0.98, 4.96]
Forbes 1983	13/26	5/26		3.4	2.60 [1.08, 6.25]

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Study	Para. 600/650 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Forbes 1984a	10/39	0/36		0.4	19.43 [1.18, 319.95]
Forbes 1984b	11/31	4/33		2.6	2.93 [1.04, 8.23]
Forbes 1989	1/22	0/23		0.3	3.13 [0.13, 72.99]
Forbes 1990b	7/36	0/34		0.3	14.19 [0.84, 239.28]
Honig 1984	11/28	6/30		3.9	1.96 [0.84, 4.60]
Jain 1986	13/29	10/30		6.7	1.34 [0.70, 2.57]
Sunshine 1986	15/30	10/30		6.8	1.50 [0.81, 2.79]
Sunshine 1989	22/75	0/50		0.4	30.20 [1.87, 486.70]
Sunshine 1993	22/48	20/48		13.6	1.10 [0.70, 1.73]
Young 1979	15/30	14/29		9.7	1.04 [0.62, 1.74]
Total (95% CI)	**954**	**932**		**100.0**	**2.42 [2.05, 2.84]**

Total events: 358 (Para. 600/650 mg), 145 (Placebo)

Test for heterogeneity chi-square=82.03 df=18 p=<0.0001 I^2 =78.1%

Test for overall effect z=10.61 p<0.00001

0.1 0.2 0.5 1 2 5 10

Favours placebo Favours paracetamol

Analysis 03.02. Comparison 03 Paracetamol 600/650 mg versus placebo, Outcome 02 3rd molar surgery: no. patients >50% pain relief

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 03 Paracetamol 600/650 mg versus placebo

Outcome: 02 3rd molar surgery: no. patients >50% pain relief

Study	Para. 600/650 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cooper 1981	21/37	6/37		7.8	3.50 [1.60, 7.67]
Cooper 1988	12/36	9/40		11.1	1.48 [0.71, 3.10]
Cooper 1991a	10/37	9/44		10.7	1.32 [0.60, 2.90]
Dionne 1994	24/27	18/25		24.4	1.23 [0.93, 1.63]
Edwards 2002	108/340	14/339		18.3	7.69 [4.50, 13.15]
Forbes 1982	15/34	6/30		8.3	2.21 [0.98, 4.96]
Forbes 1984a	11/31	4/33		5.1	2.93 [1.04, 8.23]
Forbes 1989	1/22	0/23		0.6	3.13 [0.13, 72.99]

0.1 0.2 0.5 1 2 5 10

Favours placebo Favours paracetamol

(*Continued* . . .)

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(. . . *Continued*)

Study	Para. 600/650 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Forbes 1990b	7/36	0/34		0.7	14.19 [0.84, 239.28]
Sunshine 1986	15/30	10/30		13.0	1.50 [0.81, 2.79]
Total (95% CI)	**630**	**635**		**100.0**	**2.93 [2.34, 3.66]**

Total events: 224 (Para. 600/650 mg), 76 (Placebo)

Test for heterogeneity chi-square=62.97 df=9 p=<0.0001 I^2 =85.7%

Test for overall effect z=9.43 p<0.00001

Analysis 03.03. Comparison 03 Paracetamol 600/650 mg versus placebo, Outcome 03 Other surgery: no. patients >50% pain relief

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 03 Paracetamol 600/650 mg versus placebo

Outcome: 03 Other surgery: no. patients >50% pain relief

Study	Para. 600/650 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bhounsule 1990	7/20	6/20		8.6	1.17 [0.48, 2.86]
Fassolt 1983	21/29	8/28		11.6	2.53 [1.35, 4.75]
Forbes 1983	13/26	5/26		7.1	2.60 [1.08, 6.25]
Forbes 1984b	10/39	0/36		0.7	19.43 [1.18, 319.95]
Honig 1984	11/28	6/30		8.3	1.96 [0.84, 4.60]
Jain 1986	13/29	10/30		14.0	1.34 [0.70, 2.57]
Sunshine 1989	22/75	0/50		0.9	30.20 [1.87, 486.70]
Sunshine 1993	22/48	20/48		28.5	1.10 [0.70, 1.73]
Young 1979	15/30	14/29		20.3	1.04 [0.62, 1.74]
Total (95% CI)	**324**	**297**		**100.0**	**1.86 [1.46, 2.36]**

Total events: 134 (Para. 600/650 mg), 69 (Placebo)

Test for heterogeneity chi-square=20.01 df=8 p=0.01 I^2 =60.0%

Test for overall effect z=5.06 p<0.00001

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Analysis 04.01. Comparison 04 Paracetamol 975/1000 mg versus placebo, Outcome 01 No. patients with >50% pain relief

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 04 Paracetamol 975/1000 mg versus placebo

Outcome: 01 No. patients with >50% pain relief

Study	Para. 975/1000 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bentley 1987	19/41	4/17		2.3	1.97 [0.79, 4.93]
Berry 1975	63/76	18/76		7.4	3.50 [2.31, 5.31]
Bjune 1996	12/43	0/21		0.3	12.50 [0.78, 201.48]
Cooper 1986	20/38	3/22		1.6	3.86 [1.29, 11.53]
Cooper 1989	27/59	9/64		3.6	3.25 [1.67, 6.34]
Cooper 1998	17/50	3/26		1.6	2.95 [0.95, 9.14]
Edwards 2002	45/100	25/100		10.3	1.80 [1.20, 2.69]
Hersch 2000	35/63	5/27		2.9	3.00 [1.32, 6.82]
Kiersch 1994	21/92	3/45		1.7	3.42 [1.08, 10.88]
Laska 1983 (Study 3)	49/81	22/57		10.7	1.57 [1.08, 2.27]
Lehnert 1990	24/49	5/40		2.3	3.92 [1.64, 9.34]
McQuay 1988	10/30	3/30		1.2	3.33 [1.02, 10.92]
Mehlisch 1984	16/58	0/55		0.2	31.32 [1.92, 509.77]
Mehlisch 1990	131/306	9/85		5.8	4.04 [2.15, 7.60]
Mehlisch 1995	35/101	1/40		0.6	13.86 [1.96, 97.79]
Moller 2000	27/120	0/122		0.2	55.91 [3.45, 906.27]
Rubin 1984	86/123	52/109		22.8	1.47 [1.17, 1.84]
Sakata 1986	17/30	3/27		1.3	5.10 [1.68, 15.50]
Santos Pereira 1986	22/28	22/29		8.9	1.04 [0.78, 1.37]
Schachtel 1989	20/37	13/38		5.3	1.58 [0.93, 2.69]
Seymour 1996	21/41	10/41		4.1	2.10 [1.13, 3.89]
Winnem 1981	9/20	3/20		1.2	3.00 [0.95, 9.48]
Winter 1983	20/41	9/41		3.7	2.22 [1.15, 4.29]
Total (95% CI)	**1627**	**1132**		**100.0**	**2.47 [2.18, 2.81]**

Total events: 746 (Para. 975/1000 mg), 222 (Placebo)

Test for heterogeneity chi-square=90.42 df=22 p=<0.0001 I^2 =75.7%

Test for overall effect z=13.91 p<0.00001

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Analysis 04.02. Comparison 04 Paracetamol 975/1000 mg versus placebo, Outcome 02 3rd molar surgery: no. patients >50% pain relief

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 04 Paracetamol 975/1000 mg versus placebo

Outcome: 02 3rd molar surgery: no. patients >50% pain relief

Study	Para 975/1000 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bentley 1987	19/41	4/17		12.1	1.97 [0.79, 4.93]
Cooper 1989	27/59	9/64		18.5	3.25 [1.67, 6.34]
Cooper 1998	17/50	3/26		8.5	2.95 [0.95, 9.14]
Hersch 2000	35/63	5/27		15.0	3.00 [1.32, 6.82]
Kiersch 1994	21/92	3/45		8.6	3.42 [1.08, 10.88]
Lehnert 1990	24/49	5/40		11.8	3.92 [1.64, 9.34]
Mehlisch 1995	35/101	1/40		3.1	13.86 [1.96, 97.79]
Moller 2000	15/60	0/60		1.1	31.00 [1.90, 506.59]
Seymour 1996	21/41	10/41		21.4	2.10 [1.13, 3.89]
Total (95% CI)	**556**	**360**		**100.0**	**3.50 [2.57, 4.77]**

Total events: 214 (Para 975/1000 mg), 40 (Placebo)

Test for heterogeneity chi-square=8.74 df=8 p=0.36 I^2 =8.5%

Test for overall effect z=7.94 p<0.00001

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Analysis 04.03. Comparison 04 Paracetamol 975/1000 mg versus placebo, Outcome 03 Other surgery: no. patients >50% pain relief

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 04 Paracetamol 975/1000 mg versus placebo

Outcome: 03 Other surgery: no. patients >50% pain relief

Study	Para. 975/1000 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Berry 1975	63/76	18/76		9.2	3.50 [2.31, 5.31]
Bjune 1996	12/43	0/21		0.3	12.50 [0.78, 201.48]
Cooper 1986	20/38	3/22		1.9	3.86 [1.29, 11.53]
Edwards 2002	45/100	25/100		12.8	1.80 [1.20, 2.69]
Laska 1983 (Study 3)	49/81	22/57		13.2	1.57 [1.08, 2.27]
McQuay 1988	10/30	3/30		1.5	3.33 [1.02, 10.92]
Mehlisch 1984	16/58	0/55		0.3	31.32 [1.92, 509.77]
Mehlisch 1990	131/306	9/85		7.2	4.04 [2.15, 7.60]
Rubin 1984	86/123	52/109		28.2	1.47 [1.17, 1.84]
Sakata 1986	17/30	3/27		1.6	5.10 [1.68, 15.50]
Santos Pereira 1986	22/28	22/29		11.0	1.04 [0.78, 1.37]
Schachtel 1989	20/37	13/38		6.6	1.58 [0.93, 2.69]
Winnem 1981	9/20	3/20		1.5	3.00 [0.95, 9.48]
Winter 1983	20/41	9/41		4.6	2.22 [1.15, 4.29]
Total (95% CI)	**1011**	**710**		**100.0**	**2.16 [1.88, 2.48]**

Total events: 520 (Para. 975/1000 mg), 182 (Placebo)

Test for heterogeneity chi-square=60.52 df=13 p=<0.0001 I^2 =78.5%

Test for overall effect z=10.94 p<0.00001

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Analysis 04.04. Comparison 04 Paracetamol 975/1000 mg versus placebo, Outcome 04 No. patients with drowsiness / sleepiness / somnolence

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 04 Paracetamol 975/1000 mg versus placebo

Outcome: 04 No. patients with drowsiness / sleepiness / somnolence

Study	Para. 975/1000 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bentley 1987	2/42	4/19		23.0	0.23 [0.05, 1.13]
Cooper 1989	7/59	11/64		44.1	0.69 [0.29, 1.66]
Cooper 1991a	1/37	3/44		11.4	0.40 [0.04, 3.65]
Cooper 1998	16/50	1/26		5.5	8.32 [1.17, 59.30]
Kiersch 1994	2/92	1/45		5.6	0.98 [0.09, 10.50]
Moller 2000	0/120	2/122		10.4	0.20 [0.01, 4.19]
Total (95% CI)	**400**	**320**		**100.0**	**0.93 [0.53, 1.64]**

Total events: 28 (Para. 975/1000 mg), 22 (Placebo)

Test for heterogeneity chi-square=9.76 df=5 p=0.08 I^2 =48.8%

Test for overall effect z=0.23 p=0.8

Analysis 04.05. Comparison 04 Paracetamol 975/1000 mg versus placebo, Outcome 05 No. patients with dizziness

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 04 Paracetamol 975/1000 mg versus placebo

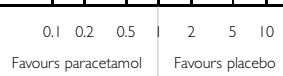
Outcome: 05 No. patients with dizziness

Study	Para. 975/1000 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bentley 1987	5/42	2/19		25.3	1.13 [0.24, 5.32]
Berry 1975	0/1	0/1		0.0	Not estimable
Cooper 1991a	0/37	1/44		12.6	0.39 [0.02, 9.41]
Cooper 1998	2/50	1/26		12.1	1.04 [0.10, 10.94]
Hersch 2000	0/63	1/27		19.2	0.15 [0.01, 3.47]
Kiersch 1994	1/92	1/45		12.4	0.49 [0.03, 7.64]
McQuay 1988	2/30	2/30		18.4	1.00 [0.15, 6.64]
Total (95% CI)	**315**	**192**		**100.0**	**0.73 [0.31, 1.75]**

Total events: 10 (Para. 975/1000 mg), 8 (Placebo)

Test for heterogeneity chi-square=1.72 df=5 p=0.89 I^2 =0.0%

Test for overall effect z=0.70 p=0.5



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Analysis 04.06. Comparison 04 Paracetamol 975/1000 mg versus placebo, Outcome 06 No. patients with nausea

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 04 Paracetamol 975/1000 mg versus placebo

Outcome: 06 No. patients with nausea

Study	Para. 975/1000 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bentley 1987	7/42	5/19		36.3	0.63 [0.23, 1.74]
Cooper 1991a	2/37	2/44		9.6	1.19 [0.18, 8.04]
Hersch 2000	3/63	1/27		7.4	1.29 [0.14, 11.81]
Kiersch 1994	12/92	4/45		28.3	1.47 [0.50, 4.29]
McQuay 1988	2/30	2/30		10.5	1.00 [0.15, 6.64]
Moller 2000	0/120	1/122		7.8	0.34 [0.01, 8.24]
Total (95% CI)	**384**	**287**		**100.0**	**0.99 [0.54, 1.80]**

Total events: 26 (Para. 975/1000 mg), 15 (Placebo)

Test for heterogeneity chi-square=1.79 df=5 p=0.88 I^2 =0.0%

Test for overall effect z=0.04 p=1

Analysis 04.07. Comparison 04 Paracetamol 975/1000 mg versus placebo, Outcome 07 No. patients with vomiting

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 04 Paracetamol 975/1000 mg versus placebo

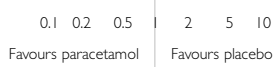
Outcome: 07 No. patients with vomiting

Study	Para. 975/1000 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bentley 1987	6/42	2/19		31.5	1.36 [0.30, 6.12]
Hersch 2000	1/63	2/27		32.0	0.21 [0.02, 2.26]
Kiersch 1994	9/92	2/45		30.7	2.20 [0.50, 9.77]
McQuay 1988	1/30	0/30		5.7	3.00 [0.13, 70.83]
Total (95% CI)	**227**	**121**		**100.0**	**1.34 [0.57, 3.17]**

Total events: 17 (Para. 975/1000 mg), 6 (Placebo)

Test for heterogeneity chi-square=3.00 df=3 p=0.39 I^2 =0.0%

Test for overall effect z=0.68 p=0.5



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Analysis 04.08. Comparison 04 Paracetamol 975/1000 mg versus placebo, Outcome 08 No. patients with headache

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 04 Paracetamol 975/1000 mg versus placebo

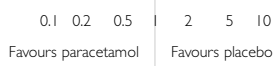
Outcome: 08 No. patients with headache

Study	Para. 975/1000 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bentley 1987	1/42	0/19		1.8	1.40 [0.06, 32.77]
Cooper 1991a	2/37	3/44		7.0	0.79 [0.14, 4.49]
Cooper 1998	4/50	2/26		6.8	1.04 [0.20, 5.31]
Hersch 2000	3/63	1/27		3.6	1.29 [0.14, 11.81]
Kiersch 1994	12/92	3/45		10.3	1.96 [0.58, 6.59]
McQuay 1988	1/30	0/30		1.3	3.00 [0.13, 70.83]
Mehlisch 1995	0/101	9/40		34.8	0.02 [0.00, 0.36]
Moller 2000	17/120	11/122		28.0	1.57 [0.77, 3.21]
Schachtel 1989	0/37	2/36		6.5	0.19 [0.01, 3.92]
Total (95% CI)	**572**	**389**		**100.0**	**0.90 [0.59, 1.37]**

Total events: 40 (Para. 975/1000 mg), 31 (Placebo)

Test for heterogeneity chi-square=12.51 df=8 p=0.13 I^2 =36.0%

Test for overall effect z=0.50 p=0.6



Analysis 05.01. Comparison 05 Paracetamol 1500 mg versus placebo, Outcome 01 No. patients with >50% pain relief

Review: Single dose oral paracetamol (acetaminophen) for postoperative pain

Comparison: 05 Paracetamol 1500 mg versus placebo

Outcome: 01 No. patients with >50% pain relief

Study	Paracetamol 1500 mg n/N	Placebo n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
Laska 1983 (Study 3)	53/81	22/57		1.70 [1.18, 2.44]

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Clinical Pharmacology and Biopharmaceutics

Since propoxyphene is an old drug, the Clinical Pharmacology and Biopharmaceutics aspects of propoxyphene are not available to the same level of extensive detail compared to drugs that are developed more recently. Further, information obtained from the literature is based on conclusions drawn by the study authors. The following is a brief summary of Clinical Pharmacology information available in the Agency's database and from published literature.

Equimolar doses of propoxyphene whether administered as propoxyphene hydrochloride (Darvon®) or propoxyphene napsylate (Darvocet-N®) provide similar plasma concentrations. Because of differences in molecular weight, a dose of 100 mg (176.8 μmol) of propoxyphene napsylate is required to supply an amount of propoxyphene equivalent to that present in 65 mg (172.9 μmol) of propoxyphene hydrochloride. Following administration of 65, 130 or 195 mg of propoxyphene hydrochloride, the bioavailability of propoxyphene is equivalent to that of 100, 200 or 300 mg respectively of propoxyphene napsylate.

Propoxyphene undergoes extensive first-pass metabolism by intestinal and hepatic enzymes. The major route of metabolism is CYP3A4 mediated *N*-demethylation to norpropoxyphene, which is excreted by the kidneys. CYP2D6 isozyme was historically thought to be the most important enzyme in propoxyphene metabolism but a pharmacokinetic study published in 2004 in subjects who are extensive (EMs) and poor (PMs) metabolizers of CYP2D6 isozyme revealed no clinically significant differences in propoxyphene metabolism. In addition, the same study also revealed that norpropoxyphene formation in liver microsomes from CYP2D6 isozyme EMs was significantly inhibited in the presence of CYP3A4 inhibitors such as ketoconazole and omeprazole showing that CYP3A4 isozyme plays a key role in the metabolism of propoxyphene. Norpropoxyphene is pharmacologically active. It has, however, substantially lower CNS depressant effects than propoxyphene but is thought to have a greater local anesthetic effect, which is similar to that of amitriptyline and antiarrhythmic agents, such as lidocaine and quinidine.

After the administration of a single 65 mg oral dose of propoxyphene hydrochloride, peak plasma levels of 0.05 to.0.1 μg/mL are achieved. Peak plasma concentrations of propoxyphene are reached in 2 to 2 1/2 hours. Repeated doses of propoxyphene at 6 hour intervals lead to increasing plasma concentrations with a plateau after the ninth dose at 48 hours. Propoxyphene has a half-life of 6 to 12 hours, whereas half-life of norpropoxyphene is 30 to 36 hours.

Food does not have a clinically significant effect on the pharmacokinetics of propoxyphene or norpropoxyphene. In the elderly, pharmacokinetics of propoxyphene are significantly altered in that median propoxyphene half-life, Cmax and AUC values after single dose were significantly higher (~3 fold) in elderly aged 70-79 years compared to a younger age group of 21-28 years. Pharmacokinetic studies in hepatic cirrhosis patients and anephric patients revealed that propoxyphene and norpropoxyphene plasma

concentrations may be altered in these conditions. Oral administration of propoxyphene in patients with hepatic cirrhosis lead to much higher plasma propoxyphene (Cmax increased and AUC increased about 3 fold and 2 fold, respectively) and much lower norpropoxyphene (Cmax and AUC decreased by about 4.5 fold and 3.5 fold, respectively) concentrations than in normal subjects. In anephric patients one day after a routine dialysis treatment, mean Cmax and AUC values for propoxyphene were about twice as high compared to subjects with normal renal function. Norpropoxyphene concentrations were also higher and more persistent in the anephric patients (renal excretion is a major pathway of norpropoxyphene elimination in normal subjects).

BACKGROUND FOR THE PROPOXYPHENE ADVISORY COMMITTEE

NONCLINICAL SAFETY

Introduction

This presentation will cover nonclinical pharmacology and toxicology findings that are relevant to therapeutic and supratherapeutic (overdose) use of propoxyphene. Since the majority of nonclinical studies were conducted in the 1950's and 1960's and have since been published, emphasis will be on information obtained since the last propoxyphene Advisory Committee meeting in 1979 in response to a 1978 Petition (also from Public Citizen). It was claimed then that the major metabolite, norpropoxyphene, was instrumental in causing cardiotoxicity and this issue is a critical element of safety raised in the current 2006 Petition. Therefore, this presentation will address new information on propoxyphene pharmacology and nonclinical data pertaining to cardiac toxicity.

Pharmacology

Propoxyphene

Propoxyphene is a synthetic diphenyl heptane analgesic with structural similarity to methadone (Appendix, Figure 1). There are four propoxyphene stereoisomers. The alpha dextro-propoxyphene isomer possesses analgesic activity (Gruber et al 1955) and was patented in 1955 by Eli Lilly, marketed beginning in 1957, and is the propoxyphene form which is the subject of this meeting. The levo-propoxyphene isomer possesses antitussive activity (Miller et al 1963), but negligible analgesic activity. Levo-propoxyphene products were approved and marketed in the US, but have since been discontinued.

Pharmacological studies were conducted in the 1950s and 1960s by administering alpha dextropropoxyphene (hereafter referred to as propoxyphene) to various animal species and comparing the pharmacologic and physiologic responses to the effects obtained from known drugs. In animals and/or humans, effects included analgesia, euphoria, respiratory depression, and gastrointestinal stasis effects. Nonlethal toxicologic signs at high doses in dogs include ataxia, vocalization, tremors and convulsions (Emmerson et al 1971). The therapeutic pharmacodynamic properties have since been attributed to activation of multiple opioid receptor subtypes. Its analgesic effects were considered "weak" at the time of development, but this was considered advantageous since it lacked "strong" morphine-like addictive properties (based on human use), although it is classified with narcotics.

Two salt formulations of propoxyphene were developed, initially the hydrochloride salt, followed by the napsylate salt of propoxyphene. With oral administration, the napsylate salt is absorbed more slowly than that of the hydrochloride salt since it has a lower solubility; however, oral bioavailabilities are approximately equal. Excretion occurs

through renal (less than 10% as parent compound propoxyphene) and biliary routes. Propoxyphene has a circulatory half-life of 6 to 12 hours in the human (Flanagan et al., 1985).

Norpropoxyphene

The toxicity, particularly cardiotoxicity, of propoxyphene is often attributed to the major metabolite norpropoxyphene (Appendix Figure 2; Nickander et al., 1984). CYP3A4 is the main metabolic enzyme in involved in norpropoxyphene formation. Early work suggested that propoxyphene metabolism was due to CYP2D6 based on evidence it was a substrate and inhibitor of CYP2D6 (Sanz and Bertilsson 1990; Kerry *et al.* 1994). However, recent evidence with human subjects that are known fast or slow CYP2D6 metabolizers indicated no alteration of propoxyphene metabolism, and this was confirmed with in vitro metabolism studies with liver microsomes obtained from these genotyped subjects (Somogyi et al., 2004).

Compared to propoxyphene, norpropoxyphene lacks significant opioid activity, has less CNS depressant activity, and has a slightly greater local anesthetic effect (Nickander et al., 1977, 1984). Norpropoxyphene has a half life of 30-36 hours in man (Flanagan et al., 1985), much longer than propoxyphene. Norpropoxyphene is excreted through renal and biliary routes similar to the parent compound (Nickander et al., 1984).

Based on pharmacology and toxicokinetics, it has been proposed that the accumulation of norpropoxyphene likely contributes to and may precipitate CNS depression, cardiac arrest and respiratory depression and death (Bennet 1993; Davis et al 1996).

Receptor Interactions

Opiate Receptors

Opiate receptor studies were conducted by Lochner and Hynes (1984; refer to Appendix Figure 3). Using [^{3}H]-naloxone as a mu receptor ligand, propoxyphene had a K_i of 492 nM which is comparable to codeine (K_i = 600 nM). This affinity for the mu-opiate receptor was substantially less than morphine (K_i = 6 nM), and l-methadone (K_i =10 nM). For delta opioid activity, propoxyphene had a K_i of 367 nM, approximately equal to that of its mu opioid receptor affinity. It essentially had no activity at kappa opiate receptors. Of importance, norpropoxyphene lacked activity at these opiate receptor subtypes. Although interactions with mu1, mu2 and kappa opiate receptors have been invoked to explain the behavioral and physiological responses in animals and humans, supporting data for these claims has not been identified from the published literature.

In recent years propoxyphene interaction with other types of receptors and with ion channels indicates that propoxyphene is not solely a opiate receptor ligand, a conclusion suggested by Nickander in 1977 upon review of propoxyphene pharmacology. These include activity as:

- Na channel antagonist

- K+ channel modulator (involved in cardiac cell repolarization)
- Nicotinic receptor (α3β4) antagonist (noncompetitive)
- N-methyl-D-aspartate (NMDA) receptor antagonist (noncompetitive)

Besides the possible contributions to analgesia, several of these non-opioid receptor interactions likely contribute to cardiotoxicity and are discussed below.

Na^+ Channel

Propoxyphene and norpropoxyphene possesses a local anesthetic effect similar to that of lidocaine evidenced by a reduction in action potential amplitude of in vitro cervical sympthetic nerve preparations after electrical stimulation (Nickander 1977; refer to Appendix Figure 4). The metabolite, norpropoxyphene, is slightly more potent than dextropropoxyphene, and both are approximately an order of magnitude more potent than lidocaine. Both propoxyphene and norpropoxyphene thus appear to have qualities that are characteristics of Class IC anti-arrhythmics. Lidocaine was an effective treatment for a patient with propoxyphene overdose and exhibiting QRS widening (Whitcomb et al 1989). Further study of this effect conducted with in vitro cultures of rabbit heart atrial cells demonstrated that both lidocaine and propoxyphene blocked inward sodium current, in agreement with the findings described by Nickander (1977). Further analysis of the binding kinetics of propoxyphene and lidocaine provided evidence that the rapid binding-dissociation kinetics of lidocaine to the Na^+ channel displaced propoxyphene which possesses slower dissociation kinetics. Norpropoxyphene concentrations were not determined in the patient and similar in vitro studies with norpropoxyphene were not conducted by Whitcomb and colleagues (1989).

K^+ Channel (hERG channels)

Repolarization of action potentials in cardiac muscle involves a rapidly-activating delayed rectifiier K^+ current that are commonly evaluated in studies using Xenopus oocytes transfected with human ether-a-go-go-related gene (hERG) K^+ channels. Using this model, Ulens and colleagues (1999) found that low concentrations (5 μmol/L) of propoxyphene and norpropoxyphene facilitated hERG currents, while higher drug concentrations blocked hERG currents (IC_{50} ~40 μmol/L). Both compounds also slowed K^+ channel activation deactivation kinetics. Therefore both propoxyphene and norpropoxyphene have the potential to alter gating properties of cardiac muscle. They also found a reversal potential shift to a more positive value because of a 30-fold increase in Na^+-permeability, however whether this alteration in Na^+-permeability is confined to the oocyte preparation or can be extrapolated to mammalian cardiac cells remains unclear.

Nicotinic Receptor

In recent years there has been a renewed interest in the analgesic potential of drugs that act at nicotinic receptors. Xiao and colleagues (2001) studied the effects of methadone and related analgesics that included propoxyphene on rat α3β4 neuronal acetylcholine (nicotinic) receptors stably expressed in a human embryonic kidney (HEK 293) cell line. They demonstrated that methadone and its metabolite, as well as propoxyphene, are potent noncompetitive nicotinic receptor antagonists (inhibited nicotine-stimulated rubidium [$^{86}Rb^{+}$] efflux from $^{86}Rb^{+}$ preloaded cells in a concentration-dependent manner with an IC_{50} value for methadone 1.9 ± 0.2 μM, propoxyphene 2.7 ± 0.4 μM, and norpropoxyphene 1.8 ± 0.1 μM). The maximum nicotine-stimulated $^{86}Rb^{+}$ efflux was markedly decreased, but the EC_{50} value for nicotine stimulation was minimally altered indicating a noncompetitive block of the α3β4 nicotinic receptor. This finding is also consistent with the observation that neither methadone, its metabolites, nor its structural analogs competed effectively with [^{3}H]-epibatidine for the agonist recognition site of the neuronal acetylcholine receptor

N-methyl-D-aspartate (NMDA) Receptor

Ebert and colleagues 1998a evaluated opiate drugs for their potential to affect the phenomenon of "wind-up" in neuropathic pain in which hyperalgesia develops following a series of constant repetitive stimuli and is highly dependent on NMDA receptor activation. In this receptor binding study, they demonstrated that propoxyphene has a high affinity (IC_{50} = 5 μM) as an antagonist at rat brain cortex NMDA receptors using the ^{3}H-MK-801 ligand. Further study indicated the binding to be noncompetitive. This is similar to methadone (Gorman et al 1997), but other opiate analgesics such as codeine, etorphine, fentanyl or morphine lacked direct NMDA receptor activity (Ebert et al. 1998a, 1998b).

Cardiotoxicity

Studies Submitted to the FDA

Eli Lilly submitted a number of nonclinical studies in their applications for the development and approval of various propoxyphene formulations from the 1950s to the 1970s. These applications incorporated various evaluations of cardiovascular toxicity, the results of which have been published in the medical literature and incorporated into a number of reviews (Nickander et al 1977, 1984; Barkin 2006).

In 1980, the FDA reevaluated clinical and nonclinical dextropropoxyphene toxicity in response to issues raised in a Nov 21, 1978 Petition to the FDA by the Health Research Group of Public Citizen and that subsequently was discussed at an Advisory Committee meeting in 1979. Lilly also provided published in vitro studies of utilizing cardiac tissue of cats (Amsterdam et al., 1981) and dogs (Holland and Steinberg, 1979), in vivo cardiovascular studies in conscious rabbits (Lund-Jacobsen et al 1978), and in vivo ECG

studies of dogs (Holland and Steinberg, 1979; Page et al 1979). These are summarized in Appendix Figures 5 and 6; from Nickander 1984)

Dose-dependent negative inotropic effects of propoxyphene and norpropoxyphene on isolated rabbit cardiac papillary muscle was demonstrated by Amsterdam and colleagues (1981). In combination, an additive effect was demonstrated. The negative inotropic effects were not reversed with naloxone, but was reversed with isoproterenol. As previously indicated altered conduction through Na^+ channels and nicotinic receptors may be mechanisms for this observation. Thus, either of these compounds could be detrimental to cardiac function at concentrations greater than therapeutic levels.

In 1983 additional studies were submitted evaluating cardiovascular function, ECG and plasma concentrations of propoxyphene and norpropoxyphene. In the dog after a single 50 mg/kg dose of propoxyphene napsylate, peak propoxyphene and norpropoxyphene concentrations were 2.3 µg/mL and 18.4 µg/mL, respectively (Page et al., 1979), which is generally considered above the lethal limits in man.

In a pig model of circulatory shock, Sorenson and colleagues (1984, 1985; a preliminary manuscript was submitted to the FDA by Eli Lilly in 1983 that conveyed a more quantitative analysis of the results) administered propoxyphene intravenously at 15 mg/min to pentobarbital anesthetized pigs until the animals were in cardiovascular shock defined as systolic blood pressure below 60 mm Hg and a cardiac index of approximately 2.0 L/min/m^2. This resulted in a total administered dose of 675 to 2025 mg of propoxyphene corresponding to plasma concentrations of propoxyphene and norpropoxyphene concentrations ranging from 9.6 to 15.3 µg/mL and 0.7 to 2.0 µg/mL. It is not clear if the lower norpropoxyphene levels in pigs are due to differences in metabolism, compared to values found in other species; however, the intravenous route of administration coupled to metabolic competition for CYP3A4 with pentobarbital may be the explanation. Nevertheless, these data indicate that elevated propoxyphene concentrations, in the presence of relatively lower norpropoxyphene concentrations than the dog or human, has detrimental effects on cardiovascular function in the pig model. The effects noted during propoxyphene infusion included respiratory hypoxia with subsequent peripheral vasodilatation, reduction of arterial pressure, left ventricular contractility, and cardiac output. Prolongation of the PQ and QRS intervals occurred but sinus rhythm was maintained until just before death. The absence of a compensatory tachycardia in the face of hypotension and circulatory collapse might be indicative of an indirect CNS depression or a direct effect on cardiac (i.e. baroreceptor) reflexes or nerve conduction.

Eli Lilly also conducted a conscious dog ECG study to address issues concerning polysubstance abuse and the potential for synergistic cardiotoxicity. In this study, which was submitted to the FDA in 1983, propoxyphene was administered together with ethanol and diazepam. Propoxyphene administration alone resulted in increases in the QRS (6-8%), and QTc interval (7-12%). Alcohol, but not diazepam increased the PR interval (8-18%), but there were no additional effects on QRS, or QT intervals. Following a single 50 mg/mL dose of propoxyphene peak plasma propoxyphene and norpropoxyphene

concentrations were 0.52 μg/mL and 1.60 μg/mL, respectively. With twice daily dosing for 4 to 7 days, the peak plasma propoxyphene concentrations remained fairly level at 0.47 to 0.68 μg/mL, but norpropoxyphene concentrations increased to 3.35 to 4.17 μg/mL.

Other than the aforementioned articles and relevant studies by the Applicant, no additional nonclinical toxicology studies regarding propoxyphene and the active metabolite norpropoxyphene have been submitted to the FDA or published in the scientific literature

Conclusions

Propoxyphene was characterized as a "weak" opiate analgesic, advantageous for analgesia at the time of approval, since less narcotic dependency and abuse would be expected. In nonclinical studies submitted for NDA approval in the 1950's and 1960's, there were no animal deaths that could be attributed to cardiovascular changes. Histopathic evaluation of the heart was unremarkable. Deaths at high doses were preceded by CNS signs, ataxia, tremors and convulsions, although again in hindsight, cardiovascular events may have preceded or contributed to these events. Nonclinical studies conducted in response to the 1979 Advisory Committee meeting revealed small dose-related changes in prolongation of PR, QRS, and QTc intervals in association with reduced cardiac function. Recent receptor studies provide evidence that propoxyphene and/or norpropoxyphene may directly influence cardiac function through Na^+ channels and K^+ repolarization (hERG) channels of cardiac myocytes, or through interaction at neural α3β4 nicotinic receptors and NMDA receptors.

Thus the nonclinical studies support the clinical findings and the hypothesis that deaths due to overdose of propoxyphene could be due to cardiotoxicity from propoxyphene and/or norpropoxyphene. Unfortunately, whether these effects occur at therapeutic dose levels is uncertain from the in vivo animal studies submitted to the various propoxyphene NDAs, since there is insufficient animal toxicokinetic information with which to compare to human exposure.

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APPENDIX

Figure 1
Structures of propoxyphene, norpropoxyphene, and methadone

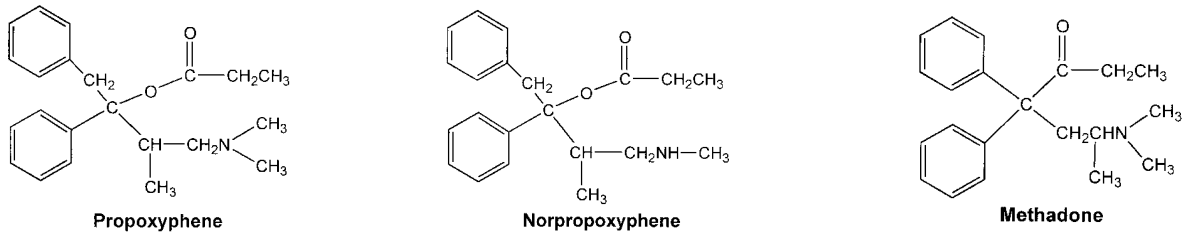

Figure 2
Propoxyphene Metabolism (from Nickander et al., 1984)

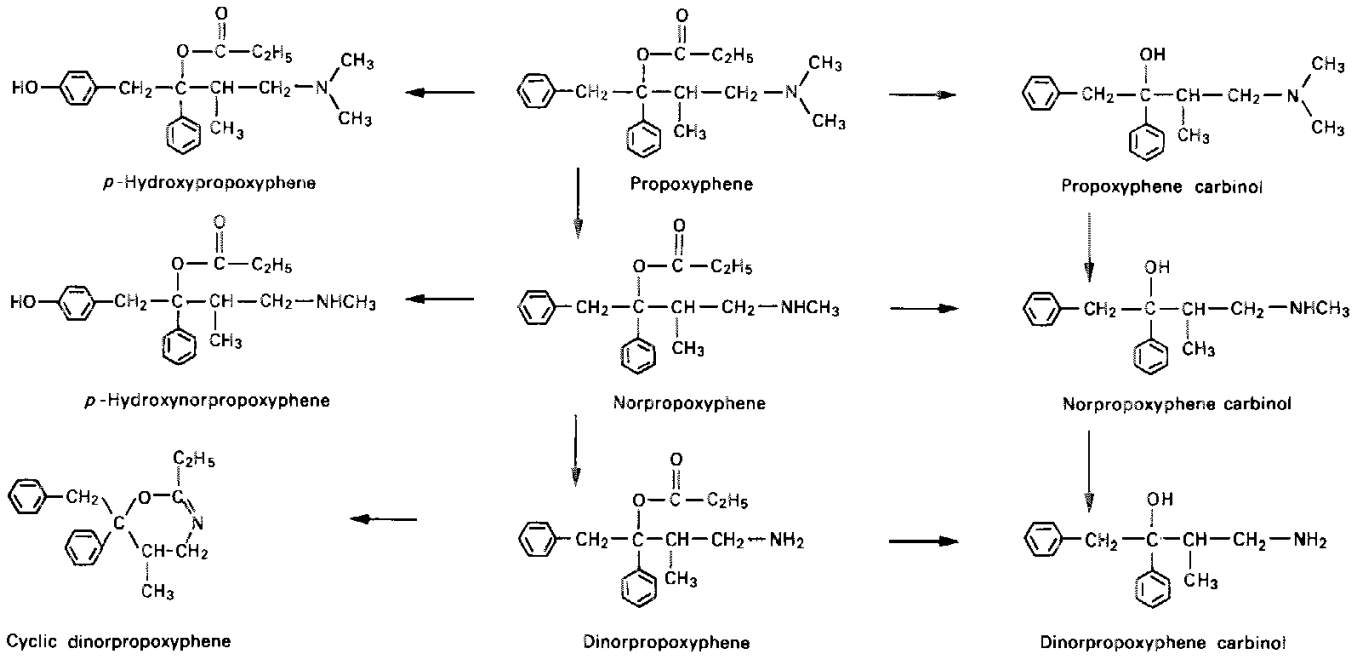

Figure 2 Pathways of biotransformation of dextropropoxyphene in man and animals

Figure 3
Opiate Receptor Binding (Lochner and Hynes 1984)

Table 1 Affinity of dextropropoxyphene for opioid receptors labelled *in vitro* with [^{3}H]naloxone, [^{3}H]-D-Ala^2-D-Leu^5-enkephalin or [^{3}H]ethylketocyclazocine with reference to standard analgesics

	Inhibition of stereospecific binding K_I *(nM)*		
Compound	*[^{3}H]Naloxone (μ site)*	*[^{3}H]-D-Ala^2-D-Leu^5-Enkephalin (δ site)*	*[^{3}H]Ethylketocyclazocine (κ site)*
Buprenorphine	1	10	17
Butorphanol	2	5	2
Morphine	6	74	167
Pentazocine	7	50	75
Nalbuphine	10	59	28
l-Methadone	10	63	>1000
Met-Enkephalin	39	6	>1000
Dextropropoxyphene	492	367	>1000
Codeine	600	5600	>1000
d,l-Propoxyphene hydrochloride	>1000	>1000	>1000
d-Propoxyphene napsylate	527	412	>1000
d-Propoxyphene hydrochloride	492	367	>1000
l-Propoxyphene napsylate	>1000	>1000	>1000
d-Norpropoxyphene	>1000	>1000	>1000
d,l-Dinorpropoxyphene	>1000	>1000	>1000

Figure 4
Local Anesthetic-like Effect (Nickander 1977)

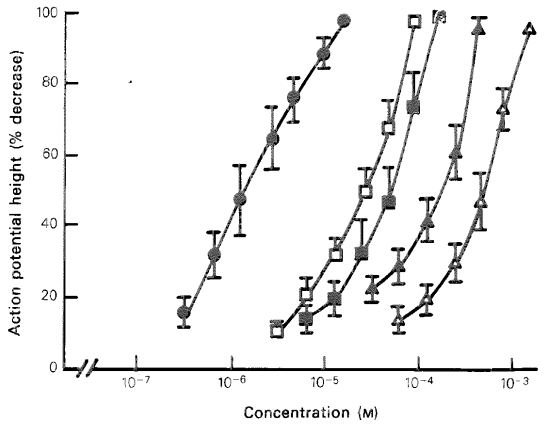

Figure 5 Inhibition of cervical sympathetic action potential amplitude by dextropropoxyphene, norpropoxyphene and local anaesthetics. Ordinate; action potential height expressed as percentage decrease from control amplitude: dibucaine (●), norpropoxyphene (□); dextropropoxyphene (■); cocaine (▲); lidocaine (△). Each point represents the percentage decrease (mean ± SE) in four to seven tissues. (Reproduced by permission, Nickander *et al.*, 1977)

Figure 5
Summary of cardiac effects in isolated tissues (from Nickander 1984)

Table 6 Cardiac effects of dextropropoxyphene or norpropoxyphene in isolated tissues

	Effect	*Concentration P/NP (μg/ml)*	*Reference*
Canine Purkinje fibre action potential			
Duration	↓+++	1/1	Holland & Steinberg (1979)
Rate of rise	↓++	3/1	
Contractility			
Papillary muscle	↓+	3/1	Amsterdam *et al.* (1981)
Atria	↓+	10/3	Holland & Steinberg (1979)
Atrial rate	↓+	3/3	Holland & Steinberg (1979)

P or NP refers to minimum concentration of dextropropoxyphene or norpropoxyphene added to tissue bath causing indicated effect

Figure 6
Summary of cardiac effects in intact animals (from Nickander 1984)

Table 7 Acute cardiovascular effects of dextropropoxyphene or norpropoxyphene in intact animals

	Effect	*Blood concentration P/NP (μg/ml)*	*Reference*
PR interval (AH interval)	↑+++	1.5/2	Holland & Steinberg (1979) Lund-Jacobsen (1978)
QRS duration (HV interval)	↑++	2/1.5	Holland & Steinberg (1979) Lund-Jacobsen (1978)
Heart rate	↓+	3/—	Holland & Steinberg (1979) Lund-Jacobsen (1978) Sorenson (1984)
Contractility (dP/dt)	↓++	3/—	Sorenson (1984)
Mean blood pressure	↓++	5/—	Sorenson (1984)

P or NP refers to minimum level of dextropropoxyphene or norpropoxyphene respectively, causing the indicated effect. NP levels reflect dosing with that substance rather than that formed from P

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 15, 2008
To:	Bob Rappaport, M.D., Director Division of Anesthesia, Analgesia, and Rheumatology Drug Products
Through:	Robert Boucher, M.D., M.P.H., Acting Deputy Director Yoo Jung Chang, Pharm.D. and Peter Diak, Pharm.D., M.P.H., Acting Team Leaders Division of Pharmacovigilance II Solomon Iyasu, M.D., M.P.H., Director Laura Governale, Pharm.D., M.B.A., Drug Use Data Team Leader Division of Epidemiology
From:	Joann H. Lee, Pharm.D., Safety Evaluator Division of Pharmacovigilance II Fatmatta Kuyateh, M.D., M.S., Medical Officer Hina Mehta, Pharm.D., Drug Use Data Analyst Division of Epidemiology
Subject:	Serious Adverse Events
Drug Name(s):	Propoxyphene and Darvocet
Application Type/Number:	NDA: 10-997, 16-862, 17-122, 40-139, 40-507, 40-569, 70-145, 70-146, 70-443, 70-910, 74-119, 74-743, 75-738, 76-429, 76-609, 76-743, 76-750, 77-196, 77-677, 77-821, 80-269, 83-501, 83-978, 88-615, 89-959
Applicant/sponsor:	Xanodyne
OSE RCM #:	2008-1517

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EXECUTIVE SUMMARY

This review is in response to a request from the Division of Analgesics, Anesthetics, and Rheumatology Products (DAARP) for an updated Adverse Event Reporting System (AERS), drug utilization, and published literature[i] review associated with propoxyphene containing products[ii]. A Citizen's Petition (CP) from Public Citizen's Health Research group (February 28, 2006) requested that FDA initiate a phased withdrawal of all propoxyphene-containing products "...because this drug has considerable human toxicity, addiction potential, abuse liability, but very limited therapeutic usefulness."[iii] The CP cited the phased withdrawal of propoxyphene-containing drugs by the UK due to poor benefit-risk ratio, a combination of "poorly established" efficacy and risk of toxicity. The CP also specified concerns for propoxyphene use in elderly patients and its potential for cardiovascular effects with overdosage. The CP request resulted in an Advisory Committee (AC) Meeting (January 30, 2009) to review the safety and the efficacy profile of this drug.

Regarding AERS data, a previously completed OSE postmarketing safety review of propoxyphene containing products (2005) is included in the background package for the upcoming AC Meeting in January 2009[iv]. Data from the 2005 review are referenced, for contextual purposes, in the updated AERS section of this document.

UPDATED AERS CASES (N=65)

The AERS database was searched for all U.S. serious reports of propoxyphene containing products from 1/1/2006 to 12/31/2007. (A prior OSE safety review[iv] [included in the background package] summarized AERS data from drug marketing [1957] to February, 2005). Sixty-five unique reports of serious adverse events were included in this case series to update the safety profile for the therapeutic[v] use of propoxyphene containing products.

A majority of the cases (51/65, 78%) reported the use of a propoxyphene combination product containing acetaminophen[vi], nine-percent of the cases (6/65, 9%) reported the use of a single ingredient propoxyphene, and the formulation used was unknown in twelve-percent of the cases (8/65, 12%). Cases with psychiatric (12) and cardiac (11) related events were most common, followed by drug ineffective (10), and multiple accidental drug

---

[i] The literature review was focused on propoxyphene associated cardiotoxicity and the elderly population.

[ii] "propoxyphene containing products" refers to both single ingredient propoxyphene and combination with acetaminophen. No other combination products (e.g. aspirin) with propoxypene were reported in this case series.

[iii] Other safety issues raised in citizen's petition include inappropriate use by the elderly, drug ineffective, implicated in suicide, dependence, and abuse.

[iv] Recent OSE postmarketing review of propoxyphene and Darvocet®: Bonnel RA, Dormitzer C, Ahmad SR. Review of Serious Adverse Events reported in association with propoxyphene and Darvocet®, 7/25/2005 (AERS search date: 2/2/2005).

[v] Cases reporting "accidental overdose" were included in the detailed analysis

[vi] Drug strength was not specified (particularly the acetaminophen component) in a majority of the cases.

overdose (9). The remaining 23 cases varied widely; some were single reports with no particular pattern or notable characteristics. In some cases propoxyphene product was one of multiple co-suspect or concomitant medications either taken as needed, or as an on-going pain reliever; as such, its role could not be clearly assessed in these 23 cases[vii].

Sixty-five-percent (42/65) of the cases reported the use of concomitant medications. Most frequently reported CNS associated drugs concomitantly used with propoxyphene products were opioids (e.g. oxycodone and duragesic), psychotropics[viii], and benzodiazepines. Contributing factors[ix] (medical history or labeled medications) were reported in almost half (29/65, 45%) of the cases and unknown in 55% (36/65) of the cases.

In forty-percent (26/65) of the cases, patients were 65 years of age or older. A majority of these cases (20/26, 77%) reported underlying medical history or multiple co-suspect medications. However, propoxyphene containing products may have contributed to the events reported in the elderly population as temporal association (10/26, 38%) and positive dechallenge (4/26, 15%) were noted in some cases, particularly for psychiatric related events.

Almost all cardiac associated cases (8/11, 73%) reported contributing medical history including hypertension, chronic diastolic heart failure, cardiomyopathy, coronary artery bypass graft, atrial fibrillation, hypercholesterolemia, or use of concomitant medications labeled for cardiac related events. Propoxyphene products may have had additive effects in these cases but a direct causal role could not be determined given the contributing factors cited. In the remaining three cardiac cases (3/11), two were notable for drug interactions with metoprolol and duloxetine. The third case reported bradycardia in an 80-year-old male with a significant cardiac medical history and the use of concomitant medications labeled for cardiac events. However, based on a plausible temporal association (event onset after 2 days of starting the drug), propoxyphene may be associated with the bradycardia reported in this case. The remaining two cases also suggest propoxyphene could be associated with potentiating cardiac events through possible drug interactions.

Most of the fatal (8/12, 67%) cases involved accidental overdose with use of multiple drugs, including alcohol (3 of 8 cases). A direct causal role of propoxyphene products in these death cases could not be established given the multiple concomitant drugs (e.g. opioids, and benzodiazepines) and contributing medical history (included cardiomyopathy and history of drug abuse). Additive propoxyphene effects, however, could not be ruled out. The remaining four cases were cardiac related deaths implicating an overdosage of

---

[vii] There was one (1/23) case of a plausible drug interaction involving carbamazepine in a female patient of unknown age. Drug interaction with carbamazepine and propoxyphene is labeled in the current propoxyphene labeling.

[viii] Psychotropics: antidepressants, sedatives, and antipsychotics

[ix] Contributing factors refers to an underlying medical condition, past medical history or use of labeled concomitant medications that could have contributed to the reported adverse events.

propoxyphene products[x] (see sec. 3.1 for case details), two of which were also confounded by contributing medical history (cardiomyopathy and scoliosis).

LITERATURE REVIEW OF CARDIOTOXICITY

The Division of Epidemiology within the Office of Surveillance and Epidemiology reviewed the medical literature for evidence of an association between propoxyphene containing products and cardiotoxicity in humans.

We used PubMed and EMBASE to perform queries. We indentified a total of 16 publications for the final review, three of which described epidemiological studies. The remaining 13 publications consisted of case reports and a case series.

Of the three epidemiological study publications, two described randomized controlled studies examining cardiac effects with therapeutic dose of propoxyphene. One randomized study found no effect that could be attributed to propoxyphene. The other randomized study found a significant difference in one of the cardiac conduction abnormality measures. However, this difference did not translate to clinically significant cardiac function defects.

The third publication described two seperate observational studies evaluating cardiotoxicity outcomes in overdose patients. The prospective study found significant differences in cardiac conduction (prolonged QRS duration) on echocardiogram. The measures, however, were not clinically abnormal. The retrospective study found a significant correlation between QRS duration and propoxyphene concentration.

OVERALL CONCLUSIONS

- Propoxyphene products may have had additive effects that contributed to cardiac adverse events based on temporal association[xi] and positive dechallenge cited in some cases[xii].
- Propoxyphene products may have contributed to psychiatric adverse events given the temporal association[xiii] and positive dechallenge noted in some cases.
- Over one third of adverse event reports involving elderly patients (65 years or older) included psychiatric (e.g. hallucination, confusion, mental status changes) events that may reflect pharmacodynamic effects of propoxyphene in this population.
- Cases of drug interactions in this review suggest that propoxyphene taken concomitantly with certain drugs may be associated with increased concentrations

[x] The four death cases included drug interaction-1 (ISR # 5483387), documented over-ingestion in an autopsy report-1 (ISR # 5538276), and cases from an Annual Report of the American Association of Poison Control Centers-2 (ISR #'s 5223417 and 5280841).

[xi] Five cases reported the estimated onset from 3 hrs to 21 days from starting the propoxyphene product.

[xii] All three dechallenge cases reported bradycardia. Cardiac associated events in the five cases with temporal association were bradycardia-3 and tachycardia-2

[xiii] Estimated onset from day 1 of starting propoxyphene products: 2 doses to 14 days (n= 7)

of propoxyphene or the co-administered drug, resulting in potentially life threatening toxicity (including cardiac events).

- The increased risk of fatalities from overdosage when propoxyphene products are used in combination with opioids, benzodiazepines, antidepressants, or other CNS depressants noted in this review is reflected in the **WARNINGS section** of the current product labeling. However, a direct causal role in fatalities for therapeutically administered propoxyphene could not be established given the patients' underlying medical history, or use of multiple co-suspect drugs, or both, noted in a majority of the updated reviewed cases.
- The findings in the updated review of propoxyphene product associated events are qualitatively similar to the 2005 OSE Postmarketing Review. The direct causal role of propoxyphene containing products in both the 2005 and updated OSE reviews could not be determined based on the underlying medical conditions or multiple co-suspect medications.
- The top 20 event terms reported for serious U.S. cases (2006 to 2007) were qualitatively similar to the event terms reported for all U.S. cases reported from approval (1957) to 9/24/2008.
- Despite current propoxyphene label warnings, narcotic pain relievers and other CNS related drugs continue to be prescribed and used with propoxyphene containing products, including in elderly patients.
- Literature review revealed mostly anecdotal reports of propoxyphene-related cardiotoxicity and lacked sound scientific evidence to support an association between propoxyphene-contanining products and cardiotoxicity.
- In 2007, the majority of sales of single-agent and combination propoxyphene products were to retail pharmacy settings. The propoxyphene/APAP combination product is the most commonly dispensed to all age groups and is reflected in both the 2005 and this updated review.
- The trends for patient data (i.e., prescriptions received) were similar to prescription data (i.e., prescriptions filled).
- General Practice/Family Medicine/Doctor of Osteopathy physicians are the most common prescribing healthcare providers for all propoxyphene containing products.

RECOMMENDATION

Although serious adverse events, including death, many involving accidental and intentional overdosages with other, often multiple medications, continue to be reported with the use of propoxyphene containing products, the AERS data in this review are alone insufficient to substantially inform the question of phased withdrawal of propoxyphene containing drugs from the market requested in the Citizen's Petition. In OSE's opinion, the regulatory action recommended for FDA by the upcoming AC should be based on clear clinical evidence of propoxyphene efficacy satisfactory to inform a robust discussion of the risk/benefit profile for these drugs.

Should propoxyphene containing drugs remain on the market, we recommend consideration of additional regulatory action (e.g., strengthened labeling, or Risk Evaluation and Mitigation Strategies [REMS], or both) to address the ongoing concomitant use of these products with opioids, benzodiazepines, alcohol, and other problematic medications that continues despite current labeling precautions. Additionally, we recommend consideration of a post-marketing commitment for a clinical safety trial(s) should these products remain market approved.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Analgesics, Anesthetics, and Rheumatology Products (DAARP) for an integrated AERS update, drug utilization, and literature[xiv] review of propoxyphene containing products. A Citizen's Petition (CP) from Public Citizen's Health Research Group (2006) requested that FDA initiate a phased withdrawal of all propoxyphene-containing products based on its questionable efficacy and low margin of safety[xv]. The petition also expressed specific concerns for use in elderly patients and the potential for cardiovascular effects with overdosage. Pursuant to the CP, an Advisory Committee (AC) Meeting is scheduled for January 30, 2009 to review the safety and the efficacy profile of propoxyphene containing drugs.

Propoxyphene products were withdrawn from the Swiss market in 2003 and from the Swedish market in 2005 after a number of deaths were reported from accidental overdoses. The United Kingdom (UK) withdrew all propoxyphene containing products in 2007, after finding approximately 400 deaths due to overdoses, with one in five reported as accidental[xvi].

A previous detailed OSE review[xvii] of propoxyphene containing products (July 25, 2005) found a majority of the 91 U.S. death reports[4] naming Darvocet® (propoxyphene/APAP) were overdoses involving other medications in addition to propoxyphene containing products, or involved significant underlying medical conditions, or both. A direct causal role for propoxyphene/APAP in many cases, therefore, could not be determined.

[xiv] The literature review was focused on propoxyphene associated cardiotoxicity and the elderly population.

[xv] Other safety issues raised in the citizen's petition include inappropriate use by the elderly, drug ineffective, implicated in suicides, dependence, and abuse.

[xvi] Prescrire International February 2006, volume 15 (81)

[xvii] Recent OSE postmarketing reviews of propoxyphene and Darvocet® : Bonnel RA, Dormitzer C, Ahmad SR. Review of Serious Adverse Events reported in association with propoxyphene and Darvocet®, 7/25/2005 (AERS search date: 2/2/2005).

1.2 REGULATORY HISTORY

A total of 22 propoxyphene/APAP combination products and six propoxyphene (single ingredient) products are currently marketed in the US. Reference listed products are presented in the table below:

Table 1. **Products (RLD*) with propoxyphene/APAP combination**		
Formulation	Approval Date	Sponsor
Darvocet N-50 Tablets (50 mg propoxyphene napsylate and 325 mg APAP)	12/19/1972 *NDA 17-122	Xanodyne Pharm
Darvocet N-100 Tablets (100 mg propoxyphene napsylate and 650 mg APAP)	12/19/1972 NDA 17-122	Xanodyne Pharm
Formulation	Approval Date	Sponsor
Propoxyphene/APAP Tablets (65 mg propoxyphnene HCl and 650 mg APAP)	12/16/1996 *ANDA 40-139	Watson Labs
Products (RLD*) with propoxyphene as single ingredient		
Darvon Capsules (65 mg propoxyphene HCl)	8/16/1957 NDA 10-997	Xanodyne Pharm
Darvon-N Tablets (100 mg propoxyphene napsylate)	9/9/1971 NDA 16-862	Xanodyne Pharm

*Abbreviations: RLD-reference listed drug, NDA-new drug application, ANDA-abbreviated new drug application, APAP-acetaminophen

Approved indication (from current labeling):

- Darvocet: For the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever; 1-2 tablets every 4 hours prn
- Darvon: For the relief of mild to moderate pain; 1 tablet every 4 hours prn

1.3 PRODUCT LABELING[xviii]

WARNINGS:

- *Do not prescribe propoxyphene for patients who are suicidal or addiction-prone.*
- *Prescribe propoxyphene with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess.*
- *Tell your patients not to exceed the recommended dose and to limit their intake of alcohol*

  Propoxyphene products, in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug related deaths. Fatalities within the first hour of overdosage are not uncommon. In a survey of deaths due to overdosage conducted in 1975, in approximately 20% of the fatal cases, death occurred within the first hour (5% occurred within 15 minutes).

[xviii] http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=6075

Propoxyphene should not be taken in doses higher than those recommended by the Physician. The judicious prescribing of propoxyphene is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of propoxyphene products and alcohol because of potentially

serious CNS-additive effects of these agents. Because of its added depressant effects, propoxyphene should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedative, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

Many of the propoxyphene-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of propoxyphene alone or in combination with other drugs. Patients taking propoxyphene should be warned not to exceed the dosage recommended by the physician.

PRECAUTIONS:

Drug Interactions—The CNS-depressant effect of propoxyphene is additive with that of other CNS depressants, including alcohol. As is the case with many medicinal agents, propoxyphene may slow the metabolism of a concomitantly administered drug. Should this occur, the higher serum concentrations of that drug may result in increased pharmacologic or adverse effects of that drug. Such occurrences have been reported when propoxyphene was administered to patients on antidepressants, anticonvulsants, or warfarin-like drugs. Severe neuologic signs, including coma, have occurred with concurrent use of carbamazepine.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

To provide an overall postmarketing context for propoxyphene-related[xix] safety issues, U.S. adverse event reports were retrieved for the product's life-cycle (approved in 1957) up to September 24, 2008 (data lock date). A total of 3038 (serious and non-serious) adverse event reports were retrieved from the AERS database. This search result includes the AERS data from a prior (2005) OSE postmarketing review [xvi] and the updated AERS data

[xix] In this review propoxyphene containing products refers to: combination of propoxyphene/acetaminophen (Darvocet) or propoxyphene (Darvon). No other propoxyphene combination products were reported or specified in this case series.

covering 2006 to 2007. (These crude counts are presented under Results section 3.1, Tables 3 through 7).

2.2 UPDATED AERS SELECTION OF CASES

For this updated review, the AERS database was searched for all U.S. serious reports of propoxyphene containing products for the two years (1/1/2006 to 12/31/2007). Of the 192 U.S. serious adverse event reports retrieved from this search, 127 (127/192) reports were excluded from further analysis (see exclusion table for details). The remaining sixty-five (65/192) unique cases were included in this case series to provide a more accurate safety profile with the therapeutic[xx] use of propoxyphene containing products.

Table 2. Excluded Cases

Reasons for Exclusion	N
Duplicate reports	44
Completed suicides – Intentional	43
Intentional overdose/suicide attempt	11
Drug dependence/abuse/misuse	17
Homicide case	1
Event unlikely related to Propoxyphene/APAP	9
Medication error	1
Miscoded (foreign report)	1
TOTAL	**127**

2.3 LITERATURE REVIEW OF CARDIOTOXICITY

The literature search for cardiotoxicity identified a total of 124 articles for initial review. Of these studies only 3 epidemiological studies[1-3] and 13 case reports/series[4-16] met the selection criteria. There were no studies comparing elderly participants to younger subjects.

The publications were grouped according to propoxyphene dosage:

1. Propoxyphene taken in therapeutic dose
2. Propoxyphene taken in overdose

Studies published between 1960 and 2009 about propoxyphene and its cardiotoxic effects were identified through searches of PubMed and EMBASE using the following terms: cardiotoxicity, cardiac toxicity, cardiovascular risk, cardiovascular toxicity, cardiovascular side effects; combined with dextropropoxyphene [MESH]/adverse effects or toxicity or poisoning, norpropoxyphene, d-propoxyphene. Additional publications were identified from searching the cited bibliography of articles identified by the two databases. The term

[xx] Cases reporting "accidental overdose" were included for detailed analysis

"elderly" was added to the previous search terms in order to identify a subset of publications focusing on propoxyphene safety in the elderly. Publications were screened for inclusion in this literature review using the following criteria:

- Human studies
- Exposure propoxyphene product
- Information about cardiotoxic event outcome
- English version of publication available

Epidemiology studies that were not designed for the purposes of detecting cardiac events as the primary outcome or as an adverse event were excluded. For the purposes of this review a cardiotoxic event was defined as having a deleterious effect on the action of the heart due to abnormal activity of the cardiac muscle and/or its conduction system. Case reports have been included as well to provide a more complete view of the available evidence.

2.4 DRUG USE DATA

DETERMINING SETTINGS OF CARE AND DATA SOURCES USED

The IMS Health, IMS National Sales Perspectives™ (see Appendix 1 for database descriptions) was used to determine the various retail and non-retail channels of distribution for single-agent and combination propoxyphene products. During year 2007, propoxyphene/APAP products accounted for nearly 90% of all propoxyphene sales.[xxi] Of the propoxyphene/APAP products, approximately 54% were sold toward retail pharmacy settings while about 31% and 14% were sold to non-retail and mail order channels, respectively. Retail pharmacy settings include chain, independent, and food stores with pharmacies, whereas non-retail pharmacy settings include non-federal hospitals, home health care, clinics, long-term care, federal facilities, prisons, universities, etc.

Single-ingredient propoxyphene products accounted for approximately 10% of overall propoxyphene sales. For these products, approximately 80% were sold toward retail pharmacy settings, 12% were toward non-retail pharmacy settings, and 8% were toward mail order settings.

Propoxyphene/asa/caffeine products accounted for less than 1% of the overall market of propoxyphene containing products. Retail distribution accounted for about 60% of sales and mail service distribution accounted for about 40% of sales during year 2007. In this analysis, we examined outpatient utilization patterns, excluding mail order.

DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

We examined total dispensed prescriptions by product using SDI Vector One®: National (VONA) (see Appendix 1 for full description) for calendar years 2006-2007. We also examined the number of patients who received a prescription in the outpatient retail pharmacy setting using SDI Vector One®: Total Patient Tracker (TPT) for calendar years 2006-2007.

[xxi] IMS Health, IMS Nationals Sales Perspectives™, Data extracted 10-29-08. File: 0810prop.dvr

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that single-agent and combination propoxyphene products are distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these non-federal hospital channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

3 RESULTS

3.1 UPDATED AERS CASES

To provide an overall safety context for propoxyphene associated AERS reports, a search was performed from drug marketing (1957) to 9/24/2008 (data lock date). This search included the AERS data from a prior (7/2005) OSE postmarketing review of propoxyphene products[xvi]. A total of 3038 (serious and non-serious) U.S. adverse event reports for propoxyphene containing products[xxii] were retrieved.

For the updated crude count for serious events, an additional search was performed in AERS limited to all US reports of propoxyphene containing products from 1/1/2006 to 12/31/2007. This search produced a total of 192 US serious adverse event reports. A total of 127 (127/192) reports were excluded from further analysis (see Table 2 for details). Sixty-five (65/192) unique cases were included in this US case series and represent the most recent passive surveillance post-marketing safety profile for the therapeutic[xxiii] use of propoxyphene containing products.

The tables below summarize the 20 most frequently reported US adverse events (all types) for propoxyphene containing products over all marketed years since initial approval (data lock date 9/24/2008). The AERS search results totals were: serious and nonserious reports, n=3038; serious reports, n=2136; and death as an outcome, n=1452. (It is important to note these results are crude counts only. Additionally, the crude counts may contain duplicate reports and the events may not necessarily be associated with propoxyphene containing products).

The adverse event terms bolded in the tables below are terms found in both the 2005 and this updated review and are generally representative of the most frequently reported adverse event terms since initial product approval.

[xxii] Propoxyphene containing products includes:

[xxiii] Cases reporting "accidental overdose" were included for detailed analysis

AERS CRUDE COUNTS

The most frequently reported event terms from approval (1957) to 9/24/2008 were overdose, including intentional, multiple drug, or accidental overdoses, followed by completed suicides, drug dependence and cardiac arrest. These are summarized in Table 3, below.

Table 3. Top 20 Adverse Event Terms (U.S. All Events, n=3038; marketing [1957] to 9/24/2008)

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Completed Suicide	**433**		Nausea	122
Intentional Overdose	**341**		Respiratory Arrest	109
Overdose	**319**		Vomiting	107
Multiple Drug Overdose	**191**		**Cardio-Respiratory Arrest**	**104**
Drug Dependence	**168**		**Death**	**98**
Cardiac Arrest	**161**		Dizziness	98
Accidental Overdose	**159**		**Drug Interaction**	**94**
Coma	154		Convulsion	79
Drug Ineffective	**130**		**Confusional State**	**75**
Drug Toxicity	**126**		Dizziness	98

Serious outcomes were reported in 2136 of the 3038 reports from approval to 9/24/2008. The most frequently reported adverse event terms in Table 4 (below) were similar to those in Table 3 (e.g. overdose of any type, completed suicide, cardiac arrest, and drug toxicity).

Table 4. Top 20 Adverse Event Terms (U.S. Serious Events, n=2136; marketing [1957] to 9/24/2008)

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Completed Suicide	**433**		**Death**	**98**
Intentional Overdose	**303**		**Drug Interaction**	**75**
Overdose	**286**		Pulmonary Oedema	74
Multiple Drug Overdose	**191**		**Multiple Drug Overdose Intentional**	**68**
Accidental Overdose	**156**		Vomiting	64

Cardiac Arrest	**153**		Drug Level Above Therapeutic	63
Drug Toxicity	**125**		Hypotension	63
Coma	122		Nausea	62
Respiratory Arrest	108		**Suicide Attempt**	**59**
Cardio-Respiratory Arrest	**104**		Dyspnoea	58

The AERS database was searched for death as an outcome which retrieved a total of 1452 reports from marketing (1957) to 9/24/2008[xxiv]. The most reported adverse event terms for the U.S. death cases (refer to Table 5, below) were similar to the event terms for all propoxyphene cases (serious and nonserious) including completed suicides and overdose or intentional overdose.

Table 5. Top 20 Adverse Event Terms (U.S. Deaths, n=1452; marketing [1957] to 9/24/2008)

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Completed Suicide	**433**		Coma	96
Intentional Overdose	**282**		Pulmonary Oedema	70
Overdose	**255**		**Multiple Drug Overdose, Intentional**	**67**
Multiple Drug Overdose	**173**		Drug Level Above Therapeutic	49
Accidental Overdose	**152**		Pulmonary Congestion	45
Cardiac Arrest	**148**		Toxicologic Test Abnormal	43
Drug Toxicity	**117**		Hypotension	41
Cardio-Respiratory Arrest	**103**		**Drug Abuser**	**40**
Respiratory Arrest	102		**Intentional Drug Misuse**	**40**
Death	**98**		**Suicide Attempt**	**39**

[xxiv] Note the 91 death cases reported in a prior 2005 OSE Review were associated only with trade name Darvocet (search dates from 1957 to 2/2/2005). The updated review included both the trade and generic propoxyphene containing products to search the database which retrieved a total of 98 death reports for the two years (2006 to 2007).

For an updated comparison of top adverse event terms, an additional search was performed in the AERS database for updated serious (Table 6) and death cases (Table 7) limited to the two years (1/1/06 to 12/31/07).

Table 6. Top 20 Adverse Event Terms (U.S. Serious Events, n=192; 1/1/2006 to 12/31/2007)

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Completed Suicide	**50**		Hyponatraemia	10
Cardiac Arrest	**24**		Bradycardia	9
Respiratory Arrest	21		**Intentional Overdose**	**9**
Dizziness	17		Loss of Consciousness	9
Intentional Drug Misuse	**16**		**Overdose**	**9**
Drug Toxicity	**15**		**Confusional State**	**8**
Drug Interaction	**14**		Fall	8
Somnolence	14		Hip Fracture	8
Cardio-Respiratory Arrest	**12**		Pain	8
Drug Abuser	**11**		Vomiting	8

A total of 192 U.S. serious cases were retrieved from the AERS database, and the top event terms are presented in Table 6. These top 20 adverse event terms were a fair representation of the adverse event terms reported for all U.S. cases from approval to 9/24/2008. Completed suicide, cardiac arrest, and intentional drug misuse were the most reported terms.

For the updated crude counts, AERS was searched for all propoxyphene containing products with death as an outcome from 1/1/2006 to 12/31/2007. A total of 98 death reports[xxiii] were retrieved and the top 20 event terms reported in these reports[xxv] (Table 7 below) followed a consistent trend as the U.S. cases for serious and nonserious events reported for all years of propoxyphene product marketing to 9/24/2008. Completed suicide and cardiac arrest were most reported terms.

Table 7. Top 20 Adverse Event Terms (U.S. Deaths, n=98; 1/1/2006 to 12/31/2007)

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Completed Suicide	**50**		**Death**	**6**
Cardiac Arrest	**23**		Dehydration	6
Respiratory Arrest	20		**Drug Abuser**	**6**
Intentional Drug Misuse	**15**		**Overdose**	**6**
Drug Toxicity	**14**		Aortic Valve Calcification	5
Cardio-Respiratory Arrest	**12**		Cardiomegaly	5
Somnolence	8		Hepatic Steatosis	5
Intentional Overdose	**7**		Pulmonary Oedema	5
Pulmonary Congestion	7		Spleen congestion	5
Vomiting	7		Asthma	4

[xxv] Note: A report may contain more than one preferred (PT) event term.

Updated AERS Cases of Serious Adverse Events (N=65)

From 1/1/2006 to 12/31/2007 there were 65 unique U.S. reports of serious events with propoxyphene containing products found in AERS and included for this review. The demographic characteristics and the narrative of representative cases are described in Table 8, below.

Table 8. Demographics and other parameters of U.S. Serious cases reported with propoxyphene containing products from 1/1/2006 to 12/31/2007 (N=65)	
Age (yrs): n=53	Range: 19-92 (median-62)
Gender:	Female (42), Male (21), Not reported (2)
Drug product[xxvi]: n=57	Propoxyphene/acetaminophen (51), propoxyphene (6)
Indication for use: n=31	Pain (unspecified) (13), ankle pain (1), back pain (6), dental/surgical pain (3), joint/hip pain (3), leg/knee pain (2), osteoarthritis (2), nerve pain (1)
Total daily dose: n=13	Range 100 mg – 800 mg (median-200 mg)
Estimated time of onset[xxvii]: n=18	Range 1 dose to 4 years (median-1 day)
dechallenge[xxviii]	Positive (8)
Estimated duration of therapy: n=16	Range 1 day to 16 years (median-15 days)
Outcome*	Death (12), Hospitalization (29), Life-Threatening (5), Other {medically significant} (38)
Report type	Expedited (38), Direct (18), Periodic (9)
Reporter: n=58	Physician (15), Pharmacist (8), Other Health Care Professionals (18), Attorney (2), Consumer (15),

*A case may have more than one outcome

[xxvi] "Propoxyphene product" in this review refers to both single ingredient propoxyphene and propoxyphene combination with acetaminophen.

[xxvii] Time to onset from day 1 of starting the drug

[xxviii] Rechallenge cases-none

The reported adverse events possibly associated with the propoxyphene containing products were categorized according to the AERS system organ classes (SOC) as listed below (a given report may contain more than one adverse event term):

System Organ Class (14): Preferred Terms (n)

Cardiac disorders: arrhythmia (1), bradycardia (6), cardiac/respiratory arrest (3), congestive arrest (3), congestive heart failure (CHF), tachycardia (2), myocardial infarction (MI) (1)

Eye disorder: eye swelling (1), vision blurred (1)

General disorder and administration site conditions: drug ineffective (10), drug ineraction (5), drug intolerance (1), influenza like illness (1), injection site bruising (1), drug withdrawal syndrome (1)

Gastrointestinal disorder: gastrointestinal bleed (1), acute pancreatitis (1)

Hepatobiliary disorder: hepatic steatosis (1), hepatomegaly (1), hepatocellurlar injury (1)

Immune system disorder: hypersensitivity (2)

Injury poisoning and procedural complications: drug toxicity (1), hip fracture (1), multiple drug overdose[xxix] (11), narcotic overdose[1] (1)

Investigations: blood pressure decreased (3), heart rate elevated/abnormal (4)

Metabolism and nutrition disorder: metabolic acidosis (1)

Nervous system disorder: ataxia (1), cerebral haemorrhage (1), coma (1), dizziness (2), somnolence (1), syncope (1)

Psychiatric: abnormal behavior (1), confusional state (3), hallucinations (5), mental status change (6)

Respiratory, thoracic and mediastinal disorders: respiratory depression (1), dyspnoea (1)

Skin and subcutaneous tissue disorder: rash (1), itch (1)

Social circumstances: abortion induced (1)

[xxix] These overdose events were reported as accidental (7) or they were unintentional overdoses (4) based on the descriptions in the narratives.

Clinically significant and other selected events of interest are grouped and summarized in greater detail as follows:

Cardiac Related Event Cases (N=11)

Eleven cases reported cardiac related events (arrhythmia -1, bradycardia[xxx]-4, cardio-respiratory arrest-2, congestive heart failure-1, myocardial infarction-1, tachycardia-2). Almost all cases (9/11, 82%) also reported contributing medical history including hypertension, chronic diastolic heart failure, cardiomyopathy, coronary artery bypass graft, atrial fibrillation, hypercholesterolemia, or use of concomitant medications labeled for cardiac related events. This information was unknown in two (2/11) cases. In most cases (8/11, 73%), another drug was reported as the primary suspect drug (fioricet, diphenhydramine, duloxetine, donepezil, vicodin, pregabalin, infliximab, and rofecoxib). In the remaining three cases (3/11), propoxyphene was listed as the primary or co-suspect drug, and two of these cases reported notable drug interactions, while the third case reported bradycardia in an 80-year-old male using multiple concomitant medications for various associated medical conditions.

Summary of the 3 notable cases (includes one literature report[xxxi]):

The first case involves a 48-year-old male with life-threatening bradycardia who was concomitantly taking 100 mg metoprolol and 200 mg propoxyphene napsylate with 1300 mg acetaminophen. Metoprolol was his usual maintenance drug for atrial fibrillation and the propoxyphene/acetaminophen was newly added as a post-operative pain medication[xxxii]. At the time of the event, the patient's heart rate dropped to 30 to 40 beats per minute; he was subsequently discharged with a heart rate (HR) of 70 beats per minute.

The second case involved a 61-year-old female with a medical history of cardiomyopathy. The only two reported drugs were duloxetine and propoxyphene. Cardiac arrhythmia was reported as the immediate cause of death. No other drugs were detected during the postmortem analysis.

These first two cases plausibly represent drug interactions: the CYP450 effects of propoxyphene may be associated with the cardiac events of bradycardia and arrhythmia based on its pharmacological properties when used with other (e.g. metoprolol and duloxetine) drugs also involved in this CYP450 pathway (see representative cases for details).

In the third case an 80-year-old male patient was hospitalized for bradycardia and low blood pressure two days after taking propoxyphene (dose and duration of use unknown) every 6 hours for dental pain. Contributing medical history included coronary artery disease, chronic diastolic heart failure, and aortic valve stenosis. Possible contributing

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[xxx] One case was coded as bradycardia and drug interaction

[xxxi] Marraffa J, Lang L, et al. Profound metoprolol-induced bradycardia precipitated by acetaminophen-propoxyphene. Clinical Pharmacology & Therapeutics: 79(3):282-286, March 2006.

[xxxii] Patient underwent umbilical hernia repair. Other concomitant medications included diltiazem, atorvastatin, levothyroxine, fosinopril, amitriptyline, warfarin.

concomitant medications included felodipine, atenolol, and lisinopril (bradycardia is a labeled event in these three drugs). The event resolved after the propoxyphene product was discontinued and the patient was discharged with instructions to take only acetaminophen for pain if needed. In this case, bradycardia and low blood pressure resolved after treatment with atropine and dopamine; the event did not recur during the hospital stay (propoxyphene was discontinued). Propoxyphene could have contributed to the reported events based on its temporal (event onset of 2 days after ingestion) association. However, given the confounding factors of a previous history of cardiac related events, and the use of concomitant medications also labeled for cardiac associated events, the role of propoxyphene can not clearly established.

Representative Cases

ISR # 5185760 (Expedited Report, 2006)

A 48 year-old man presented with complaints of dizziness approximately 3 hours after taking his usual dose of metoprolol 100 mg and two tablets of propoxyphene 100/APAP 650. His blood pressure (BP) was 98/65 and the cardiac monitoring showed atrial fibrillation with ventricular response at 30-40 beats per minute. After treatment of the event (bradycardia), his heart rate (HR) increased to 50-70 beats per minute. At discharge (8 hours after presentation) his HR was 70 beats per minute. Serum drug profile concentrations obtained 30 minutes after presentation were metoprolol (160 ng/mL), diltiazem (99 ng/mL) and dextropropoxyphene (0.15 mcg/mL), which were within therapeutic levels[xxxiii]. Ten months later, this patient returned for a steady state metoprolol pharmacokinetic protocol. A peak metoprolol serum concentration of 89 ng/mL was observed at 3.5 hours. His HR significantly decreased with increasing metoprolol serum concentrations. This was reported as a case of profound bradycardia likely resulting from inhibition of metoprolol hepatic clearance by detropropoxyphene's effect on CYP 450 Enzyme System.

ISR #5483387 (Direct Report, 2007)

A 61-year-old female with a past medical history of an undetermined form of cardiomyopathy was found dead in her home. The circumstances at the scene were reported as typical for a sudden collapse due to a cardiac arrhythmia. Cardiomyopathy was the only reported past medical history. Postmortem analysis revealed a propoxyphene level of 2880 ng/mL (therapeutic range 200-800 ng/mL), Norpropoxyphene level of 6428 ng/mL (therapeutic range not established), duloxetine of 225 ng/mL (therapeutic range not established[xxxiv]). It was noted that duloxetine could have possibly increased the effects of propoxyphene, causing death due to arrhythmia; conversely, death could have been a

[xxxiii] Therapeutic levels for adults: metoprolol (beta-blocking activity)-35 to 212 ng/mL, diltiazem (antihypertensive activity)-40 to 200 ng/mL, propoxyphene-0.1 to 0.4 mcg/mL, nor-propoxyphene (metabolite)-0.1 to 0.15 mcg/mL.

[xxxiv] Oral administration of 20 and 30 mg duloxetine twice daily in healthy subjects, showed 15 ng/mL and 20 ng/mL respectively in one study (Sharma, et al, 2000).

complication of cardiomyopathy, independent of drug interaction effects. There were no other concomitant medications noted in the AERS report and no other drugs were detected during the postmortem analysis. Cardiac arrhythmias, ventricular fibrillation or cardiac arrest are labeled under symptoms of overdosage in the current labeling for propoxyphene containing products.

Psychiatric Related Event Cases (12)

There were 12 psychiatric related cases[xxxv] reported with use of a propoxyphene product: abnormal behavior-1, confusional state-3, hallucination-5, and mental status changes-6.

All 12 cases (12/12) reported using the propoxyphene combination product with acetaminophen (Darvocet). The onset of events related to treatment ranged from 2 doses to 14 days (n=7), with one case reporting a positive dechallenge (negative dechallenge-2, unknown-9). Six (6/12) cases reported a possible contributing medical history (i.e., thyroid disorder, decreased kidney function, senile dementia, drug sensitivity) or use of labeled concomitant medications (unknown-6). The concomitant medications labeled for psychiatric related events included sedatives, benzodiazepines, donepizil, fluoxetine, levetiracetam, gabapentin, opiods, and pregabalin. Propoxyphene products are labeled for hallucination. Eighty-three-percent of these cases (10/12, 83%), reported a contributing medical history or reported using concomitant medications labeled for CNS effects, however, a temporal association (n=7) and a positive dechallenge (n=1) suggest that propoxyphene products may be associated with the reported events in some cases. Further, the reduced metabolism in the elderly population and the pharmacodynamic[xxxvi] effects may also have contributed to these events.

Representative Cases

ISR #4889414 (Expedited, 2006)

A 68 year old patient became "nasty, agitated, mean, impatient, enraged, etc." after one week of treatment with a different "brand" of Darvocet-N 100. (She reported previous use of Darvocet for 7 years as needed for pain [dose not specified]). This event continued for 3 weeks and self-resolved. Diazepam[xxxvii] was the only concomitant medication reported (specific dose and duration of use not given). She believed the refilled Darvocet prescription was a generic or contained Nutrasweet. She had a similar experience with Nutrasweet in the past. Darvocet-N 100 was continued from two new prescriptions with no further problems. No other pertinent information was provided.

[xxxv] A case may have more than one reported preferred term

[xxxvi] Barkin R, et al. American Journal of Therapeutics 13, 538 (2006)

[xxxvii] Current diazepam labeling include hyperexcited states, hallucination, anxiety and rage.

ISR #5011076 (Direct, 2006)

A pharmacist reported that a 92-year-old female with a past medical history of hypertension, blindness, and temporal arteritis was admitted to the hospital for a 2-week history of altered mental status. The patient had begun taking Darvocet for back pain 2 weeks prior to admission and started having hallucinations, loss of appetite, and confusion. Her review of systems was otherwise negative. She stopped taking Darvocet three days prior to admission. The patient's altered mental status was attributed to Darvocet, and the patient was discharged to a nursing home. Concomitant medications were unknown and no follow-up information was provided.

ISR #5131914 (Expedited, 2006)

A 78 yr old female Alzheimer patient was admitted to the hospital due to a fall. Darvocet was prescribed during hospitalization for complaint of back pain. The patient's daughter observed in her mother the same sedative effects ("spacey") from Darvocet that her mother displayed while taking Percocet in the past. Ongoing concomitant medications were donepezil and fluoxetine[xxxviii]. No other pertinent medical history was reported. A week after hospitalization, the patient was transferred to a rehabilitation facility. A month later, Darvocet was discontinued and the reported event resolved.

Multiple Drug Overdose Cases (N=9)

Nine cases were reported as accidental drug overdose[xxxix]. Outcomes for these cases were death-8 and hospitalization-1. Almost all (8/9) cases reported using multiple drugs, and in two (2/8) cases alcohol was also involved. The most commonly reported suspect concomitant drugs were opioids[xl](n=8) or benzodiazepines (n=5). Only one case reported using a nonopiod concomitant drug (mirtazipine) in addition to propoxyphene. A history of drug abuse or addiction was reported in six (6/9) cases[xli]. In these six cases, outcome was attributed to ingestion of multiple drugs producing mixed drug toxicity and accidental death. In two of the three remaining cases, oxycodone was the primary suspect drug but the role of propoxyphene containing products could not be ruled out. In the remaining case, accidental death of a 30 year old female was attributed to propoxyphene, with mirtazipine reported as the contributory drug (see representative case below for details).

[xxxviii] Somnolence was a reported adverse event during the clinical trials for both donepezil and fluoxetine.

[xxxix] One case was reported as "narcotic overdose."

[xl] Oxydocone was most commonly reported suspect concomitant drug. Duragesic, morphine, methadone, hydromorphone, codeine, cocaine, and hydrocodone were also included as the suspect drugs.

[xli] Two (2/6) cases reported cocaine or ethanol abuse in addition to other drugs.

Representative Cases

ISR #5538276 (Expedited, 2007)

A 30-year-old female died after using single ingredient propoxyphene (Darvon) to treat back pain due to severe scoliosis and post-operative pain. Dose, frequency, and specific dates were unknown. According to the autopsy report, the patient died during sleep from an accidental over-ingestion of propoxyphene. Autopsy findings included pulmonary edema, cerebral edema, and diffuse visceral congestion. Therapeutic levels of mirtazapine were also reported as contributing to the events.

Drug Ineffective Cases (N=10)

All 10 cases reported the use of the propoxyphene/acetaminophen (Darvocet) combination product for pain (back, joint, leg, muscle, nerve)-6, pain (location not specified)-3, and osteoarthritis-1 [xlii]. Drug sensitivity or drug intolerance to aspirin, codeine, morphine, and Vicodin were reported as contributing past medical history in two (2/10) cases.

Six of the 10 cases reported the drug was ineffective or caused side effects (dizziness, nausea, vomiting) after switching from one brand (trade or generic brand) to a different generic product. Three cases suggested a lack of efficacy when used for an unlabeled indication (nerve pain)-1 and suboptimal potency at therapeutic doses-2. One case could not be assessed due to lack of information. The remaining six of the 10 cases reporting a product switch suggest a possible suboptimal potency associated with certain propoxyphene containing products (brands were not specified).

Elderly Population Cases (65 years or greater, N=26)

In forty percent (26/65, 40%) of the cases, patients were 65 years of age or older. Frequently reported adverse events in this age group were labeled events for the propoxyphene products (12/26, 46%) involving psychiatric (hallucination, confusion, mental status changes, abnormal behavior) or central nervous system (coma, ataxia) related events. There was no notable or consistent pattern of adverse events in the remaining 14 cases (14/26, 54%). The reported events varied widely and included cardiac related events (bradycardia, tachycardia)-3, liver function test elevated-2, drug ineffective-3, drug interaction[xliii]-1, and others (hypersensitivity, hip fracture, accidental drug overdose, and skin bruising, hepatomegaly)-5.

In one case, the use of warfarin with propoxyphene in a 79 year old male patient resulted in a significant increase in INR (14.1). The patient was treated with vitamin K and released from the hospital with an INR of 1.2. The only new medication recently added to the patient's regimen (phenytoin and warfarin) was propoxyphene. There was no pertinent contributing medical history. A drug interaction for propoxyphene with warfarin is a

[xlii] Duration of use prior to the reported event or switching to a different brand was reported in two (2/10) cases: 2.5 years and 16 years (unknown-8).

[xliii] The drug interaction involved warfarin and a single ingredient propoxyphene. Drug interaction with warfarin is a labeled event.

labeled event in the propoxyphene labeling[xliv]. Although a majority of these cases (20/26, 77%) reported underlying medical history or multiple co-suspect medications, propoxyphene containing products may have contributed to the events reported in the elderly population given the temporal association (10/26, 38%) and positive dechallenge (4/26, 15%) in some cases (most notably for psychiatric events).

There was one additional case of a plausible drug interaction involving carbamazepine in a female patient of unknown age. After two doses of Darvocet N 50 mg, the patient became unresponsive. She subsequently recovered after treatment with naloxone in the ER. Concomitant medications were carbamazepine 600 mg twice daily, Depakote EC 750 daily, and pregabalin 50 mg twice daily. Carbamazepine, depakote, and APAP levels were measured; carbamazepine levels were elevated at 19 mcg/mL[xlv]. After Darvocet and carbamazepine were held due to a suspected drug-drug interaction, the patient was much more alert and responsive the next morning. Carbamazepine level was now at13 mcg/mL. Drug interaction with carbamazepine is labeled in the current propoxyphene labeling.

Death Cases (N=12)

There were a total of 12 (12/65) fatal cases. Eleven (11/12) of these are described in previous sections (accidental overdose and cardiac) of the review. The cause of death in these 11 cases were reported as accidental overdose-8, cardiac-respiratory arrest-2, and arrhythmia-1. The remaining death case reported cerebral haemorrhage-1 as the cause. In this case, a 50-year-old male nursing home patient experienced a massive right hemispheric intracerebral hematoma with intraventricular hemorrhage. His medical history included hypertension, renal insufficiency, thrombus of left ventricle, congestive heart failure and cardiomyopathy. Rofecoxib (dose, duration, indication not reported) was reported as the primary suspect drug and the concomitant medications were atorvastatin, digoxin, warfarin, and Darvocet-N. After receiving meperidine and promethazine for joint pain, the patient became somnolent for a few hours and he was subsequently found unconscious with agonal respiration. The patient was given a CPR and intubated, then transferred to an ICU in a comatose state. The death certificate listed the cause of death as intracerebral hemorrhage.

3.2 LITERATURE REVIEW

3.2.1 Cardiac Effects of Therapeutic Doses of Propoxyphene

Two studies were identified comparing therapeutic dose propoxyphene to another drug or placebo (Appendix 1 Table 1). The first study by Salzman et al. compared propoxyphene hydrochloride to suprofen in a randomized parallel study. [1] Sixty-one percent of participants completed the study. Withdrawal rates were similar in both treatment groups and participants on propoxyphene withdrew due to non-cardiac side effects. No clinically significant changes in pulse or blood pressure were detected. Four participants had

[xliv] Refers to all current propoxyphene containing product labeling.

[xlv] Therapeutic levels of carbamazepine for seizure disorder: 4 to 12 mcg/mL

abnormal electrocardiograms (ECG) after the 24-week period. The authors concluded that the changes were not related to the study medications, though the reasons for their conclusion were not specified.

The study by Lang-Jensen et al. compared dextropropoxyphene napsylate to placebo in a younger patient sample.[2] In this case-crossover study design in which subjects served as their own controls, the completion rate was 90%. Only 10 young healthy males participated in the study and took propoxyphene or placebo three times daily for 16 days then switched to placebo or propoxyphene, respectively, after a one month washout period. The hemodynamic measurements taken at rest and during 30% and 60% work load showed a longer pre-ejection period in the propoxyphene group (mean =125ms) compared to the placebo group (mean =119). Overall hemodynamic measurements showed no effect on cardiac muscle contractility.

3.2.2 Cardiac Effects of Propoxyphene Overdose

We identified 14 publications describing cardiotoxic effects of propoxyphene when taken in overdose. All but one were case reports or case series (Appendix 1 Tables 2 & 3).

Afshari et al. 2005 conducted a two-part observational study, one included a prospective cohort design, and the other was a retrospective cohort without a comparison group. [3] The prospective study found an increase in QRS duration on ECG in the propoxyphene-paracetamol group (mean=99.36 milliseconds (ms); 95%CI = [96.19, 102.53]) compared to the group on other opioid-paracetamol combinations (mean = 82.84 ms; 95% C I= [80.81, 84.88]). None of the patients had abnormally prolonged QRS (> 0.12sec). In their retrospective study, they found a significant correlation between QRS duration and the plasma paracetamol concentration, which was used as an estimate of ingested propoxyphene dose (r = 0.338, p=0.003).

We identified 12 case reports describing a total of 14 cases. Four reports describe cases of propoxyphene overdose in older patients (aged 45 to 60 years) who experienced cardiac events.[4-7] Six patients had electrocardiograms showing widened QRS complexes (> 0.1sec). Respiratory depression preceded cardiac event in 3 of those patients, one patient had sudden cardio-respiratory failure, and the other 2 showed no signs of respiratory depression. First degree atrioventricular (AV) block was experienced by 5 patients.[5,8-11]

Sloth et al. described a case series of 222 patients with various cardiac events including bradycardia, tachycardia, and ventricular arrhythmias following propoxyphene overdose.[16]

3.3 DRUG USE DATA

3.3.1 Outpatient Dispensed Prescriptions

Table 1 in Appendix 3 shows the total number of prescriptions dispensed in the outpatient retail setting (mail order excluded) for single-agent and combination propoxyphene products. There has been a slight decrease in the number of prescriptions dispensed for

propoxyphene products between years 2006 and 2007. During year 2007, approximately 22.3 million prescriptions were dispensed for all propoxyphene containing products with the majority of prescriptions being dispensed for propoxyphene/APAP (21.7 million dispensed prescriptions, 97.5%). The number of prescriptions dispensed for propoxyphene/asa/caffeine has decreased over the two years from nearly 6,800 prescriptions in year 2006 to approximately 400 prescriptions dispensed in year 2007.

3.3.2 Outpatient Dispensed Prescriptions by Age

Table 2 in Appendix 3 shows the total number of prescriptions dispensed by product and age in the outpatient retail setting for single-agent and combination propoxyphene products. For propoxyphene/APAP products, the majority of prescriptions dispensed were evenly split between adults age 45-64 years and elderly 65 years and greater with 38% in year 2007. While propoxyphene and propoxyphene/asa/caffeine were dispensed to adults age 45-64 years (48% and 42%, respectively) with a slightly greater frequency than elderly 65 years and greater (35% and 40%, respectively).

3.3.3 Patient Count

Trends for patient data were similar to that of prescription data, (Appendix 3: Table 3). For the entire study period, the majority of patients received propoxyphene/APAP products in the outpatient retail pharmacy setting. In year 2007, a total of 9.8 million patients received a prescription for a propoxyphene containing product. Of those, approximately 9.7 million (98.7%) patients were prescribed propoxyphene/APAP followed by propoxyphene with 182,000 (2%) patients.

3.3.4 Patient Count by Age

Table 4 in Appendix 3 shows the total number of patients receiving a prescription for single-agent and combination propoxyphene products by age. For propoxyphene/APAP products, the majority of patients receiving a prescription were evenly split among adults 18-44, 45-64, and 65 years and greater with approximately 3.1 million, 3.4 million, and 3.1 million, respectively. Patients aged 45-64 years receive a prescription for propoxyphene and propoxyphene/asa/caffeine with a slightly greater frequency than elderly 65 years and greater.

3.3.5 Prescriber Specialty

General Practice/Family Medicine/Doctor of Osteopathy was the most common prescribing specialty for all the products of single-agent and combination propoxyphene followed by Internal Medicine (Appendix 3: Table 5). During the most recent calendar year 2007, approximately 29% of the dispensed prescriptions were written by General Practice/Family Medicine/Doctor of Osteopathy for propoxyphene/APAP followed by 19% written by Internal Medicine physicians. In year 2007, 31% of dispensed prescriptions for propoxyphene and 38% of prescriptions for propoxyphene/asa/caffeine were written by General Practice/Family Medicine/Doctor of Osteopathy followed by Internal Medicine physicians with 23% and 13%, respectively.

4 DISCUSSION

4.1 UPDATED AERS CASES (N=65, 2006-2007)

The findings of this updated review were qualitatively similar to the findings in a prior OSE review completed in 2005[iv]. A direct causal role of propoxyphene products could not be established based on the underlying medical conditions and the use of multiple co-suspect medications in both the 2005 and the updated reviews.

Seventy-eight-percent of the cases (51/65) reported using the propoxyphene combination product containing acetaminophen[xlvi], 9% (6/65) reported using the single ingredient (propoxyphene), and an unknown formulation was used in 12% (8/65). A majority of the cases did not report the dose (52/65, 80%), time to onset of events (47/65, 72%), or duration of therapy (49/65, 75%). Of the 13 cases reporting a dose, most (12/13, 92%) reported using within the recommended daily dose (600 mg). Only one case (1/13) reported using a dose above the recommended daily dose (800 mg). The estimated time to adverse event onset was a median of one day (range 1 day to 4 years) in the 18 cases reporting this information. Sixty-five percent (42/65) reported using concomitant medications. Most frequently reported CNS associated concomitant drugs were opioids (e.g. oxycodone and duragesic), psychotropics[xlvii], and benzodiazepines. Contributing factors[xlviii] (medical history or labeled medications) were reported in almost half (29/65, 45%) of the cases and unknown in 55% (36/65) of the cases.

Psychiatric (12) and cardiac (11) related events were the most frequently reported events followed by drug ineffective (10), and multiple accidental drug overdose (9). The remaining 23 cases varied widely in terms of type of events reported and included some reports with no particular pattern or notable characteristics. In 18 of the 23 cases the primary suspect drugs included Forteo, varenicline, taxotere, Enbrel, Ketek, Vicodin, Medrol, Keflex, pregabalin, Vfend, acetaminophen, duragesic, tramadol, and trileptal. A propoxyphene product was one of several co-suspect or concomitant medications (taken as needed or as an on-going pain reliever) in many of these cases, therefore, its role could not be clearly assessed[xlix].

Selected events are discussed and summarized below:

<u>Cardiac Events</u>

In most (8/11, 73%) of the cardiac related cases, the propoxyphene product was one of multiple concomitant medications which made it difficult to assess a clear drug- to-event association. The reported events (bradycardia-2, cardiac arrhythmia-1) in the three

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[xlvi] Drug strength was not specified (particularly the acetaminophen component) in a majority of the cases.

[xlvii] Psychotropics: antidepressants, sedatives, antipsychotics.

[xlviii] Contributing factors refers to an underlying medical condition, past medical history or use of labeled concomitant medications that could have contributed to the reported adverse events.

[xlix] There was one (1/23) case of a plausible drug interaction involving carbamazepine in a female patient of unknown age. Drug interaction with carbamazepine and propoxyphene is labeled in the current propoxyphene labeling.

remaining cases may be associated with the use of propoxyphene product. There was a temporal association in one case reporting bradycardia (contributing factors were history of cardiomyopathy and labeled concomitant medications). The remaining two cases also suggested propoxyphene could be associated with potentiating cardiac events through possible drug interactions.

Elderly Population

In patients who were 65 years of age or older, 40% (26/65) of the cases reported adverse events that are labeled events for the propoxyphene products; 46% of these 26 cases (12/26) involved psychiatric (hallucination, confusion, mental status changes, abnormal behavior) or central nervous system (coma, ataxia) related events. While a majority of these cases (20/26, 77%) reported an underlying medical history or multiple co-suspect medications, propoxyphene containing products may have contributed to the reported events given the temporal associations (10/26, 38%) and positive dechallenges (4/26, 15%).

Deaths

Most of the fatal (8/12, 67%) cases involved accidental overdose with use of multiple medications including alcohol (in 3 of 8 cases) thereby rendering an assessment of propoxyphene's role problematic. Concomitant drugs included opioids and benzodiazepines, which themselves can be implicated in accidental overdose. Nonetheless, an additive effect for propoxyphene can not be ruled out. The remaining four (4/12) cases reported the use of a propoxyphene product with one other medication (fiorinal, diphenhydramine, duloxetine, and mirtazipine). All four cases implicated an overdosage of propoxyphene products[ix].

4.2 LITERATURE REVIEW

The body of literature is populated with more anecdotal reports describing cardiotoxicity than with epidemiology studies, and these case reports have overshadowed those few epidemiology studies that make inferences based on analytic data. Case reports and case series do not provide a scientific basis to infer causal associations and are generally used for generation of hypotheses upon which epidemiological studies can be designed.

The cardiac safety profile of propoxyphene and its metabolite norpropoxyphene have been scarcely studied in humans. Researchers intending to conduct such studies are faced with a number of methodological issues, some of which are manifested in the 3 prospective studies included in this review. Cases of overdose in which propoxyphene has been implicated usually involve other drugs and substances of abuse. In some instances up to 75% of propoxyphene overdose cases involved the co-ingestion of alcohol and/or another drug. [17] In their study, Afshari et al. barely addressed this issue and failed to screen for and adjust for such potential confounders. Although Salzman et al. did randomize their patients to treatment groups the study sample included older patients who suffered from other medical ailments and were prescribed other medications for those conditions. This is

important especially since the authors attribute the observed ECG changes to factors (unspecified in the publication) other than the two study drugs.

Drug screens have confirmed multi-drug ingestions in overdose patients even when little clinical suspicion exists. [17] Propoxyphene ingestion was verified by drug screen in only 3 of the 14 case reports and in 2 of the cases at least one other drug was detected.[4,10,12] In all the other case reports, ingestion was verified either by the patient or by counts of missing pills.

Until recently the methods used to measure propoxyphene and norpropoxyphene levels in human body fluids were unreliable and produced high variations even in inter-laboratory values.[17] In practice measurement of propoxyphene levels is usually regarded as irrelevant primarily due to the fact that naloxone has been very effective in treatment and management of overdose patients and its success has not been dependent on the ingested dose of propoxyphene.[18] This lack of availability of drug concentration complicates efforts to study and interpret any dose-response relationship that may exist. In their study, Afshari et al. attempted to retrospectively estimate propoxyphene concentrations at certain time points during the patients' clinical course by using routinely measured plasma paracetamol concentrations and an estimated paracetamol half-life of 4 hours. The authors assumed the plasma concentration ratios of the propoxyphene and paracetamol would mirror the ratio of the two components found in the combination pills. However, they did not adjust for the difference in their elimination kinetics. Thus the correlation detected between paracetamol concentrations and QRS duration cannot be correctly assumed to hold true for propoxyphene based on this methodology. In addition, they did not use a comparison group and in essence cannot interpret a correlation as a causal association. In the Salzman et al. study and in 2 case reports[6,12] propoxyphene and/or norpropoxyphene levels were directly measured and that data was used to show when steady states of the drug were reached but not to evaluate dose-response associations.

The occurrence of respiratory depression in relation to the timing of cardiovascular abnormalities adds to the controversy of propoxyphene poisoning. Hypoxia due to a respiratory-depression effect of propoxyphene could produce cardiovascular changes including cardiac conduction abnormalities but this has been refuted by some in vitro and animal studies that conclude the two pathways are separate.[10,19-21] In the Salzman et al. and the Lang-Jensen et al. studies none of the participants were monitored for signs of respiratory depression, and Afshari et al. made no mention of respiratory compromise in their patients even though all of them had presented with overdose. With regards to propoxyphene products, a better comprehension of this complex cardio-respiratory relationship and a more lucid outcome definition would aid in designing studies that could control for the potential confounding effects of respiratory depression on cardiotoxicity.

5 OVERALL CONCLUSIONS

- Propoxyphene products may have had additive effects that contributed to cardiac events given the temporal association[l] (5/11, 45%) and positive dechallenge (3/11, 27%) in some cases.
- Propoxyphene products may have contributed to the psychiatric related events in some cases given temporal associations[li] (7/12, 58%) and a positive dechallenge (1/12).
- Over one-third (10/26, 38%) of the cases involving the elderly patients (65 years or older) reported psychiatric (e.g. hallucination, confusion, mental status changes) events which may reflect pharmacodynamic effects of propoxyphene in this population.
- Cases of plausible drug interactions in this review suggest that propoxyphene taken concomitantly with certain drugs[lii] may be associated with increased concentrations of propoxyphene or the co-administered drug, resulting in potentially life threatening toxicity (including cardiac events).
- The increased risk of fatalities from overdosage when propoxyphene products are used in combination with opioids, benzodiazepines, antidepressants, or other CNS depressants noted in this review is consistent with current product labeling. However, a direct causal role in fatalities for therapeutically administered propoxyphene could not be established given patients' underlying medical history, or use of multiple co-suspect drugs, or both, noted in a majority of reviewed cases.
- The findings in this updated review of propoxyphene product associated events are consistent with the 2005 OSE Postmarketing Review. The direct causal role of Darvocet in all 91 death cases in the prior OSE review could not be determined based on the underlying medical conditions or multiple co-suspect medications. In addition**, t**he top 20 event terms reported for serious U.S. cases (2006 to 2007) fairly represented the event terms reported for all U.S. cases reported from approval to 9/24/2008. The most reported terms were completed suicides, overdose (all types), and cardiac arrest.
- Despite current propoxyphene label warnings, narcotic pain relievers and other CNS related drugs continue to be prescribed and used with propoxyphene containing products, including in elderly patients.
- Literature review revealed mostly anecdotal reports of propoxyphene-related cardiotoxicity and lacked sound scientific evidence to support an association between propoxyphene-contanining products and cardiotoxicity.
- In 2007, the majority of sales of single-agent and combination propoxyphene products were to retail pharmacy settings. The propoxyphene/APAP product is the

[l] Five cases reported the estimated onset from 3 hrs to 21 days from starting the propoxyphene product.

[li] Estimated onset from day 1 of starting propoxyphene products: 2 doses to 14 days (n= 7)

[lii] Carbamazepine, duloxetine, metoprolol, and warfarin

most commonly dispensed to all the age groups, and is reflected in both the 2005 and this updated review.

- The trends for patient data (i.e., prescriptions received) were similar to prescription data (i.e., prescriptions filled) with respect to the propoxyphene formulations.
- General Practice/Family Medicine/Doctor of Osteopathy physicians are the most common prescribing healthcare providers for all propoxyphene containing products.

6 RECOMMENDATIONS

Although serious adverse events including death, many involving accidental and intentional overdosages with other, often multiple medications, continue to be reported with the use of propoxyphene containing products, the AERS data in this review are alone insufficient to substantially inform the question of phased withdrawal of propoxyphene containing drugs from the market requested by the Citizen's Petition. In OSE's opinion, the regulatory action recommended for FDA by the upcoming AC should be based on clear clinical evidence of propoxyphene efficacy satisfactory to inform a robust discussion of the risk/benefit profile for these drugs.

Should propoxyphene containing drugs remain on the market, we recommend consideration of additional regulatory action (e.g., strengthened labeling, or Risk Evaluation and Mitigation Strategies [REMS], or both) to address the ongoing concomitant use of these products with opioids, benzodiazepines, alcohol, and other problematic medications that continues despite current labeling precautions. Additionally, we recommend consideration of a post-marketing commitment for a clinical safety trial(s) should these products remain market approved.

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APPENDIX 1:

TABLE 1. EPIDEMIOLOGICAL STUDIES: PROPOXYPHENE IN THERAPEUTIC DOSE					
Reference	**Population**	**Study Design**	**Exposure Variables**	**Outcome Measures**	**Key Findings**
Salzman 1983[1]	Adults (mean age 60.25) with chronic pain & osteoarthritis n=114	Double-blind randomized controlled study	PPX 65mg versus Suprofen 200mg four times daily for 24 weeks	ECG changes measured at baseline and at 24 weeks	- 2 of 59 (3.4%) patients on suprofen and 2 of 55 (3.6%) patients on PPX had abnormal ECG changes not related to PPX - type of change not specified
Lang-Jensen 1989[2]	Healthy young male volunteers n=10	Double-blind randomized pre-post study	100mg DPX napsylate versus placebo t.i.d for 16 days	Cardiac output measures; HR, PEP, LVET, STI, STD, VHR, MAP	- Prolonged PEP in DPX group (125ms ± 11.34) compared to placebo (119ms ±11.34) at 60% of maximum work -No decrease cardiac contractility -No significant change at other work loads or in other measures

PPX=propoxyphene, DPX = Dextropropoxyphene, HR = heart rate, PEP= pre-ejection period, LVET = left ventricular ejection time, STI = systolic time interval, STD = stroke distance, VHR= maximum velocity of blood in ascending aorta X HR, MAP = mean arterial pressure

TABLE 2. EPIDEMIOLOGICAL STUDIES: PROPOXYPHENE IN OVERDOSE					
Reference	**Population**	**Study Design**	**Exposure Variables**	**Outcome Measures**	**Key Findings**
Afshari 2005[3]	Patients admitted with diagnosis of PPX overdose n=30	Prospective Cohort	PPX-paracetamol versus other opioid-paracetamol combo	ECG changes at 4hrs post-ingestion then q6-8 hr post-ingestion; QRS duration, PR interval, QTc interval	- Significant difference in QRS duration; PPX group mean duration = 99.36msec [95% CI = 96.19, 102.53] compared to Control group mean = 82.84msec [95% CI = 80.81, 84.88]
	Unspecified population n=74	Retrospective Cohort (no comparison group)	Plasma Paracetamol concentration as proxy for PPX dose	Cardiac indices; BP, HR, and QRS duration, PR interval and QTc interval on ECG	- Correlation between estimated paracetamol concentration and QRS duration (r=0.338, p=0.003)

PPX=propoxyphene, HR = heart rate, BP = blood pressure

TABLE 3. CASE REPORTS OF CARDIOTOXICITY	
Reference	**Case Findings**
Sigurd 1971[4]	• 45 year old male experienced sudden circulatory arrest with no preceding respiratory depression. • ECG initially revealed asystole, followed by widened QRS complexes with no identifiable P waves after treatment with 1mg adrenaline. • He remained hypotensive and without pulse until treatment with 5mg isoprenaline after which his ECG showed tachycardia with right axis deviation. • Propoxyphene and barbiturate discovered in urine and serum respectively
Stork 1995[5]	• 54 year old female ingested approximately 100 propoxyphene hydrochloride pills (6500mg) • Developed seizures followed by cardio-respiratory arrest. After resuscitation ECG showed wide QRS complexes with no identifiable P waves. ECG returned to normal sinus rhythm after receiving 200mEq sodium bicarbonate
Hantson	Case 1: 60 year old female with pre-end stage renal disease being treated for 1 year with

1995[6]	dextropropoxyphene-acetaminophen (515mg daily) for Paget's bone disease was admitted for shock and acute dyspnea. ECG changes: • Few weeks pre-admission – normal sinus rhythm with 1st degree AV block • Day 1 admission 1st ECG – 3rd degree SA block AV junction escape with left bundle branch block • Day 1 admission post-naloxone - sinus rhythm, prolonged PR interval .22 sec (1st degree AV block) • Day 2 admission – sinus rhythm, 1st degree AV block Case 2: 30 year old male admitted with 22.5gm overdose of dextropropoxyphene experienced decreased left ventricular stroke work index (18 gm/m^2; normal = 40 to 50 gm/m^2) which normalized after administration of naloxone, and ECG showed irregular sinus rhythm, tachycardia (110 beats/min).
Marraffa 2006[7]	• 48 year old male with long-standing atrial fibrillation on maintenance dose of 100mg metoprolol • Experiences profound bradycardia (30 beats/min) 4 hours after ingestion of metoprolol and first dose ever of propoxyphene napsylate 200mg/acetominophene 1300mg.
Qureshi 1964[8]	• 18 year old female suffered convulsions and respiratory depression following ingestion of 832 mg of propoxyphene hydrochloride. • ECG findings upon admission included sinus tachycardia and widened QRS complexes consistent with right bundle branch block.
Barraclough 1982[9]	• 18 year old male ingested 50 pills of propoxyphene 32.5mg/paracetamol 325mg following moderate intake of beer. • ECG revealed wide QRS complexes and right axis deviation. • No respiratory arrest or hypoxia was experienced throughout his hospital course.
Whitcomb 1989[10]	• 35 year old female's drug screen showed toxic levels of propoxyphene and traces of antidepressant • Presented with seizures, bradycardia, and progressively prolonged QRS duration

TABLE 3 CONTD. CASE REPORTS OF CARDIOTOXICITY	
Staikowsky 2005[11]	Case 1: 29 year old male former heroin addict ingested 1300mg dextropropoxyphene along with benzodiazepines and paracetamol. • ECG showed broad QRS complexes with, right bundle branch block, and absent P waves Case 2: 21 year old drug-addicted female ingested unknown amount of propoxyphene and benzodiazepine. • ECG revealed 1st degree AV block
Ogbuihi 1980[12]	• Autopsy on 21 year old female. • Histological evaluation of myocardium revealed signs suggestive of cardiotoxicity. • Body fluid analysis estimated ingestion of approximately 1500mg propoxyphene hydrochloride about 2.5 hours prior to death. • No other medications detected.
Heaney 1983[13]	• 20 year old male with a history of recreational drug use and seizure disorder for which he took phenytoin 100mg three times a day. • Developed Grade I/II systolic murmur with splitting of S1 and S2, and left bundle

	branch block with 1st degree AV block after taking an overdose of 1105mg of propoxyphene hydrochloride. • The cardiac signs resolved after 8 hours of admission during which he received 3 doses of naloxone 0.4 mg IV and intravenous saline infusion.
Starkey 1978[14]	• 15 year old female suspected of taking 50 pills of propoxyphene 32.5mg/paracetamol 325mg • ECG showed asystole which changed to 1st degree heart block, complete right bundle branch block and extreme axis deviation after resuscitation.
Marsden 1996[15]	• 30 year old female ingested 80 tablets of dextropropoxyphene 32.5mg/paracetamol 325mg. • Suffered convulsions and cardio-respiratory arrest • Returned to sinus tachycardia after administration of 2 doses of 0.4mg naloxone IV. • Declared brain dead due to cerebral anoxia 24 hours later.
Sloth 1984[16]	222 consecutive cases of propoxyphene poisoning. • Impaired circulation in 48% • Bradycardia in 9% • Tachycardia in 15% • ECG abnormalities in 41% (43 patients with widened QRS complexes, 1 with 1st degree AV Block, 19 with ventricular arrhythmias

APPENDIX 2: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription

claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

APPENDIX 3: TABLES

Table 1: Total Number of Dispensed Prescriptions of Single Agent and Combination Propoxyphene by Product Through U.S Outpatient Retail Pharmacies, 2006-2007

	2006		2007	
	Retail TRxs N	*Share %*	Retail TRxs N	*Share %*
TOTAL MARKET	**23,098,536**	***100.0%***	**22,327,677**	***100.0%***
Propoxyphene/APAP	22,519,909	*97.5%*	21,770,334	*97.5%*
Propoxyphene-N/APAP	21,939,637	*97.4%*	21,329,727	*98.0%*
Darvocet-N 100	290,994	*1.3%*	235,424	*1.1%*
Propoxyphene w/APAP	173,719	*0.8%*	144,915	*0.7%*
Balacet 325	86,864	*0.4%*	47,639	*0.2%*
Darvocet A500	21,479	*0.1%*	8,707	*0.0%*
Darvocet-N 50	7,139	*0.0%*	3,820	*0.0%*
Propacet 100	43	*0.0%*	57	*0.0%*
Wygesic	20	*0.0%*	36	*0.0%*
Trycet	14	*0.0%*	9	*0.0%*
Propoxyphene	571,850	*2.5%*	556,926	*2.5%*
Propoxyphene	502,189	*87.8%*	491,316	*88.2%*
Darvon N	56,426	*9.9%*	55,154	*9.9%*
Darvon	13,235	*2.3%*	10,456	*1.9%*
propoxyphene/asa/caffein	6,777	*0.0%*	417	*0.0%*
Darvon Compound-65	6,560	*96.8%*	322	*77.2%*
Propoxyphene Cpd	217	*3.2%*	94	*22.5%*
Darvon Compound-32	--	--	1	*0.2%*

Source: SDI Vector One: National®. 2006-2007. Extracted 10/30/08. File: VONA 2008-1517 TRx Propoxyphene by Product.xls

Table 2: Total Number of Dispensed Prescriptions of Single Agent and Combination Propxyphene by Product and Age Through U.S Outpatient Retail Pharmacies, 2006-2007

	2006		2007	
	Retail TRxs	*Share*	Retail TRxs	*Share*
	N	%	N	%
TOTAL MARKET	**23,098,494**	***100.0%***	**22,327,745**	***100.0%***
Propoxyphene/APAP	22,519,867	*97.5%*	21,770,366	*97.5%*
Age 0-17	253,784	*1.1%*	235,895	*1.1%*
Age 18-44	5,305,875	*23.6%*	4,991,036	*22.9%*
Age 45-64	8,424,509	*37.4%*	8,181,307	*37.6%*
Age 65+	8,444,650	*37.5%*	8,297,000	*38.1%*
Age UNSPEC.	91,049	*0.4%*	65,128	*0.3%*
Propoxyphene	571,852	*2.5%*	556,956	*2.5%*
Age 0-17	2,701	*0.5%*	2,166	*0.4%*
Age 18-44	91,040	*15.9%*	86,508	*15.5%*
Age 45-64	278,111	*48.6%*	269,564	*48.4%*
Age 65+	197,263	*34.5%*	196,041	*35.2%*
Age UNSPEC.	2,737	*0.5%*	2,677	*0.5%*
propoxyphene/asa/caffein	6,775	*0.0%*	423	*0.0%*
Age 0-17	28	*0.4%*	1	*0.2%*
Age 18-44	552	*8.1%*	72	*17.0%*
Age 45-64	2,763	*40.8%*	179	*42.3%*
Age 65+	3,394	*50.1%*	167	*39.5%*
Age UNSPEC.	38	*0.6%*	4	*0.9%*

Source: SDI Vector One: National®. 2006-2007. Extracted 10/30/08. File: VONA 2008-1517 TRx Propoxyphene by Age.xls

Table 3: Total Number of Unique Patients Receiving a Prescription of Single Agent and Combination Propxyphene by Product Through U.S Outpatient Retail Pharmacies, 2006-2007

	2006		2007	
	N	%	N	%
Grand Total	**10,211,876**	***100.00%***	**9,805,215**	***100.00%***
Propoxyphene/APAP	10,071,502	*98.63%*	9,671,368	*98.63%*
Propoxyphene-N/APAP	9,893,598	*98.23%*	9,546,166	*98.71%*
Darvocet-N 100	103,590	*1.03%*	81,063	*0.84%*
Propoxyphene w/APAP	73,937	*0.73%*	60,524	*0.63%*
Balacet 325	46,017	*0.46%*	21,983	*0.23%*
Darvocet A500	11,468	*0.11%*	4,143	*0.04%*
Darvocet-N 50	4,543	*0.05%*	2,422	*0.03%*
Propacet 100	31	*0.00%*	45	*0.00%*
Wygesic	16	*0.00%*	19	*0.00%*
Trycet	12	*0.00%*	9	*0.00%*
Propoxyphene	190,663	*1.87%*	182,312	*1.86%*
Propoxyphene	168,017	*88.12%*	160,961	*88.29%*
Darvon N	22,201	*11.64%*	21,319	*11.69%*
Darvon	3,276	*1.72%*	2,349	*1.29%*
propoxyphene/asa/caffein	4,487	*0.04%*	367	*0.00%*
Darvon Compound-65	4,330	*96.50%*	282	*76.78%*
Propoxyphene Cpd	163	*3.63%*	86	*23.42%*
Darvon Compound-32				

Source: SDI Vector One: Total Patient Tracker®. 2006-2007. Extracted 11/7/08. File: TPT 2008-1517 Propoxyphene Patient Count by Product.xls, TPT 2008-1517 Propoxyphene Asa Caff Patient Count.xls, TPT 2008-1517 Propoxyphene APAP Patient Count.xls

Table 4: Total Number of Unique Patients Receiving a Prescription of Single Agent and Combination Propxyphene by Age Through U.S Outpatient Retail Pharmacies, 2006-2007

	2006		2007	
	N	%	N	%
Grand Total	**10,211,876**	***100.00%***	**9,805,215**	***100.00%***
Age 0-17	**223,418**	***2.19%***	**205,626**	***2.10%***
Propoxyphene/APAP	221,696	*99.23%*	204,269	*99.34%*
Propoxyphene-N/APAP	218,522	*98.57%*	202,405	*99.09%*
Darvocet-N 100	643	*0.29%*	473	*0.23%*
Propoxyphene w/APAP	1,581	*0.71%*	1,185	*0.58%*
Balacet 325	921	*0.42%*	310	*0.15%*
Darvocet A500	213	*0.10%*	55	*0.03%*
Darvocet-N 50	173	*0.08%*	74	*0.04%*
Propacet 100	-	-	-	-
Wygesic	-	-	-	-
Trycet	-	-	-	-
Propoxyphene	1,894	*0.85%*	1,550	*0.75%*
Propoxyphene	1,686	*89.01%*	1,372	*88.52%*
Darvon N	205	*10.85%*	184	*11.88%*
Darvon	8	*0.42%*	-	-
propoxyphene/asa/caffein	24	*0.01%*	1	*0.00%*
Darvon Compound-65	24	*100.00%*	1	*100.00%*
Propoxyphene Cpd	-	-	-	-
Darvon Compound-32	-	-	-	-
Age 18-44	**3,276,893**	***32.09%***	**3,091,950**	***31.53%***
Propoxyphene/APAP	3,247,528	*99.10%*	3,063,975	*99.10%*
Propoxyphene-N/APAP	3,198,792	*98.50%*	3,033,136	*98.99%*
Darvocet-N 100	17,322	*0.53%*	12,359	*0.40%*
Propoxyphene w/APAP	24,740	*0.76%*	19,175	*0.63%*
Balacet 325	16,798	*0.52%*	7,392	*0.24%*
Darvocet A500	3,248	*0.10%*	911	*0.03%*
Darvocet-N 50	919	*0.03%*	383	*0.01%*
Propacet 100	12	*0.00%*	12	*0.00%*
Wygesic	3	*0.00%*	5	*0.00%*
Trycet	1	*0.00%*	-	-
Propoxyphene	40,253	*1.23%*	38,411	*1.24%*
Propoxyphene	35,501	*88.19%*	33,929	*88.33%*
Darvon N	4,949	*12.29%*	4,726	*12.30%*
Darvon	287	*0.71%*	186	*0.48%*
propoxyphene/asa/caffein	419	*0.01%*	64	*0.00%*
Darvon Compound-65	401	*95.76%*	54	*84.06%*
Propoxyphene Cpd	18	*4.34%*	10	*16.12%*
Darvon Compound-32	-	-	-	-
Age 45-64	**3,563,162**	***34.89%***	**3,454,618**	***35.23%***
Propoxyphene/APAP	3,505,121	*98.37%*	3,398,308	*98.37%*
Propoxyphene-N/APAP	3,439,277	*98.12%*	3,351,685	*98.63%*
Darvocet-N 100	42,134	*1.20%*	33,342	*0.98%*
Propoxyphene w/APAP	25,162	*0.72%*	20,322	*0.60%*
Balacet 325	17,762	*0.51%*	8,971	*0.26%*
Darvocet A500	4,521	*0.13%*	1,815	*0.05%*
Darvocet-N 50	1,203	*0.03%*	803	*0.02%*
Propacet 100	13	*0.00%*	10	*0.00%*
Wygesic	8	*0.00%*	7	*0.00%*
Trycet	5	*0.00%*	7	*0.00%*
Propoxyphene	79,907	*2.24%*	77,037	*2.27%*
Propoxyphene	69,609	*87.11%*	67,107	*87.11%*
Darvon N	10,358	*12.96%*	10,072	*13.07%*
Darvon	1,442	*1.80%*	1,021	*1.33%*
propoxyphene/asa/caffein	1,794	*0.05%*	152	*0.00%*
Darvon Compound-65	1,728	*96.33%*	118	*77.63%*
Propoxyphene Cpd	71	*3.93%*	34	*22.10%*
Darvon Compound-32	-	-	-	-
Age 65+	**3,176,443**	***31.11%***	**3,109,387**	***31.71%***
Propoxyphene/APAP	3,124,551	*98.37%*	3,060,634	*98.43%*
Propoxyphene-N/APAP	3,063,170	*98.04%*	3,013,767	*98.47%*
Darvocet-N 100	43,566	*1.39%*	34,941	*1.14%*
Propoxyphene w/APAP	22,755	*0.73%*	20,006	*0.65%*
Balacet 325	10,472	*0.34%*	5,340	*0.17%*
Darvocet A500	3,465	*0.11%*	1,337	*0.04%*
Darvocet-N 50	2,190	*0.07%*	1,137	*0.04%*
Propacet 100	6	*0.00%*	19	*0.00%*
Wygesic	5	*0.00%*	3	*0.00%*
Trycet	7	*0.00%*	2	*0.00%*
Propoxyphene	68,199	*2.15%*	65,132	*2.09%*
Propoxyphene	60,819	*89.18%*	58,301	*89.51%*
Darvon N	6,687	*9.81%*	6,358	*9.76%*
Darvon	1,526	*2.24%*	1,160	*1.78%*
propoxyphene/asa/caffein	2,224	*0.07%*	145	*0.00%*
Darvon Compound-65	2,155	*96.88%*	104	*71.73%*
Propoxyphene Cpd	68	*3.05%*	43	*29.90%*
Darvon Compound-32	-	-	-	-
Age Unspec.	**146,180**	***1.43%***	**133,185**	***1.36%***
Propoxyphene/APAP	142,745	*97.65%*	129,826	*97.48%*
Propoxyphene-N/APAP	139,673	*97.85%*	127,305	*98.06%*
Darvocet-N 100	1,794	*1.26%*	1,584	*1.22%*
Propoxyphene w/APAP	1,021	*0.72%*	884	*0.68%*
Balacet 325	416	*0.29%*	199	*0.15%*
Darvocet A500	103	*0.07%*	104	*0.08%*
Darvocet-N 50	79	*0.06%*	35	*0.03%*
Propacet 100	2	*0.00%*	-	-
Wygesic	-	-	-	-
Trycet	-	-	-	-
Propoxyphene	3,685	*2.52%*	3,602	*2.70%*
Propoxyphene	3,327	*90.28%*	3,344	*92.83%*
Darvon N	268	*7.28%*	227	*6.30%*
Darvon	98	*2.66%*	39	*1.08%*
propoxyphene/asa/caffein	44	*0.03%*	4	*0.00%*
Darvon Compound-65	38	*86.04%*	4	*100.00%*
Propoxyphene Cpd	6	*13.96%*	-	-
Darvon Compound-32	-	-	-	-

Source: SDI Vector One: Total Patient Tracker®. 2006-2007. Extracted 11/7/08. File: TPT 2008-1517 Propoxyphene Patient Count by Age.xls, TPT 2008-1517 Propoxyphene by Age.xls, TPT 2008-1517 Propoxyphene APAP by Age.xls, TPT 2008-1517 Propoxyphene Asa Caff by Age.xls

Table 5: Total Number of Dispensed Prescriptions of Single Agent and Combination Propxyphene by Prescriber Specialty Through U.S Outpatient Retail Pharmacies, 2006-2007

	2006		2007	
	Retail TRxs N	*Share %*	Retail TRxs N	*Share %*
TOTAL MARKET	**23,098,560**	***100.0%***	**22,327,678**	***100.0%***
Propoxyphene/APAP	22,519,915	*97.5%*	21,770,322	*97.5%*
GP/FM/DO	6,506,989	*28.9%*	6,301,219	*28.9%*
IM	4,389,773	*19.5%*	4,184,684	*19.2%*
ORTH SURG	2,003,009	*8.9%*	1,928,175	*8.9%*
DENT	1,292,109	*5.7%*	1,271,342	*5.8%*
UNSPEC	815,191	*3.6%*	773,767	*3.6%*
OB/GYN	807,053	*3.6%*	771,653	*3.5%*
EM	765,853	*3.4%*	726,439	*3.3%*
GEN SURG	734,209	*3.3%*	672,319	*3.1%*
RHEUM	537,440	*2.4%*	525,652	*2.4%*
AO SURG	539,924	*2.4%*	516,475	*2.4%*
All Others	4,128,365	*18.3%*	4,098,597	*18.8%*
Propoxyphene	571,872	*2.5%*	556,937	*2.5%*
GP/FM/DO	180,220	*31.5%*	174,306	*31.3%*
IM	135,610	*23.7%*	129,834	*23.3%*
ORTH SURG	32,976	*5.8%*	30,841	*5.5%*
UNSPEC	24,508	*4.3%*	22,808	*4.1%*
RHEUM	22,002	*3.8%*	22,199	*4.0%*
NP	13,677	*2.4%*	15,220	*2.7%*
PA	12,107	*2.1%*	13,410	*2.4%*
PM&R	12,085	*2.1%*	13,066	*2.3%*
ANES	11,139	*1.9%*	11,504	*2.1%*
NEURO	12,048	*2.1%*	11,422	*2.1%*
All Others	115,500	*20.2%*	112,327	*20.2%*
propoxyphene/asa/caffein	6,773	*0.0%*	419	*0.0%*
GP/FM/DO	2,603	*38.4%*	159	*37.9%*
IM	1,760	*26.0%*	54	*12.9%*
ORTH SURG	275	*4.1%*	40	*9.5%*
DENT	202	*3.0%*	20	*4.8%*
UNSPEC	277	*4.1%*	18	*4.3%*
NP	99	*1.5%*	18	*4.3%*
GEN SURG	72	*1.1%*	17	*4.1%*
OB/GYN	235	*3.5%*	17	*4.1%*
EM	98	*1.4%*	9	*2.1%*
PM&R	41	*0.6%*	8	*1.9%*
All Others	1,111	*16.4%*	59	*14.1%*

Source: SDI Vector One: National®. 2006-2007. Extracted 10/30/08. File: VONA 2008-1517 TRx Propoxyphene by Prescribing Specialty.xls

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 25, 2005

From: Renan A. Bonnel, Pharm.D, MPH
Catherine Dormitzer, Ph.D, MPH
Syed Rizwanuddin Ahmad, MD, MPH
Division of Drug Risk Evaluation, HFD- 430

Through: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

To: Brian Harvey, M.D., Ph.D., Acting Director
Division of Antiinflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP), HFD-550 PID #DO50071

Subject: **This is a revision of** the review of serious adverse events reported in association with propoxyphene and Darvocet® (propoxyphene/acetaminophen);NDA #s 10996, 10997, 16827, 16829, 16861, 16862, 16863, 16864, 76429, 17122, 16844, & 17507[1]

Confidential: Contains IMS data; not to be used outside of the FDA without clearance from IMS.

EXECUTIVE SUMMARY

Following an extensive review of the risk-benefit profile of the painkiller propoxyphene plus acetaminophen combination products in the United Kingdom, it was determined that the efficacy of this product "is poorly established and the risk of toxicity in overdose, both accidental and deliberate, is unacceptable." On January 31, 2005, the Committee on Safety of Medicines announced their plans to withdraw propoxyphene products from the market over a 6-12 month period.[1] In the U.K, the license of single-ingredient propoxyphene products were already cancelled.[2] Subsequently, Dr. Sharon Hertz from the Division of Antiinflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP) requested an AERS review of the serious postmarketing adverse event reports involving the use of propoxyphene products, with particular attention to deaths, suicides, overdoses, drug abuse, and dependence. Dr. Hertz also requested the IMS prescription drug use information for propoxyphene, as well as a review of other relevant national databases.

Given the short turn around time for this request, ODS agreed to provide the crude count analyses of all serious adverse event reports involving propoxyphene and a detailed review of the US death cases for Darvocet®. In the crude count analyses, we did not attempt to match the duplicate reports or perform individual case reviews of the adverse

[1] Review by same authors prior to revision dated March 24, 2005

event reports. Since individual reviews were not conducted, the information related to dose, duration, onset, history of drug abuse, and causality could not be assessed.

A total of 3075 (US-2186) serious adverse event reports for propoxyphene were identified in the AERS database from drug marketing (approved in 1957) to February 2, 2005. There was an increase in the crude counts of adverse event reports for propoxyphene from 161 in 1999 to 319 in 2004. It is important to note that these reports cited the use of the single ingredient propoxyphene products and/or the combination products containing propoxyphene. The most commonly reported adverse event terms were completed suicide, drug dependence, and drug overdoses, involving the co-ingestion of other medications including narcotics, alcohol, TCAs, SSRIs, and benzodiazepines. The serious outcomes included hospitalization (804), disability (51), life-threatening event (78), intervention required (75), and deaths (1160).

According to the IMS data, propoxyphene use was steady from 1994 to 1996. A slight increase occurred in 1997 with an estimated 31,589,000 prescriptions dispensed in the U.S. After 1998, a slight decrease was noted each year to roughly 26,899,000 prescriptions dispensed in 2004. The IMS data indicated that propoxyphene with acetaminophen (Darvocet®) was the most commonly dispensed formulation of propoxyphene.

There were a total of 91 US deaths associated with the Darvocet® use. The majority of the deaths were related to drug overdoses and suicides involving the co-ingestion of multiple medications. There were no consistent trends of hepatic failure or cardiac disorders including arrhythmias in the death cases. Of those 91 deaths, eight were not related to multiple drug overdoses. The reported adverse events (more than one event in some cases) included Cheyne-Stokes respiration (1), acute respiratory distress syndrome (2), acute respiratory failure/CHF(1), Torsades de Pointes/QT prolongation (1), thromboembolism (1), neuroleptic malignant syndrome (1), hepatic dysfunction (2), and hepatic/renal dysfunction (1). The direct causal role of Darvocet® in all cases could not be determined due to the underlying medical conditions and multiple co-suspect medications.

An analysis of data from the Drug Abuse Warning Network (DAWN) on the numbers of emergency department (ED) visits for both propoxyphene products and the comparator drug, hydrocodone was completed. The rate for ED mentions for propoxyphene ranged from 1.8 per 10,000 prescriptions sold in 1999 to 1.6 per 10,000 prescriptions sold in 2002. The rate for ED mentions for hydrocodone ranged from 1.9 in 1999 to 2.4 in 2002 per 10,000 prescriptions sold. Using the new DAWN data for 2004, the proportion of suicide attempts was found to be slightly higher for propoxyphene single drug only (13% of ED cases) than for hydrocodone single drug only (4% of all ED cases) and the proportion of overmedication was higher for propoxyphene single drug only (33% of all ED cases) than for hydrocodone single drug only (19% of all ED cases) as well. The proportion of propoxyphene only cases seen in the ED that required an ICU admission was similar to cases involving hydrocodone only and hydrocodone/APAP combinations but higher than for cases involving propoxyphene/APAP.

In a review of reports from the Toxic Exposure Surveillance System or TESS database for a five-year period, the overall number of calls to poison control centers concerning propoxyphene as single ingredient and combination product with acetaminophen exposures increased by about 11% from 5,680 in 1999 to 6,318 in 2003. While the total of propoxyphene-associated exposure calls increased by about 11%, the total number of fatalities in association with propoxyphene (single ingredient and combo with APAP) exposures declined by a half from 28 in 1999 to 14 in 2003. Overall, propoxyphene-associated fatalities represented about 1% of the total 1,106 fatalities that were reported in the TESS database in 2003.

Most of the propoxyphene-associated fatalities occurred in individuals who ingested multiple products. In 2003, all three single-ingredient propoxyphene-associated fatalities occurred in individuals who took multiple products simultaneously. In the remaining eleven fatalities in 2003 all but three occurred in individuals who took propoxyphene plus acetaminophen combination products only.

In conclusion, there was an increase in crude AERS counts of adverse event reports for propoxyphene from 161 in 1999 to 319 in 2004. However, since the most commonly reported events with propoxyphene were drug overdoses, dependence, and suicides involving the co-ingestion of multiple drug products, the significance of this observed increase for propoxyphene could not be established in this analysis. In addition, this increase in reporting could not be explained from the IMS drug use data since there was a steady decline in the total prescriptions dispensed during this period. The rate for ED mentions for propoxyphene from DAWN was stable and ranged from 1.8 per 10,000 prescriptions sold in 1999 to 1.6 per 10,000 prescriptions sold in 2002. Data from the TESS database confirms that propoxyphene products remain an important cause of morbidity and mortality in the U.S. From 1999 to 2003 there was an 11% increase in propoxyphene-associated exposure calls, but the number of fatal exposures with propoxyphene products declined by about 50%. In contrast, both the number of calls, and the number of deaths associated with hydrocodone products have increased in the timeframe data was available for this product. In 2001, there were 15,142 calls reported with hydrocodone and in 2003 there were about 19,538 calls, an increase by 29%. Similarly the number of fatal exposures with hydrocodone products increased by 68% from 47 in 1999 to 79 in 2003. The majority of these exposures occurred in individuals who reportedly took multiple products simultaneously with suicidal intent.

1. BACKGROUND

This memorandum is organized into a number of sections; a background, a review of an analysis of AERS reports, an analysis of data from Drug Abuse Warning Network, a summary of an analysis of Poison Control summary data, and a summary of the findings from these analyses.

Propoxyphene hydrochloride (Darvon-N®, Darvon Pulvules®) is a narcotic analgesic (C-IV) and was approved on 8/16/1957 for the relief of mild-to-moderate pain. Propoxyphene hydrochloride with aspirin and caffeine (Darvon Compound- 65®) is a narcotic analgesic combination (C-IV) and was approved on 11/12/1957 for the relief of

mild-to-moderate pain. Propoxyphene napsylate with acetaminophen (Darvocet N-50®, Darvocet N- 100®) is a narcotic analgesic combination (C-IV) and was approved on 12/19/1972 for the relief of mild-to-moderate pain. Multiple generic propoxyphene products are currently available in the U.S.

Safety concerns related to 1) propoxyphene's reported relative narrow therapeutic window (as discussed by S. Calderon, CSS in a memorandum to HFD-550 April 21, 2004) and 2) the hepatotoxicity associated with acetaminophen (in combinations including those with propoxyphene) that is a well recognized adverse event and has contributed to a significant number of acute liver failure cases in a few published studies[3,4].

The current labeling for the drug contains the following warning:

WARNINGS

- **Do not prescribe propoxyphene for patients who are suicidal or addiction-prone.**
- **Prescribe propoxyphene with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess.**
- **Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.**

Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. In a survey of deaths due to overdosage conducted in 1975, in approximately 20% of the fatal cases, death occurred within the first hour (5% occurred within 15 minutes). Propoxyphene should not be taken in doses higher than those recommended by the physician. The judicious prescribing of propoxyphene is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of propoxyphene products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, propoxyphene should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

Many of the propoxyphene-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of propoxyphene alone or in combination with other drugs. Patients taking propoxyphene should be warned not to exceed the dosage recommended by the physician.

In 1980 there was a Congressional Hearing to address concerns about the abuse of propoxyphene. The Agency initiated an educational campaign in the late 1970s and early 1980s to reduce inappropriate prescribing of the product.[5]

2. DRUG USE[6]

Over 245 million prescriptions of propoxyphene tablets have been dispensed by retail pharmacies in the U.S between 1994 through 2004. The following table summarizes the projected total prescriptions of propoxyphene (Darvon®) and propoxyphene w/APAP (Darvocet®) dispensed by retail pharmacies (chain, independent, food store, and mail order, IMS NPA*Plus*™) in the U.S from 1994 to 2004. The drug use information listed below for propoxyphene (Darvon®) is not complete, since the drug was approved in 1957. It appears that the total prescriptions dispensed for propoxyphene peaked in 1998 (highlighted) with an estimated 31,951,000 prescriptions in the U.S. and had decreased each year to roughly 26,899,000 prescriptions dispensed in 2004.

This information is not to be used outside of the FDA without prior clearance by IMS Health.

Table 2.1. The projected total prescriptions of propoxyphene products dispensed by retail pharmacies from 1994 to 2004*

Drug	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Propoxyphene (total)	29,515	29,547	29,427	31,589	31,951	31,547	30,992	30,404	29,161	27,745	26,899
Propoxyphene (single ingredient)					971	938	870	819	795	690	657
Propoxyphene and APAP combination					30,706	30,375	30,375	29,927	28,234	26,959	26,163
Propoxyphene and other combinations					275	234	196	148	132	97	79

*** IMS NPA*Plus*™ Numbers are in thousands; ADD THREE 000's TO EACH FIGURE**

3. SUMMARY OF AERS ANALYSIS

3.1 OVERVIEW OF THE SERIOUS ADVERSE EVENTS WITH ALL PROPOXYPHENE PRODUCTS:

As of February 2, 2005, a total of 3075 adverse event reports for propoxyphene were identified in the AERS database, of which 2186 were domestic reports. It is important to note that these reports cited the use of the single ingredient propoxyphene products and/or the combination products containing propoxyphene.

The 30 most commonly reported adverse events were as follows (a report may contain more than one adverse event term):

Table 3.1 Top 30 Adverse Event Terms (Preferred Terms)

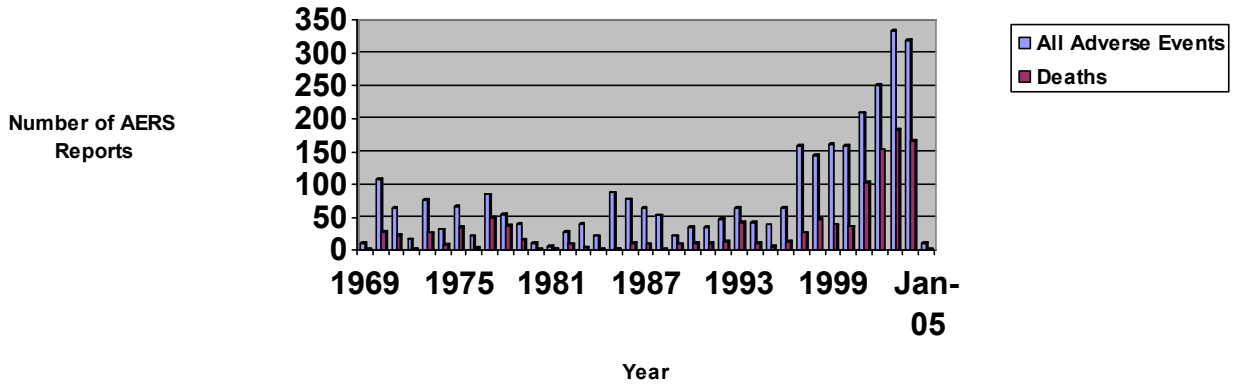
Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Intentional overdose	332		Sedation	80
Overdose	331		Confusional state	76
Completed suicide	228		Pruritus	72
Drug dependence	176		Asthenia	71
Coma	160		Death	71
Accidental overdose	146		Dermatitis	68
Nausea	131		Pulmonary oedema	66
Multiple drug overdose	123		Abdominal pain	65
Vomiting	119		Medication error	64
Convulsion	94		Dyspnoea	63
Drug toxicity	92		Hypotension	63
Drug ineffective	91		Pyrexia	62
Dizziness	90		Cardio-respiratory arrest	60
Drug interaction	90		Cardiac arrest	57
Drug level above therapeutic	83		Urticaria	57

The above table shows that the drug overdoses, suicides, and drug dependence were the most reported adverse events for propoxyphene in the AERS database.

Serious outcomes were reported in 2078 of 3075 reports, including 1160 deaths (US-950) and 804 hospitalizations. Other serious outcomes were coded as life-threatening (78), disability (51), congenital anomaly (14), and intervention required (75).

The following graph illustrates the number of reports received per year and the number of deaths per year, respectively. There appears to be an increase in the number of adverse event reports and the deaths reports related to propoxyphene from late 1999 to 2004. This increase in reporting could not be explained since there was a steady decline in total prescriptions dispensed during this period (See Table 2.1).

Figure 1. AERS Reports for Propoxyphene: All Adverse Events and Death Reports



The patient's gender was reported in 2644 of 3075 reports (M-1114, F-1530), and the age groups were as follows:

Table 3.2 Reported Age Groups

Age Groups	Counts for All Adverse Events	Counts for Death Reports		Age Groups	Counts for All Adverse Events	Counts for Death Reports
0 – <2 yrs	15	2		**41 yrs – 50 yrs**	484	254
2 yrs – 5 yrs	20	5		**51 yrs – 60 yrs**	323	131
6 yrs – 11 yrs	7	4		**61 yrs – 70 yrs**	246	72
12 yrs – 16 yrs	63	40		**71 yrs – 80 yrs**	255	55
17 yrs – 20 yrs	125	68		**81 yrs – 90 yrs**	133	21
21 yrs – 30 yrs	369	178		**91+**	20	4
31 yrs – 40 yrs	435	221		**Null age values**	579	105

The highest numbers of reports were in adults between 30 to 50 years. The adverse event cases consisted of expedited *{e.g. 15-day}* (1384), periodic (1255), direct (432), and risk assessor summary (3) reports.

The 30 most reported adverse event terms for the **U.S. cases of death** (950) associated with propoxyphene products were as follows:

Table 3.3 Top 30 Adverse Event Terms for U.S. Cases of Death

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Intentional overdose	226		Apnoea	27
Completed suicide	209		**Drug abuser**	27
Overdose	177		Hypotension	23
Accidental overdose	135		Brain oedema	22
Multiple drug overdose	106		Convulsion	22
Coma	81		Medication error	22
Drug toxicity	69		Drug interaction	19
Death	64		**Drug dependence**	17
Cardio-respiratory arrest	55		**Drug screen positive**	17
Pulmonary oedema	52		**Multiple drug overdose intentional**	16
Drug level above therapeutic	44		Depressed level of consciousness	15
Toxicologic test abnormal	42		Hepatic cirrhosis	13
Cardiac arrest	38		Multi-organ failure	13
Pulmonary congestion	30		Respiratory arrest	13
Cardiomegaly	28		Accident	12

The most reported adverse event terms from the U.S. death cases for propoxyphene are similar to the event terms for all propoxyphene cases (U.S./foreign/all outcomes) (See Table 3.1). It is interesting to note that the completed suicides and drug overdoses were the most frequently reported adverse event terms.

3.2 OVERVIEW OF THE SERIOUS ADVERSE EVENTS WITH PROPOXYPHENE /ACETAMINOPHEN (DARVOCET®)

As of February 2, 2005, a total of 490 adverse event reports for Darvocet® were identified in the AERS database, of which 472 were domestic reports. The 30 most reported adverse event terms were as follows:

Table 3.4 Top 30 Adverse Event Terms (Preferred Terms)

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Overdose	46		Pain	18
Vomiting	43		Confusional State	17
Nausea	35		Myocardial Infarction	17
Coma	32		Pharmaceutical Product Complaint	17
Intentional Overdose	31		Hypotension	16
Dizziness	29		Pruritus	16
Dyspnea	29		Pyrexia	16
Drug Interaction	27		Abdominal Pain	15
Drug Level Above Therapeutic	23		**Complete Suicide**	15
Asthenia	22		**Drug Toxicity**	15
Medication Error	21		Fall	15
Sedation	20		Headache	15
Constipation	19		Weight Decreased	15
Liver Function Test Abnormal	19		Condition Aggravated	13
Drug Ineffective	18		Depression	13

The above table shows that the drug overdose was the most reported adverse event for Darvocet® in the AERS database.

Serious outcomes were reported in 353 of 490 reports, including 93 deaths **(US-91)** and 210 hospitalizations. Other serious outcomes were coded as life-threatening (21), disability (11), congenital anomaly (2), and intervention required (33).

The patient's gender was reported in 463 of 490 reports (M- 149, F- 314), and the age groups were as follows:

Table 3.5 Reported Age Groups

Age Groups	Counts for All Adverse Events	Counts for Death Reports		Age Groups	Counts for All Adverse Events	Counts for Death Reports
0 – <2 yrs	0	0		**41 yrs – 50 yrs**	57	20
2 yrs – 5 yrs	3	0		**51 yrs – 60 yrs**	72	23
6 yrs – 11 yrs	0	0		**61 yrs – 70 yrs**	46	4
12 yrs – 16 yrs	5	2		**71 yrs – 80 yrs**	77	8
17 yrs – 20 yrs	8	0		**81 yrs – 90 yrs**	43	4
21 yrs – 30 yrs	31	8		**91+**	4	0
31 yrs – 40 yrs	67	15		**Null age values**	77	9

The highest numbers of reports were in older adults between 30 to 80 years. The highest number of death reports were in adults between 40 to 60 years. The adverse event cases consisted of expedited *{e.g. 15-day}* (217), periodic (146), direct (126), and risk assessor summary (1) reports.

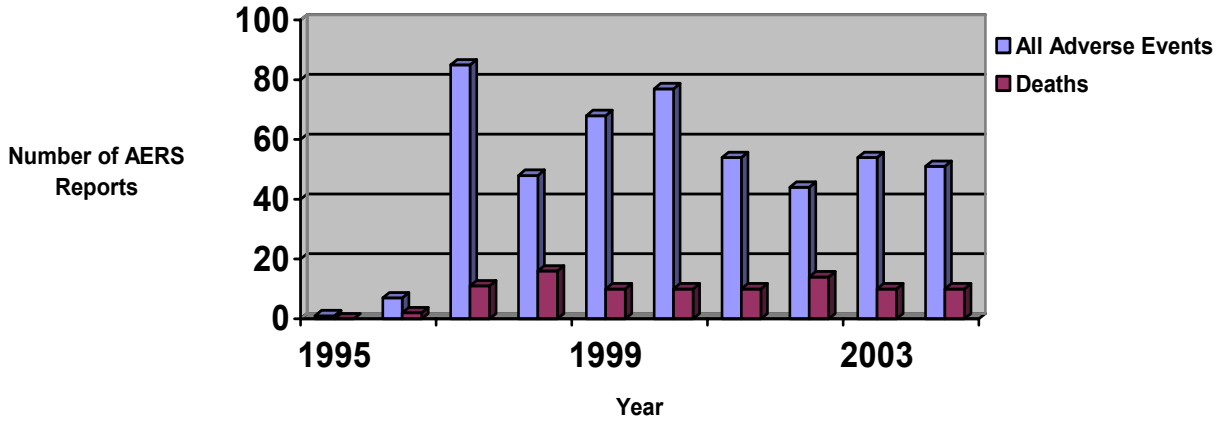
The 20 most reported adverse event terms for the **U.S. cases of death** (91) associated with Darvocet were as follows:

Table 3.6 Top 20 Adverse Event Terms for U.S. Cases of Death

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Overdose	**22**		Acute respiratory distress syndrome	7
Coma	**20**		Cardiac failure	6
Drug level therapeutic	**15**		Drug interaction	6
Completed suicide	**14**		Hypotension	6
Intentional overdose	**11**		Accidental overdose	5
Drug toxicity	9		Acidosis	5
Death	**7**		Cardiac arrest	5
Liver function test abnormal	7		Dyspnea	5
Multi-organ failure	7		Haematemesis	5
Sedation	7		Hepatic failure	5

The most reported adverse event terms from the U.S. death cases for Darvocet® (Propoxyphene /APAP) were similar to the event terms for all propoxyphene cases (U.S./foreign/all outcomes), primarily involving overdoses and suicides.

Figure 2. AERS Reports for Darvocet : All Adverse Events and Death Reports



The majority of the reports were drug overdoses, involving the co-ingestion of multiple medications including narcotics, TCAs, SSRIs, alcohol, narcotics, and benzodiazepines.

3.3 REVIEW OF U.S DEATHS UNRELATED TO INTENTIONAL MULTIPLE OVERDOSES OR SUICIDES WITH DARVOCET®:

Among 91 US death reports with Darvocet®, we identified 17 cases that appeared to be unrelated to multiple drug overdoses. Of the 17 reports, we excluded nine reports due to the following reasons:

- Carcinoma of the lung or breast with progressive metastatic disease (3)
- ARDS following chemotherapy and peg-filgrastim for lymphoma (1)
- Hepatic failure on Duract® (bromfenac) while alternating with acetaminophen (1)
- Guillain Barre Syndrome while receiving infliximab and methotrexate (1)
- Multi-organ failure and the use of 62 different medications, including 12 antibiotics in a patient with a h/o severe liver cirrhosis and renal failure (1)
- The adverse event was related to olanzapine (1)
- No information on the report (1)

The remaining 8 deaths involved 4 females and 4 males. The patient's age ranged from 21 to 77 years with a median of 55 years. The adverse events (more than one in some cases) preceding death were Cheyne-Stokes respiration (1), ARDS (2), acute respiratory failure/CHF (1), Torsades de Pointes (1), thromboembolism (1), neuroleptic malignant syndrome (1), hepatic dysfunction (2), and hepatic/renal dysfunction (1).

Seven of 8 cases reported significant underlying medical conditions (hypertension, COPD, severe gastrointestinal disorder and cardiac disease) and/or the use of multiple medications (carisoprodol, acetaminophen, erythromycin, domperidone, pergolide, nizatidine, omeprazole, prochlorperazine, baclofen, dantrolene, imipramine, metoclopramide, hydrocodone /APAP, olanzapine, and fluoxetine) that might have contributed to the reported adverse events. It is important to note that the concomitant use of acetaminophen and/or acetaminophen-containing products (Lortab® and Tylenol Flu®) in two cases might have contributed to the development of liver abnormalities. In another case, the concomitant use of erythromycin and domperidone and the patient's underlying gastrointestinal disorders may have contributed to the development of TdP and QT prolongation. The exact causal role of Darvocet® in all cases could not be determined.

A narrative of each case is presented below:

AERS# 1997177, US, Direct, 1997

A 33 year-old female with multiple drug allergies (sulfa, clarithromycin, NSAIDs) was receiving Darvocet® N-100 8 tabs daily (slightly higher than the recommended maximum daily dose of 6 tabs) for chronic pain and an unspecified dose of acetaminophen as needed for acute pain. After having a discogram, the patient received unspecified IV antibiotics and developed nausea and vomiting, which were treated with promethazine. She continued to have multiple episodes of nausea and vomiting during the day. She became very sleepy and combative after the procedure and was admitted to the hospital; she was subsequently intubated. The patient developed sepsis and ARDS, and died 10 days after the discogram. Pertinent lab values in the hospital included: AST 1150, ALT 1936, Alk Phos 250, GGT 244, total bili 15.3, albumin 2.9, and APAP 12 mcg/ml (interval unknown after the ingestion).

Reviewer's comments: It is not clear from the narrative whether the patient's liver abnormalities were due to an infectious process following the discogram, the use of the high dose acetaminophen (Darvocet® plus APAP), or both. The causal role of Darvocet® could not be determined.

AERS# 3057910, US, 15-day, 1998
A 36 year old male with a history of drug abuse/rehabilitation, hypertension, and chronic heart disease took 1-2 tablets of carisoprodol (Soma®) and 1-2 capsules of Darvocet -N® for chronic back pain. About 4-5 hours later, he demonstrated Cheyne-Stokes respiration and died. There was no evidence of drug or alcohol abuse at autopsy. The drug screen revealed only small quantities of diazepam, and meprobamate (metabolite of carisoprodol). Propoxyphene was not quantified.

Reviewer's comments: The underlying cardiac disease and/or additive effects of carisoprodol and Darvocet® on the respiratory system could have contributed to the respiratory depression. The causal role of Darvocet® could not be excluded.

AERS# 3430330 , US, 15-day, 1999
A 76 -year-old female patient with a h/o PUD, depression, acute pancreatitis, esophageal reflux, IBS, NIDDM, atypical Parkinson disorder, and back pain developed ARDS while she was receiving Prozac, Pergolide, nizatidine, Darvocet® (prn), omeprazole, and prochlorperazine. She was admitted to a hospital with a cough, pneumonia, dehydration, recent jaundice, and acute weight loss. She developed acute congestive heart failure with tachypnea and hypotension and died. The autopsy revealed bronchopneumonitis with mild ARDS, drug-induced cholestatic cholangitis, and mild hydrocephalus.

Reviewer's comments: The etiology of bronchial infection was unclear. The use of multiple hepatotoxic medications could have contributed to the liver injury. The role of Darvocet could not be determined.

AERS# 3683086 , US, 15-day, 2001
A 51-year-old paraplegic male with a h/o drug hypersensitivity (unspecified), muscle spasms, neurogenic bladder, COPD, and back pain received an unknown dose and duration of baclofen, dantrolene, Darvocet® and imipramine. He was recently treated with salbutamol, Atrovent, and metoclopramide for acute bronchitis. Within two days of the metoclopramide therapy, the patient became drowsy and more tachypneic. He developed an acute respiratory failure and congestive heart failure secondary to respiratory depression and died 3 weeks after the initiation of metoclopramide. The report mentioned that the patient had high levels of Darvocet (unspecified quantity) which was considered a co-suspect cause of the respiratory depression.

Reviewer's comments: It is possible that the high levels of Darvocet®, the patient's underlying COPD, and the acute bronchitis might have contributed to the respiratory depression.

AERS# 3907052 , US, 15-day, 2002
A 63 year old male with a history of insulin-dependent diabetes received an unknown dose of Darvocet-N® for pain and olanzapine for an unknown indication. He experienced neuroleptic malignant syndrome (NMS) and died. The autopsy results were not provided.

Reviewer's comments: The case did not provide sufficient information to evaluate the role of olanzapine or Darvocet®. Olanzapine product labeling includes NMS under the Warnings section. It is unlikely that the events were related Darvocet®.

AERS# 4021181, US, 15-day, 2002
A 59 -year -old female patient presented with hematemesis, epistaxis, chronic back pain, and a feeling of "doom". She received Darvocet® and/or Lortab® (hydrocodone bitartrate/acetaminophen) chronically for back pain and switched to Tylenol ES® (acetaminophen extra strength). She had also been taking Tylenol Flu® for cold symptoms. On admission the lab values were: ALT 3880, AST 1660, total bilirubin 4.9, INR 2.9, glucose 28, creatinine 2.2, pH 7.27, and APAP 19 mcg/ ml (interval unknown after the ingestion). She was treated with N–acetylcysteine, FFP, antibiotics, and hemodialysis. The blood cultures were positive for

E.Coli, methicillin- resistant staph aureus, and fungus. While the liver enzymes decreased, the total bilirubin (10 mcg/ml) and creatinine (9 mg/dl) increased. The patient continued to deteriorate and died.

Reviewer's comments: The concomitant use of multiple acetaminophen containing products (Darvocet®, Lortab® and Tylenol Flu®) might have contributed to the development of hepatic dysfunction. The contributory role of Darvocet® could not be excluded.

FDA 404851, US, 15-day, 2003
A 21-year-old female with a two year history of gastroparesis following a C-section and significant weight loss (100 lbs over 2 years, questionable eating disorder/depression) received Darvocet N -100®. The drug dose and duration were not reported. The concomitant medications included erythromycin (100 mg tid), fluoxetine (40 mg qd), and domperidone (10 mg tid). At an unspecified time after starting Darvocet, she developed severe epigastric/abdominal pain and vomiting, and was hospitalized. During her hospitalization, she was found unresponsive and developed Torsades de Pointes (QT/QTc: 429/492; 359/444; 240/351) and V-fib, requiring multiple cardioversions. Serum potassium levels were within the normal range. She died a day later and the autopsy determined the cause of death as myocardial infarction.

Reviewer's comments: The patient's long-standing gastric problems, profound weight loss, anorexia, and erythromycin and domperidone use might have played a role in the development of Torsades de Points and QT prolongation. The contributory role of Darvocet® was unknown.

AERS# 4269819, US, 15-day, 2004
A 77 year old male received two tablets of Darvocet N-100® to treat the pain from a broken leg. At an unspecified time after Darvocet® use, the patient experienced thickening and swelling of the tongue and difficulty eating and talking. He received Benadryl with some improvement followed by numbness. Seven days later, the patient developed a blood clot and died.

Reviewer's comments: This is the only death report that mentioned Darvocet® as the only primary suspect medication. However, the reporter did not provide any relevant clinical information including the underlying medical conditions, concomitant medications, and the patient's mobility status after the leg fracture to determine the possible cause of thrombosis in this elderly patient. The contributory role of the single dose of Darvocet® was unlikely.

4. ANALYSIS of DAWN DATA

This analysis focuses on data obtained from the Drug Abuse Warning Network (DAWN) on the numbers of emergency department (ED) visits. It compares numbers of ED mentions with drug use data from IMS Health™ for propoxyphene as well as for a comparator drug, hydrocodone, and computes the rate of DAWN emergency department drug mentions over drug usage data. Using more recent data, an analysis of the type of ED episodes or cases and the disposition of ED cases for propoxyphene and hydrocodone was also completed.

4.1 METHODS

This analysis utilizes the Drug Abuse Warning Network (DAWN) that is a public health surveillance system administered by the Substance Abuse and Mental Health Services Administration (SAMHSA). It monitors drug-related visits to hospital emergency departments (EDs). This analysis will use both "old" DAWN[7], data collected from 1994-2002 as well as "new" DAWN[8], that is data collected in 2003-2004.

Prior to 2003, data were collected on emergency room visits that involved drugs of abuse. Given that data were collected using a nationally representative sample, national estimates have been obtained for the number of ED mentions. A drug mention refers to a drug that was "mentioned" during a drug related ED episode or case. An ED case may involve up to 4 drugs and 55% of all ED cases involve more than one drug.

In 2003, a new, redesigned DAWN expanded beyond drug abuse to include all drug related ED visits. The new DAWN ED cases now consist of drug abuse and misuse, suicide attempts, overmedication, adverse reactions, accidental ingestions, malicious poisoning, underage drinking, patients seeking detoxification or drug abuse treatment. To date, only count information for the Years 2003 and 2004 can be obtained.

In the data, prior to 2003 all propoxyphene and hydrocodone mentions involve "drug abuse" cases only. That is, if a patient were to enter the ED for reasons that were not related to drug abuse or misuse; it would not be included in the DAWN data. In the DAWN data collected prior to 2003, it is not possible to ascertain how many cases involved other drugs and which drugs were present.

4.2 RESULTS

As noted in Table 4.1, the number of Narcotic Analgesic Emergency Department (ED) mentions overall has been on the rise from 1994-2004. The number of ED mentions for all narcotic analgesics for this time period rose 168%. However, the number of ED mentions for propoxyphene for the period 1994-2002 fell by 30%. The number of ED mentions during that same period for the comparator drug, hydrocodone rose 170%

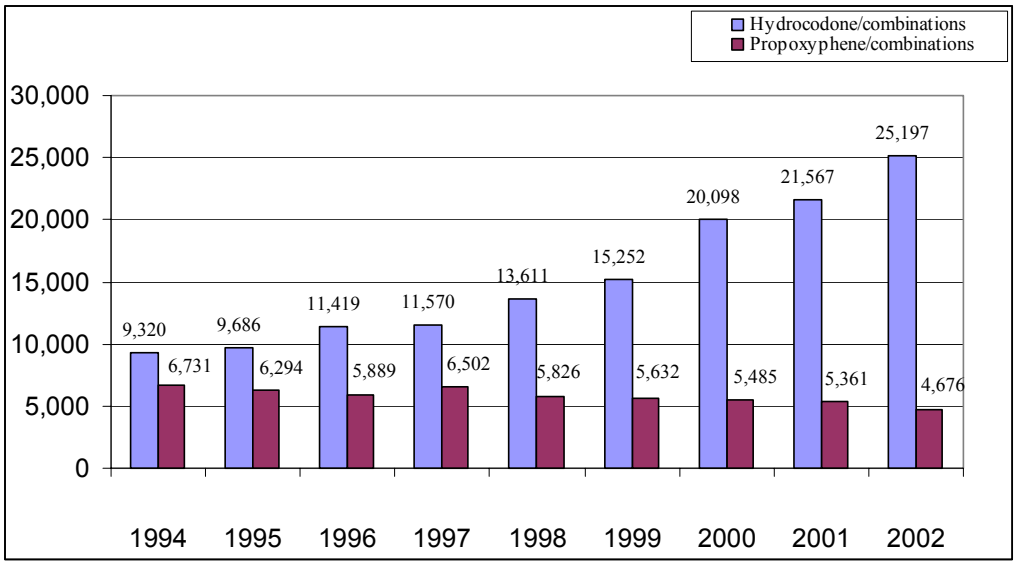
Table 4.1: DAWN ED Mentions for the Coterminous US 1994-2002

Drug name	*1994*	*1995*	*1996*	*1997*	*1998*	*1999*	*2000*	*2001*	*2002*	% change *1994 - 2002*
Narcotic analgesics/ combinations.	**44,518**	**45,254**	**46,941**	**54,116**	**58,946**	**69,011**	**82,373**	**99,317**	**119,185**	**167.7**
Narcotic analgesics	19,415	20,910	22,525	26,298	32,573	41,676	47,833	64,786	81,002	317.2
Narcotic analgesic combinations	25,102	24,343	24,416	27,819	26,373	27,335	34,540	34,531	38,183	52.1
Hydrocodone/ combinations	**9,320**	**9,686**	**11,419**	**11,570**	**13,611**	**15,252**	**20,098**	**21,567**	**25,197**	**170.4**
Hydrocodone	1,150	1,324	1,574	904	1,907	2,074	2,240	2,214	2,420	110.4
acetaminophen-hydrocodone.	8,168	8,362	9,845	10,667	11,686	13,043	17,538	19,058	22,227	172.1
Propoxyphene/ combinations	**6,731**	**6,294**	**5,889**	**6,502**	**5,826**	**5,632**	**5,485**	**5,361**	**4,676**	**-30.5**
propoxyphene.	1,515	1,068	1,065	1,166	1,109	816	593	684	492	-67.5
acetaminophen-propoxyphene.	5,216	5,224	4,822	5,337	4,714	4,816	4,891	4,675	4,168	ns

ns = not statistically significant
SOURCE: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2002 (03/2003 update)[1].

In examining Figure 3, we can see that hydrocodone mentions are on the rise and that propoxyphene mentions are declining over time.

Figure 3: DAWN Estimates of ED mentions of Propoxyphene and Hydrocodone Products for the coterminous U.S. by Year



SOURCE: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2002[1]

Although ED mentions for propoxyphene from 1994 – 2002 decreased and rose for hydrocodone, it is important to note that sales for propoxyphene also decreased and increased for hydrocodone as well. Therefore, in order to accommodate the differences in availability of the product, estimates for rate of ED mentions per prescriptions sold were computed. As seen in Table 4.2, the rate for ED mentions for propoxyphene ranged from 1.8 per 10,000 prescriptions sold in 1999 to 1.6 per 10,000 prescriptions sold in 2002. The rate for ED mentions for hydrocodone ranged from 1.9 in 1999 to 2.4 in 2002 per 10,000 prescriptions sold.

<u>This information is not to be used outside of the FDA without prior clearance by IMS Health.</u>

Table 4.2: Reporting Rate of Emergency Room Mentions for Projected Propoxyphene and Hydrocodone Sales

Drug name	1999	2000	2001	2002
DAWN Estimate of Total ED Mentions for Coterminous US				
Propoxyphene/combinations ED mentions	5,632	5,485	5,361	4,676
Hydrocodone/combinations ED mentions	15,252	20,098	21,567	25,197
IMS Health Projected Number of Total Prescriptions Dispensed				
Total Propoxyphene Sales[1]	31,547	30,992	30,404	29,161
Total Hydrocodone Sales[1]	81,725	88,778	96,318	103,645
Hydrocodone (minus cold/cough) Sales	68,802	76,631	83,216	90,261
ED Mentions Rate				
Propoxyphene Rate[2]	1.79	1.77	1.76	1.60
Hydrocodone (all) Rate[3]	1.87	2.26	2.24	2.43
Hydrocodone (minus cold/cough) Rate[3]	2.22	2.62	2.59	2.79

[1] (in thousands; add three 000's to each figure)
[2] Reporting Rate = ED Mentions/10,000 Prescriptions Sold
[3] Both hydrocodone reporting rates use total hydrocodone combinations as numerator
Source: IMS Health and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2002 (03/2003 update)[1].

Given that most DAWN ED mentions involve use of multiple drugs, data were obtained that contained only single entity propoxyphene and hydrocodone and acetaminophen combinations that were reported in the DAWN data. Table 4.3 lists the proportion of the type of case reported for both single entity propoxyphene and hydrocodone and APAP combinations. The proportion of suicide attempts was higher for propoxyphene only cases (13% of ED cases) than for hydrocodone only (4% of ED cases). It was not effectively higher when comparing APAP combinations; where suicide attempts was 6% of ED cases involving propoxyphene/APAP than for hydrocodone/APAP combinations (5% of all ED cases). The proportion of over-medication was higher for propoxyphene only cases (33% of all ED cases) than for hydrocodone only (19% of all ED cases) as well. This relationship remained when comparing APAP combinations, but the differences were attenuated; where 24% of propoxyphene/APAP ED mentions were overmedications cases versus 22% for hydrocodone/APAP.

The proportion of cases seeking detox was lower for propoxyphene only and APAP combination (0 and 1% of all ED cases respectively) than for hydrocodone and APAP combinations (9% and 10% all ED cases respectively).

Table 4.3: 2004 Type of Case by Drug listed in DAWN ED Mentions*

Single Drug Entity DAWN cases	*Suicide Attempt (%)*	*Seeking detox (%)*	*Adverse reaction (%)*	*Over-medication (%)*	*Accidental ingestion (%)*	*Other (%)*
Propoxyphene n=40	5 (13)	0 (0)	18 (45)	13 (33)	1 (2)	3 (8)
Acetaminophen-Propoxyphene n=463	30 (6)	6 (1)	299(65)	112 (24)	3 (0.6)	13 (3)
Hydrocodone n=381	15 (4)	35 (9)	212 (56)	74 (19)	15 (4)	30 (8)
Acetaminophen-Hydrocodone n=2,795	139 (5)	279 (10)	1491 (53)	630 (22)	29 (1)	227 (8)

* Tables reflect cases that have been received by DAWN as of: 3/7/05. All DAWN cases are reviewed for quality control. Based on this review, cases may be corrected or deleted. Therefore, these data are subject to change. SOURCE: Office of Applied Studies, SAMHSA, New Drug Abuse Warning Network[8]

Given the low number of cases for propoxyphene only, it is difficult to compare the proportions of case disposition with the other drug classes. Bearing that in mind, Table 4.4 indicates the proportion of ED cases that were admitted to ICU/Critical care for propoxyphene only (8% of ED cases) was similar for cases involving hydrocodone only (9%) and hydrocodone/APAP combinations (7%). It was somewhat lower for propoxyphene/APAP cases (4%).

When examining the proportion of cases transferred to another hospital unit, the proportion of propoxyphene/APAP cases (4%) was lower than for the other three drug classes, propoxyphene only (13%), hydrocodone (13%) and APAP combinations (10%). It should be noted that the number of cases listed in table is lower than in Table 4.3 because the disposition for each case is unknown or has not been recorded.

Table 4.4: 2004 Case Disposition by Drug listed in DAWN ED Mentions*

Single Drug Entity DAWN Cases	*Discharged home/police (%)*	*Referred detox/trt (%)*	*Admit ICU (%)*	*Admit CD/detox (%)*	*Admit psych (%)*	*All other admit (%)*	*Transferred (%)*	*Died (%)*
Propoxyphene n=38	21 (55)	2 (5)	3 (8)	0 (0)	2 (5)	5 (13)	5 (13)	0 (0)
Propoxyphene /APAP n=446	334 (75)	4 (1)	19 (4)	1 (0.2)	15 (3)	56 (13)	16 (4)	1 (0.2)
Hydrocodone n=218	100 (46)	14 (6)	20 (9)	15 (7)	15 (7)	24 (11)	28 (13)	2 (0.9)
Hydrocodone/APAP n=1,831	936 (51)	99 (5)	121 (7)	103 (6)	170 (9)	215 (12)	182 (10)	5 (0.3)

* Tables reflect cases that have been received by DAWN as of: 3/7/05. All DAWN cases are reviewed for quality control. Based on this review, cases may be corrected or deleted. Therefore, these data are subject to change. SOURCE: Office of Applied Studies, SAMHSA, New Drug Abuse Warning Network[3]

It is important to note that given that the information provided are based on counts and are not weighted to reflect national estimates, therefore differences in the types of cases may not necessarily be generalizable nation-wide.

4.3 DISCUSSION

It is important to keep in mind the following limitation when making any conclusions about DAWN ED data. Most DAWN mentions of propoxyphene, as well as hydrocodone, included ED visits where other drugs were reported. As a result, it is not possible to attribute definitively the ED episode specifically to propoxyphene or the comparator drug, hydrocodone

Use of propoxyphene products appears to be going down as reported by IMS Health Prescription sales data. Simultaneously, decreases in absolute number of ED mentions in DAWN mentions have also been found for propoxyphene products. At the same time that does not mean that propoxyphene is without its risk. The warning already placed in the labeling is not without foundation. The proportion of ED cases that were admitted to ICU was somewhat higher for propoxyphene products than for hydrocodone products. In addition, the proportion of ED cases that listed suicide attempt or adverse reaction was higher for propoxyphene products than for hydrocodone products.

5. REVIEW OF TOXIC EXPOSURE SURVEILLANCE SYSTEM DATA

5.1 METHODS

The Toxic Exposure Surveillance System or TESS is a poisoning surveillance database maintained by the American Association of Poison Control Centers (AAPCC) in cooperation with 64 poison control centers in the U.S.[9] In 2003 (the latest year for which we have data), poison control centers linked with AAPCC served nearly the entire U.S. population of (294.7 million) including the 50 states, the District of Columbia, and Puerto Rico. Since 1983 when TESS was started, to the present time, this database contains 36.2 million potential human poison exposure cases including 2.3 million cases reported in 2003 alone.[10]

The AAPCC's annual reports from 1999-2003 were reviewed manually to determine the extent of poisoning in association with exposure to propoxyphene and hydrocodone products. Two tables in the annual reports (Table 21: Summary of Fatal exposures, and Table 22B: Demographic Profile of Exposure Cases by Generic Category of Substances and Products) were reviewed and formed the basis of this review. Every time propoxyphene or hydrocodone products were mentioned in the table they were included in the analyses.

Definitions and terminology used:

In the annual reports, '*Death*' is when a patient dies as a result of the exposure or as a direct complication of the exposure. Only those deaths that are probably or undoubtedly related to the exposure are coded in TESS.

The various reasons for exposure are defined here. '*Unintentional general*': all unintentional exposures. *'Suspected suicidal'* is defined as an exposure resulting from the

inappropriate use of a substance for reasons that are suspected to be self-destructive or manipulative.

'Health care facilities' include acute care hospitals, physician offices or clinics, and freestanding emergency centers. Nonhealth care facility refers to the site of exposure that is usually the patient's home.

5.2 RESULTS

Table 5.1 summarizes the total number of poisoning-related calls associated with propoxyphene and hydrocodone products. In the five-year review period, the overall number of calls to poison control centers concerning propoxyphene as single ingredient and combination product with acetaminophen exposures has increased by about 11% from 5,680 in 1999 to 6,318 in 2003. For hydrocodone plus acetaminophen combination product, the overall number of calls increased by about 29% from 15,142 in 2001 to 19,538 in 2003.

Table 5.1: Total Number of Poisoning-Related Calls to Poison Control Centers

Year	Propoxyphene Single ingredient	Hydrocodone Single ingredient	Propox+APAP Combo product	Hydrocod+APAP Combo product
1999	560	NA	5,120	NA
2000	561	NA	5,578	NA
2001	567	NA	5,853	15,142
2002	519	NA	6,018	17,386
2003	448	NA	5,870	19,538

Propox= Propoxyphene; APAP=Acetaminophen; Hydrocod=Hydrocodone; Combo=Combination
NA= Data not available

Table 5.2 summarizes the outcome of the total number of calls associated with propoxyphene and hydrocodone products referred to in Table 5.1. In 2003, of the total 6,318 calls that were received by poison control centers where propoxyphene products were involved 4,036 (or about 64%) were referred to a healthcare facility for treatment and 34% were unintentional exposures. Of the nearly twenty thousand hydrocodone plus acetaminophen-associated calls that were received in 2003, about 60% were treated in a health care facility and about 34% were unintentional exposures. When comparing propoxyphene /APAP combinations and hydrocodone/APAP combinations, the percent treated in a healthcare facility and that were unintentional were similar and the distribution was found to remain fairly consistent over the period where data was available.

Table 5.2: Outcome of Poisoning-related Calls – A. Number (%) Received Treatment in Healthcare Facility; B. Number (%) Unintentional Poisonings

Year	Propoxyphene Single ingredient Rx in HCF/ Unint		Hydrocodone Single ingredient Rx in HCF/Unint	Propox+APAP Combo product Rx in HCF/Unint		Hydrocod+APAP Combo product Rx in HCF/Unint	
1999	361(64%)	193(34%)	NA	3,295(64%)	1,824(35%)	NA	
2000	366(65%)	181(32%)	NA	3,691(66%)	1,915(34%)	NA	
2001	381(67%)	192(34%)	NA	3,717(63%)	2,006(34%)	9,030(60%)	5,123(34%)
2002	351(68%)	160(31%)	NA	3,840(64%)	2,123(35%)	10,541(61%)	5,672(33%)
2003	301(67%)	144(32%)	NA	3,735(65%)	2,014(34%)	11,683(60%)	6,625(34%)

Rx in HCF = Treatment in healthcare facility; Unint = Unintentional exposure; NA = Data Not Available

Table 5.3 summarizes the five-year comparison of fatal exposures associated with propoxyphene and hydrocodone single-ingredient products and their combination with acetaminophen product. The total number of fatalities in association with propoxyphene (single ingredient and combo with APAP) exposures declined by a half from 28 in 1999 to 14 in 2003. Overall, propoxyphene-associated fatalities represented about 1% of the total 1,106 fatalities that were reported in the TESS database in 2003.

Table 5.3: Fatal Exposures Reported to Poison Control Centers

Year	Propoxyphene Single ingredient	Hydrocodone Single ingredient	Propox+APAP Combo product	Hydrocod+APAP Combo product
1999	9	3	19	44
2000	5	2	23	43
2001	12	1	23	43
2002	7	12	28	65
2003	3	3	11	76

Propox = propoxyphene; APAP = Acetaminophen; Hydrocod= Hydrocodone; Combo= Combination

Most of the propoxyphene-associated fatalities occurred in individuals who ingested multiple products. In 2003, all three single-ingredient propoxyphene-associated fatalities occurred in individuals who took multiple products simultaneously; cocaine and olanzapine in one case, diphenhydramine and mirtazapine in the second case; and ibuprofen/oxycodone and zolpidem in the third case. In the remaining eleven fatalities in 2003 all but three occurred in individuals who took propoxyphene plus acetaminophen combination products only; in the other eight fatalities, additional products were ingested aside from propoxyphene plus APAP including single ingredient acetaminophen or in combination with other opioids, and aspirin.

The total number of fatal exposures with hydrocodone products (single and in combination with APAP) increased by about 68% from 47 in 1999 to 79 in 2003. Like propoxyphene-associated fatalities, in the case of hydrocodone-associated fatalities multiple products were ingested simultaneously. Overall, in 2003, hydrocodone-associated fatalities represented about 7% of the total 1,106 fatalities that were reported in the TESS database in 2003.

6. OVERALL DISCUSSION/CONCLUSIONS

This review includes a discussion of an analysis of AERS data for propoxphene products as well as an analysis of DAWN and TESS data comparing propoxyphene to hydrocodone product information. Conclusions from this analysis include the following:

AERS ANALYSIS

- A total of 3075 serious adverse events for propoxyphene were identified; 2186 of the cases were domestic,
- There was an increase in crude counts of adverse event reports for propoxphene from 161 in 1999 to 319 in 2004 (see Figure 1). However, since the most commonly reported events with propoxphene were drug overdoses, dependence, and suicides, involving the co-ingestion of multiple drug products, the significance of this observed increase for propoxphene could not be established in this analysis (tables 3.1 and 3.3)
- This increase in reporting could not be explained from the IMS drug use data since there was a steady decline in the total prescriptions dispensed during this period; of note the use of propoxyphene single ingredient product is especially low (see Table 2.1)
- The majority of the 91 US death reports for Darvocet® were related to overdoses and involved other medications as well.

DAWN ANALYSIS

- For the years 1999-2002, the propoxyphene emergency department mention rate (ED/prescriptions) from old DAWN remained stable, but the rate was higher and increased over time for hydrocodone (see Table 4.2)
- The three most common reasons for ED mentions in the new DAWN were adverse reaction , overmedication, and suicide attempt (see Table 4.3)
- The proportion of Propoxyphene only cases seen in the ED that required an ICU admission was similar to cases involving hydrocodone only and hydrocodone/APAP combinations but higher than cases involving propoxyphene/APAP.

TESS ANALYSIS

- For the years 1999 to 2003 there was a 11% increase in propoxyphene-associated exposure calls, but the number of fatal exposures with propoxyphene products declined by about 50%; both the number of calls, and the number of deaths associated with hydrocodone products have increased in the timeframe data was available for this product.
- Unintentional calls accounted for about 30% of calls for both propoxyphene hydrocodone calls; the percent of unintentional call did not change over time for either drug (see Table 5.2)
- The majority of propoxyphene-associated exposure calls occurred in individuals who reportedly took multiple products simultaneously with suicidal intent.
- Over 60 percent of calls for both propoxyphene hydrocodone calls were from patients that were followed-up in a healthcare (see Table 5.2)
- Overall, propoxyphene-associated fatalities represented about 1% of the total 1,106 fatalities that were reported in the TESS database in 2003; compared to 7% for hydrocodone-associated fatalities

In conclusion, a review of the information available to ODS suggests that propoxphene has been associated with serious adverse outcomes, often in relation to an intentional overdose. It is unclear if there has been a change over time in adverse events but two of three databases (AERS and TESS) suggest there may be some type of increase. The data available to the team to review did not provide enough information to determine if deaths could be related to propoxphene alone, acetaminophen in combination products, and/or co-ingestion of other psychoactive medications.

Although, there is limited information to guide any regulatory decision we provide the following considerations for further discussion:

- Given that propoxyphene product labeling already contains strong *Warnings* regarding excessive doses, either alone or in combination with other CNS depressants, strengthening the labeling alone (to possibly include a *Black Box Warning*) may not fully address the continued reports of inappropriate use of these products.

- All propoxyphene sponsors should consider implementation of an extensive education campaign focused on
    - patients (patient package insert/medication guide) to emphasize avoidance of propoxphene if they have a history of drug/alcohol abuse or dependence, or suicidal thoughts and other concerns as noted in the labeling
    - physicians (Dear Healthcare Letter) to emphasize appropriate patient selection emphasizing all risk factors including use of other interacting drugs, drug or alcohol abuse or a history of depression or suicidal behavior.

- Most importantly, given that there are published studies where investigators have reported that acetaminophen and narcotic combination products were a common cause of acute liver failure[3,4,11] and that the current review also indicates that propoxyphene plus acetaminophen combination products were possibly associated with continued reports of calls to poison control centers, ED visits, overdose, and suicidal attempts, the reformulation of propoxyphene/acetaminophen products should be considered
    - In the U.K., an extensive review of the data found "no robust evidence" that the 325mg of acetaminophen in propoxyphene combo product was "superior to full strength acetaminophen alone in either acute or chronic use".[1]
    - For any combination products that are not reformulated, consideration should be given to adding a precaution that some overdoses have occurred from patient unintentionally taking multiple acetaminophen products.

- There may be a need to further assess the risk benefit profiles of other pain relieving drugs (e.g., hydrocodone, and oxycodone) and their combination with acetaminophen.

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Renan A. Bonnel. Pharm.D., MPH

Concur:

_____
Lauren Lee, Pharm.D. Acting Team Leader

_____
Catherine Dormitzer, PhD

_____
Syed Rizwanuddin Ahmad, MD, MPH

Concur:

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Mary Willy, PhD. Team Leader

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7/25/05 06:29:11 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
7/26/05 04:20:47 PM
DRUG SAFETY OFFICE REVIEWER

Drug Abuse Warning Network

The Drug Abuse Warning Network (DAWN) provides information on some of the medical consequences of substance use, misuse, and abuse that manifest in visits to hospital emergency departments. DAWN records substances associated with drug-related emergency department visits; provides a means for monitoring drug misuse and abuse patterns, trends, and the emergence of new substances; assesses some of the morbidity associated with drug misuse and abuse; and generates information for national, State, and local drug policy and program planning. DAWN is also a tool that is increasingly being utilized for postmarketing surveillance and risk management for the pharmaceuticals regulated by the Food and Drug Administration (FDA). DAWN is the responsibility of the Office of Applied Studies, a Federal statistical unit within the Substance Abuse and Mental Health Services Administration (SAMHSA).

A new data collection protocol was introduced for DAWN in 2003. The new design addressed many longstanding limitations associated with DAWN data. Because virtually every feature of DAWN changed with the redesign, data from 2004[1] and beyond are not comparable to data from 2002 and prior years.

DAWN relies on a national probability sample of non-Federal, short-stay, general hospitals that operate 24-hour emergency departments. Hospitals are oversampled in selected metropolitan areas and divisions, and a remainder sample covers hospitals in the remainder of the U.S. Based on data from sampled units, national estimates of drug-related emergency department visits for the U.S. are produced annually.

DAWN estimates for 2006 are based on a sample of 544 eligible hospitals, with 160 (28% to 70%) responding in oversample areas and 45 (23%) responding in the remainder area. Estimates reflect adjustments for the stratified sample design, unit nonresponse, and nonresponse within a facility. Whether an oversample area stands alone in the national estimate depends on its response rate and the potential for nonresponse bias. At this time, comparisons over time are available only for 2004, 2005, and 2006.

In addition, authorized users in DAWN member hospitals; Federal, State, and local public health agencies, including SAMHSA and FDA; and pharmaceutical firms receive access to the raw DAWN case data, in de-identified form, as the DAWN cases are submitted. This surveillance of sentinel events is possible through a secure, Internet-based query system called DAWN *Live!*

To collect the data, each hospital emergency department that participates in DAWN has one or more reporters who review emergency department medical records retrospectively to find DAWN cases. Cases reported to DAWN include emergency department visits caused by or related to drug use for patients of any age. The drug use must be recent; chronic effects and history of drug abuse are not reportable. Visits related to drugs used for therapeutic purposes, as well as drug misuse and abuse, are all included.

[1] Data from 2003 represent a transition year that is not comparable to prior or subsequent years.

For each reportable visit, demographic, visit, and drug characteristics are abstracted from the medical record. Each DAWN visit is classified into one of eight case types: drug-related suicide attempt, those seeking detoxification or substance abuse treatment services, underage alcohol use (with no other drug involved), adverse reactions to pharmaceuticals taken as prescribed, overmedication when the dose of a prescription or over-the-counter medication or dietary supplement was exceeded, malicious poisonings, accidental ingestions when a drug was used accidentally or unknowingly, and all others, including explicit drug abuse. This classification and the drugs reported to DAWN are used to derive analytic subgroups (e.g., for visits involving illicit drug use, alcohol use, or nonmedical use of pharmaceuticals) for a variety of purposes and audiences. Other data items characterize drug-related visits in terms of diagnoses or disposition.

DAWN captures very detailed drug information. As many as 16 drugs plus alcohol are reported for each DAWN case. Drug-related emergency department visits often include multiple drugs, on average, 1.6 drugs per visit. For adults, alcohol is reportable only when present with another reportable drug; for minors, alcohol is always reportable. Drug information is captured at the level of detail present in the medical record. The same drug may be reported to DAWN by brand, generic, chemical, street, or nonspecific name, depending on the completeness and specificity of information in the medical record. Training and automated rules prompt DAWN reporters to use all available documentation in the medical chart to record drugs by their most specific names (e.g., OxyContin, when documented as such, instead of oxycodone), not to record the same drug by different names (e.g., heroin and opiates), and to exclude current medications unrelated to the visit. Estimates are published at the generic level (e.g., acetaminophen-hydrocodone), for specific ingredients (e.g., dextromethorphan), or by drug category (e.g., opiates/opioids, benzodiazepines). Estimates attributed to particular brand or trade names (e.g., Concerta®) are generally not published.

Since data for DAWN are extracted from a retrospective review of medical records, no patients or health care providers are interviewed. Health care settings within the hospital but outside of the emergency department, or emergency facilities outside of hospitals, are not covered. Laboratory findings to detect the presence of a drug are not recorded for DAWN cases, although each drug report has an associated indicator for whether the drug was confirmed by toxicology testing. Only the patient's own drug use is considered, a patient's intent to misuse or abuse a drug is not a factor in the DAWN case determination, and source of the drug is not captured because it is so rarely available in medical records. Repeat visits by the same individual cannot be linked together. Visits due to chronic conditions associated with a history of drug abuse are explicitly excluded. While DAWN does not collect direct identifiers, such as patient name, the content of the case data does render the data individually identifiable, and individually identifiable data are protected by Federal law from disclosure without consent.

DAWN does not measure the prevalence of drug abuse in the population, and external factors unrelated to the level of drug abuse in the population may contribute to the likelihood that a person presents to a hospital emergency department for a drug-related problem. For example, the availability of health insurance and/or other sources of care may influence whether an individual seeks care in an emergency department. Purity, experience, or other factors related to the physiological effects of drugs may affect whether a condition occurs to give rise to an emergency department visit.

DAWN also collects data on drug-related deaths reviewed by medical examiners and coroners (ME/Cs) in selected metropolitan areas and selected States. The death investigation jurisdictions that participate in DAWN do not constitute a statistical sample nor is every jurisdiction within a metropolitan area necessarily a participant. As a result, extrapolation of drug-related deaths to the Nation as a whole is not possible, and metropolitan area totals are only possible if all jurisdictions within the area participate. The number of jurisdictions that participate in DAWN varies from year to year. In 2003, the last year for which mortality data have been published, 122 jurisdictions in 35 metropolitan areas and 126 jurisdictions constituting six States participated in DAWN. The case criteria and data collection procedures for drug-related deaths mirror those used in emergency departments. Causes and manner of death are captured, in lieu of case type and diagnoses.

Admissions to Substance Abuse Treatment for the Abuse of Opioid Analgesics: Findings from the Treatment Episode Data Set

Deborah Trunzo
Office of Applied Studies
Substance Abuse and Mental Health Services Administration

December, 2008

Background

The Treatment Episode Data Set (TEDS) is a data base of client level information on admissions to substance abuse treatment. The TEDS system has two major components, the Admissions Data Set and the Discharge Date Set. The TEDS Admissions Data Set is an established program that has been operational since 1992. It includes data on treatment admissions that are routinely collected by States to monitor their individual substance abuse treatment systems. The TEDS Discharge Data Set is relatively new, with first data reported for Year 2000. For both data sets, selected data items from the individual State data files are converted to a standardized format consistent across States. These standardized data constitute TEDS.

TEDS data items include:

- Demographic information
- Primary, secondary, and tertiary substances of abuse and their route of administration, frequency of use, and age at first use
- Source of referral to treatment
- Number of prior treatment episodes
- Service type, including planned use of medication-assisted opioid therapy

TEDS, while comprising a significant proportion of all admissions to substance abuse treatment, does not include all such admissions. TEDS is a compilation of facility data from State administrative systems. The scope of facilities included in TEDS is affected by differences in State licensure, certification and accreditation practices, and disbursement of public funds. In general, facilities reporting TEDS data receive State alcohol and/or drug agency funds (including Federal Block Grant funds) for the provision of substance abuse treatment services. States may report data from facilities that do not receive public funds but generally do not because of the difficulty in obtaining data from these facilities. TEDS generally does not include data from facilities operated by Federal agencies.

Limitations to be kept in mind while analyzing TEDS data include:

- TEDS is an admission-based system, and TEDS admissions do not represent individuals. Thus, for example, an individual admitted to treatment twice within a calendar year would be counted as two admissions.
- The number an client mix of TEDS admissions do not represent the total national demand for substance abuse treatment or the prevalence of substance abuse in the general population.

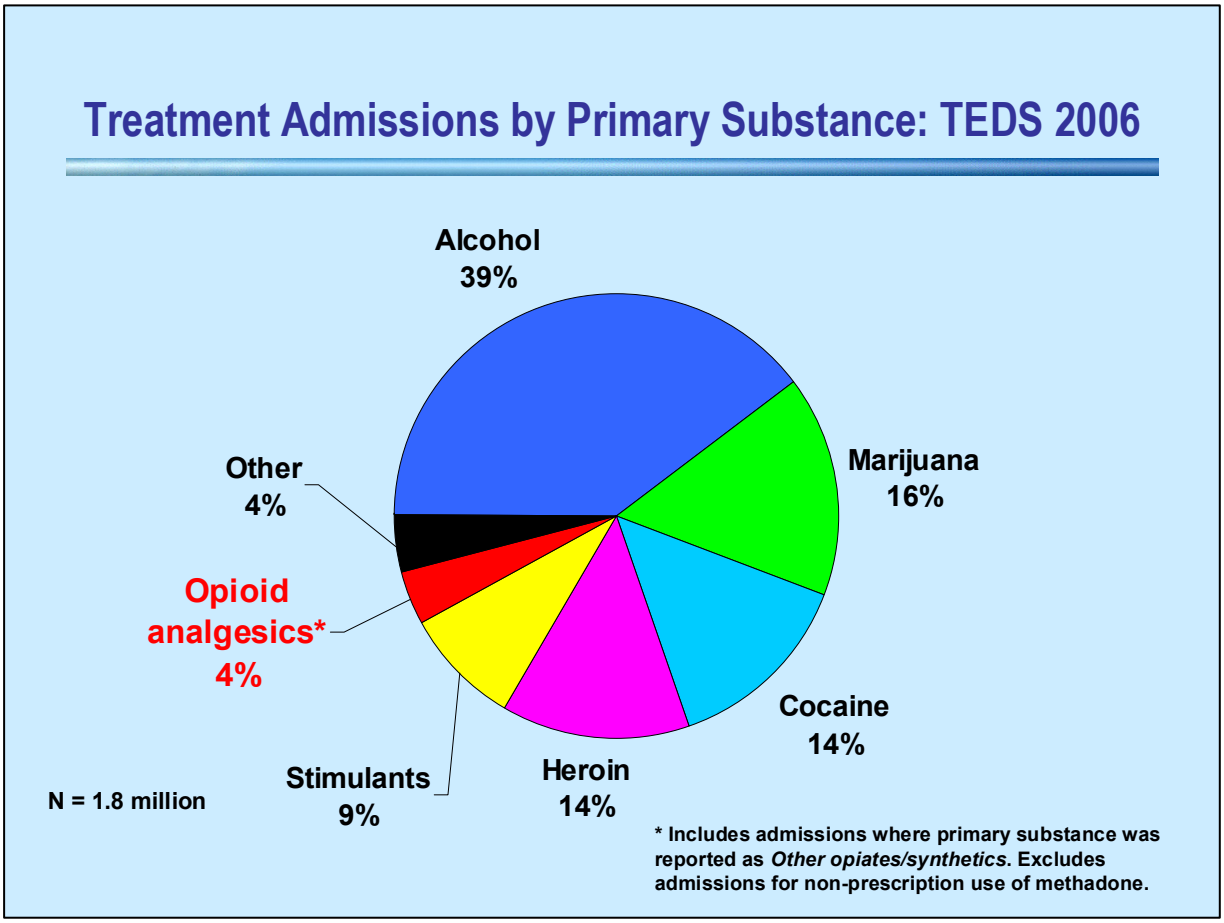
- The primary, secondary, and tertiary substances of abuse reported to TEDS are those substances that led to the treatment episode, and not necessarily a complete enumeration of all drugs used at the time of admission.

- Substances of abuse are reported in generic categories, not specific formulations or brand names, since these distinctions are not critical to the development of a treatment plan. The core TEDS data elements for substances of abuse divide opioid drugs into two broad categories, heroin and opiates other than heroin. The category "opiates other than heroin" basically consists of opioid analgesics, and is reported by all States. Sixteen States report drugs of abuse in more detail, including 8 types of opioid analgesics.

Findings

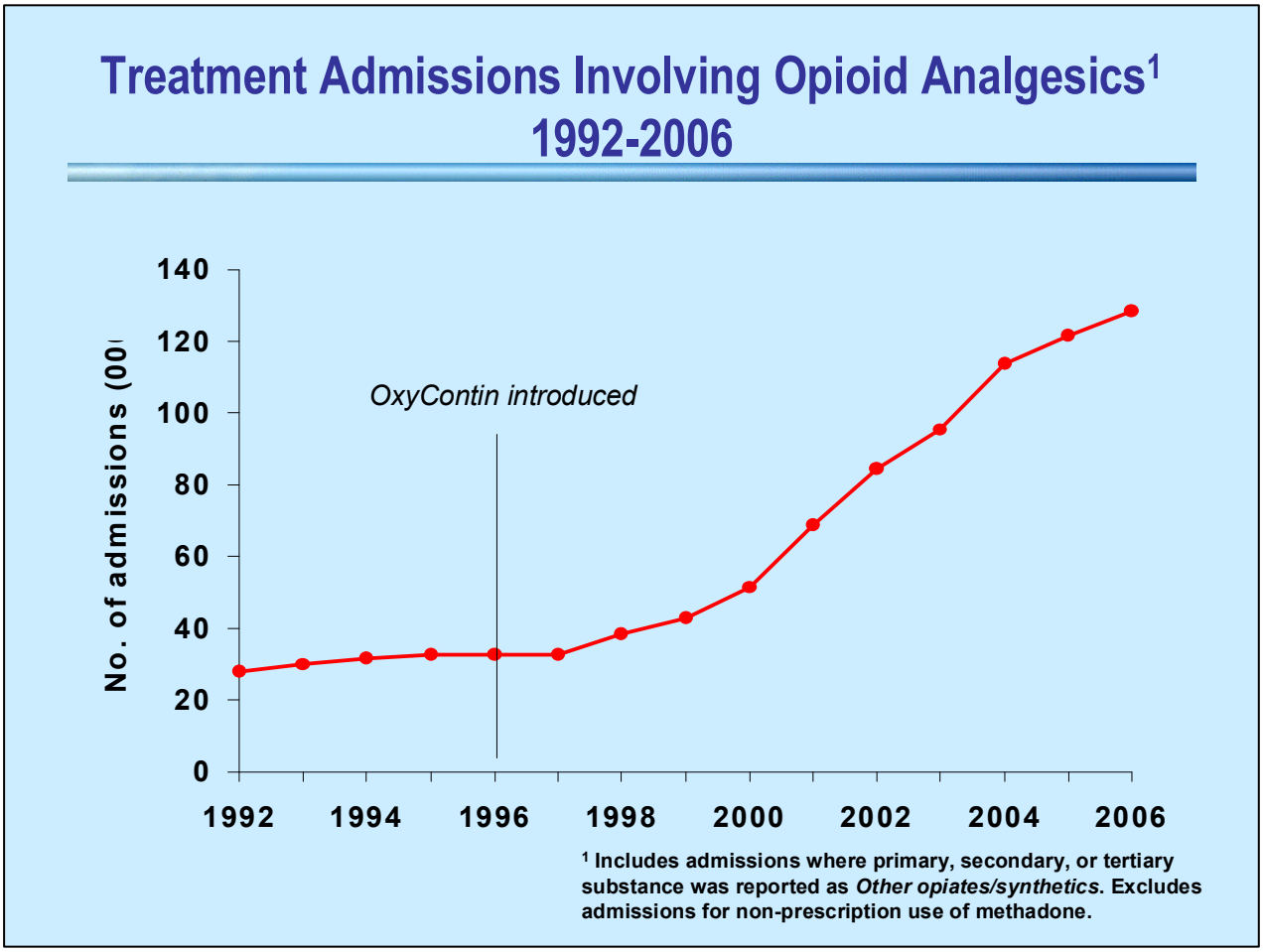
In 2006, the most recent year for which data have been released, 4 percent the 1.8 million TEDS admissions reported that their primary drug of abuse was an opioid analgesic (Figure 1). In addition to these 70,000 admissions, another 58,000 reported pain relievers as a secondary or tertiary drug. Altogether, 128,000, or 7%, of all TEDS treatment admissions reported pain relievers as either their primary, secondary or tertiary substance of abuse.

Figure 1.



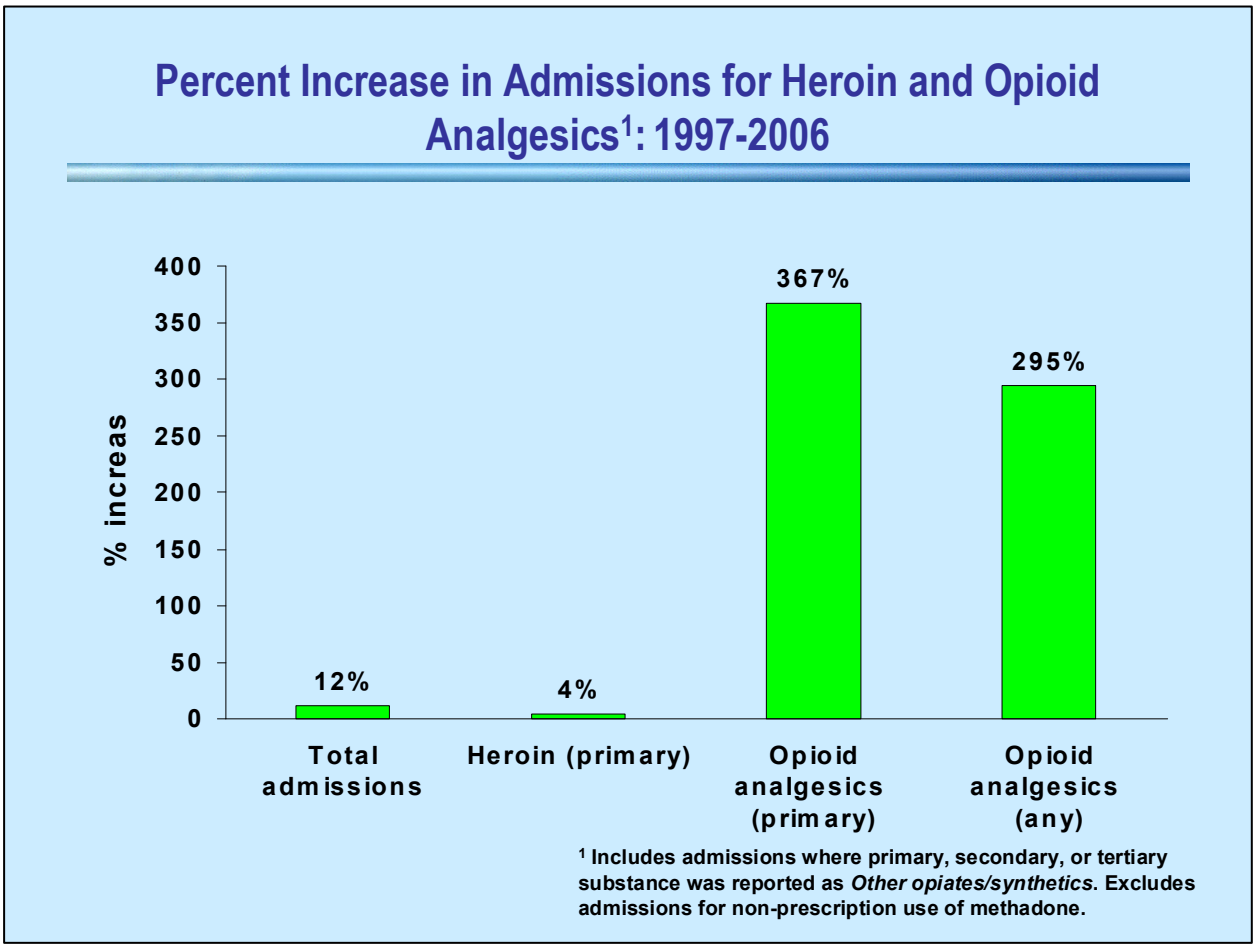
While pain relievers accounted for a relatively small number of admissions in 2006, the number of such admissions has increased dramatically in the last 10 years. Between 1992 and 997, the number of admissions involving pain relievers remained flat, at about 30,000 per year (Figure 2). In 1998, two years after the introduction of Oxycontin, admissions for abuse of opioid analgesics began a sharp upward trend. Preliminary data for 2007 indicate that this trend continues unabated.

Figure 2



The increase in admissions for abuse of opioid analgesics cannot be attributed to an increase in admissions overall. Since 1997, total admissions have gone up by 12% and primary heroin admissions by only 4% (Figure 3). In contrast, primary opioid analgesic admissions increased by almost 400% and admissions with any involvement of opioid analgesics increased by nearly 300%.

Figure 3



In 2006, 16 States were able to report opioid analgesics in more detailed categories, as shown in Figure 4. For those admissions in which a specific opioid analgesic was recorded, oxycodone was clearly the dominant substance, accounting for 82 percent of the cases. The next most frequently reported drugs, codeine and hydrocodone, accounted for 6 percent and 5 percent of the cases, respectively. Propoxyphene was specified by only 1 percent of the cases. Unfortunately, many cases ended up in the "other category." This is most likely due to failure on the part of treatment providers to record the specific drug. We have no reason to believe that there is another opioid drug not shown in Figure 4 that accounts for a large number of these admissions.

Figure 4

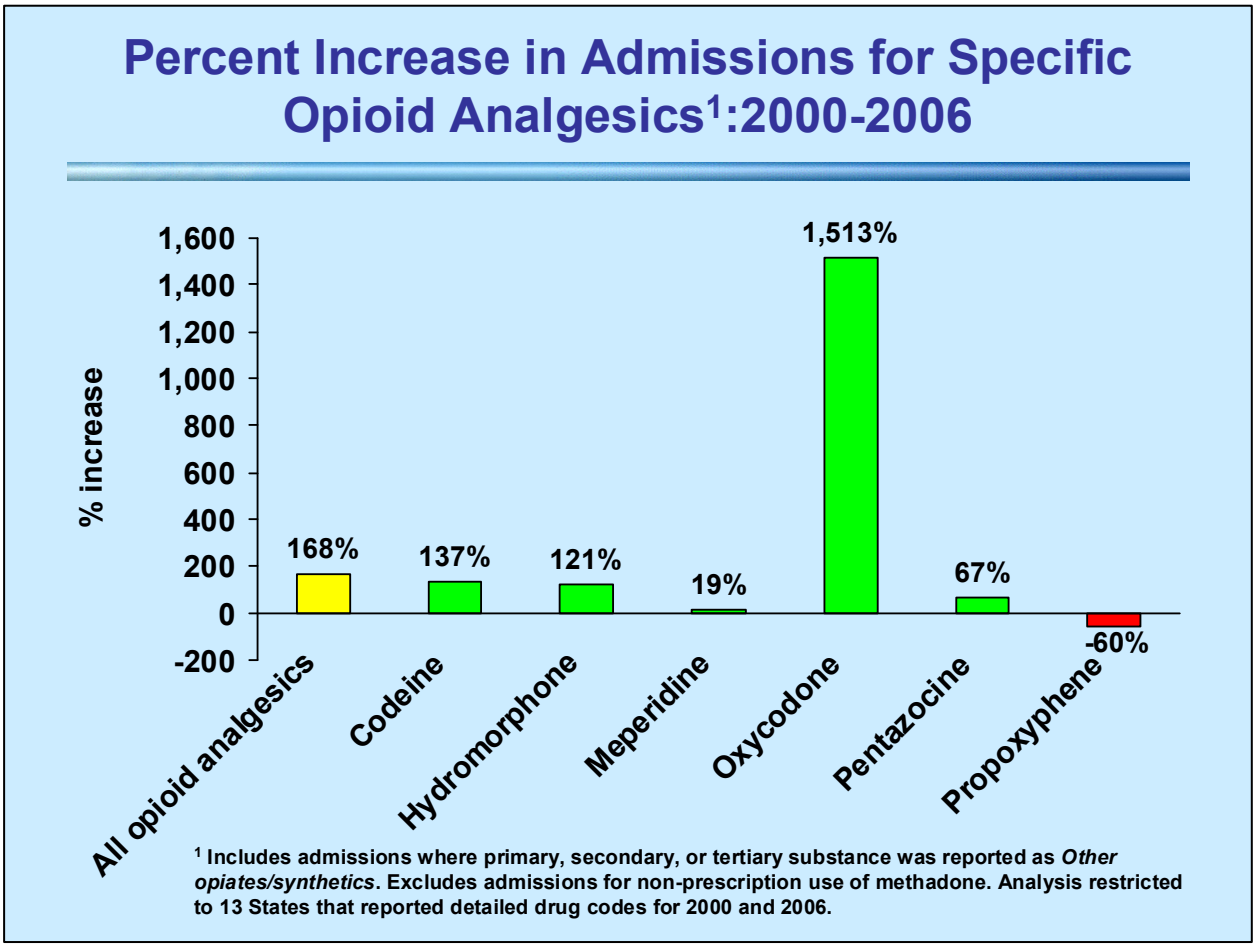
Admissions Involving Specific Opioid Analgesics[1]: 2006

Oxycodone	**15,300**
Codeine	1,200
Hydrocodone	900
Hydromorphone	800
Propoxyphene	**162**
Meperidine	80
Pentazocine	30
Tramadol	50
Other opiates or synthetics	33,100

[1]Data submitted by 16 States: AL, HI, ID, KY, MD, ME, MO, MS, ND, NH, NJ, NM, NV, NY, OH, SD

Figure 5 shows the percent change in admissions for specific pain relievers between 2000 and 2006, based on data from 13 of the same 16 States. The change for most drugs was slight, but for oxycodone, the increase was more than 1,500 percent. Sixty percent fewer admissions involving propoxyphene were reported in 2006 than in 2000.

Figure 5



One way of judging the impact of a drug on a state's treatment system is to look at the proportion of treatment admissions involving that drug. In the map in Figure, 6 States with the highest proportion of admissions for primary abuse of opioid analgesics are shown in blue (the darker the shade of blue, the larger the proportion of pain killer admissions). The white states had rates at or below the national average of 4 to 5 percent. Maine, Vermont, and West Virginia had rates exceeding 16 percent. In Maine, 21 percent of all treatment admissions were for primary pain killer abuse.

Figure 6

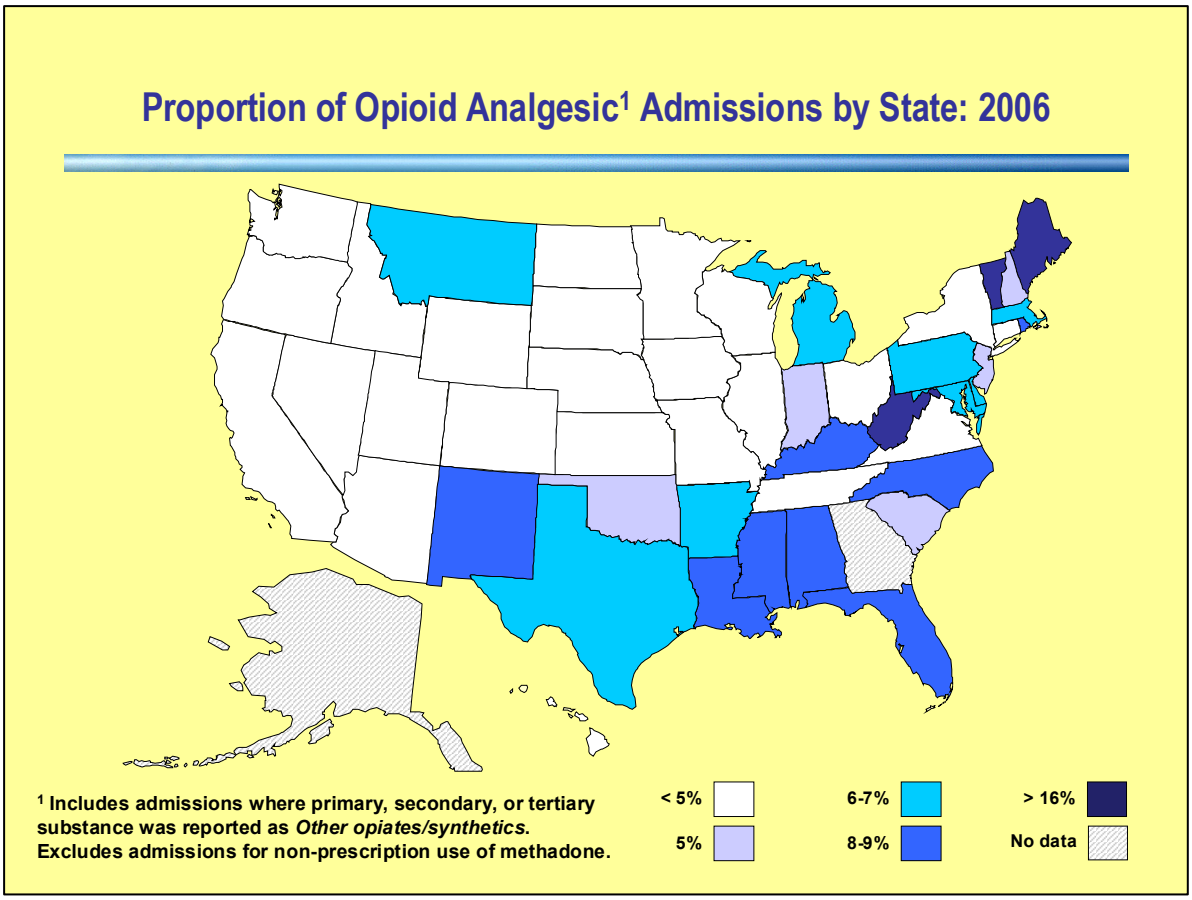


Figure 7 illustrates how route of administration for opioid analgesics varies by age. In 2006, oral was by far the most common route of administration for all ages, accounting for almost three quarters of pain reliever admissions. Inhalation accounted for 13 percent and injection for 10 percent. It is noteworthy that admissions involving inhalation and injection were concentrated in the younger age groups. Very few admissions over the age of 35 inhaled or injected these drugs.

Figure 7

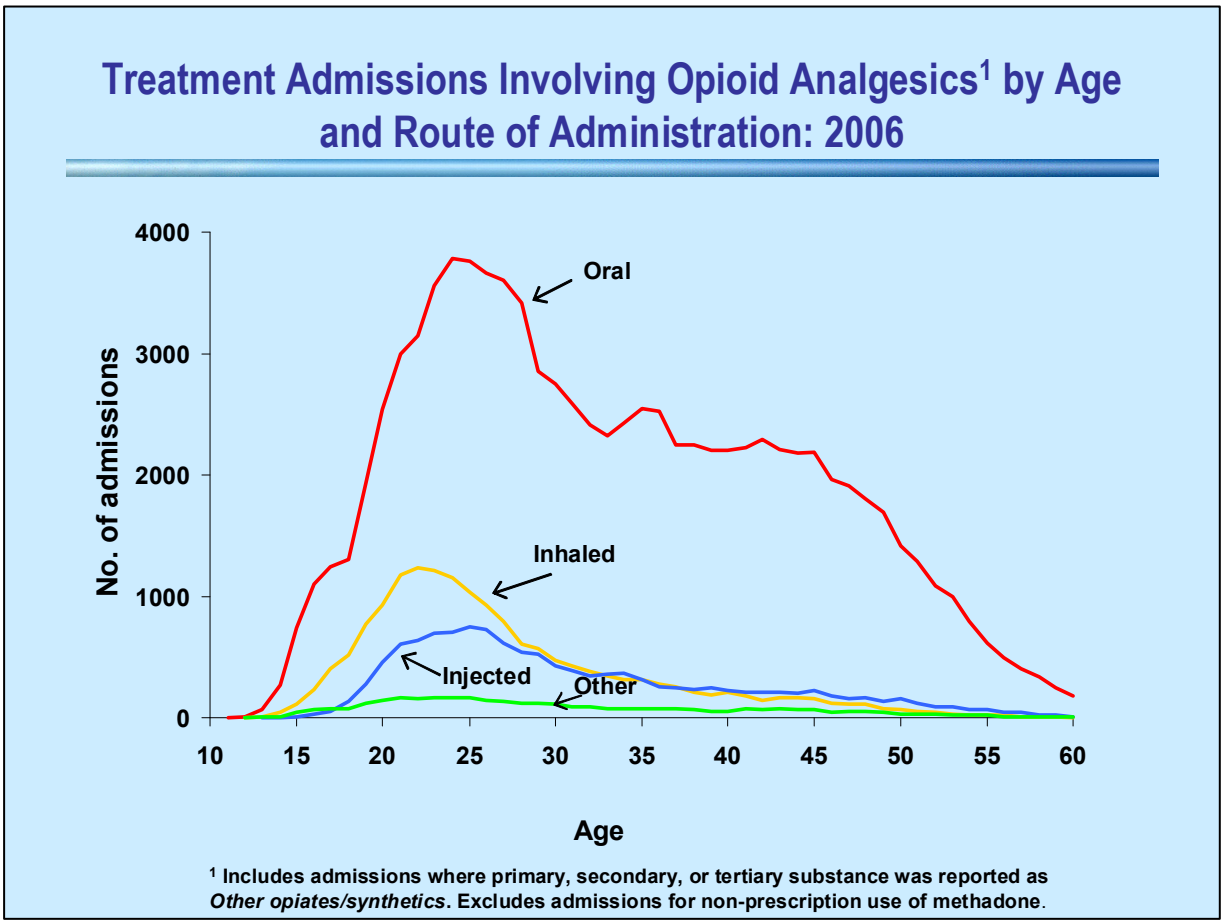


Figure 8 compares the characteristics of opioid analgesic admissions in 1997 to those in 2006. The proportion of males as remained virtually unchanged, while the proportion of whites has increased slightly from 83 percent to 88 percent. Pain reliever admissions in 2006 were younger than those in 1997, with the proportion under the age of 20 having doubled and the proportion over 30 having dropped by a third. In 2006, there were relatively more "new users" admitted to treatment, new users being those who used the drug for 3 years or less before admission to treatment. The proportion of admissions taking pain relievers orally or by injection decreased, while the percent of those inhaling the drugs increased.

Figure 8

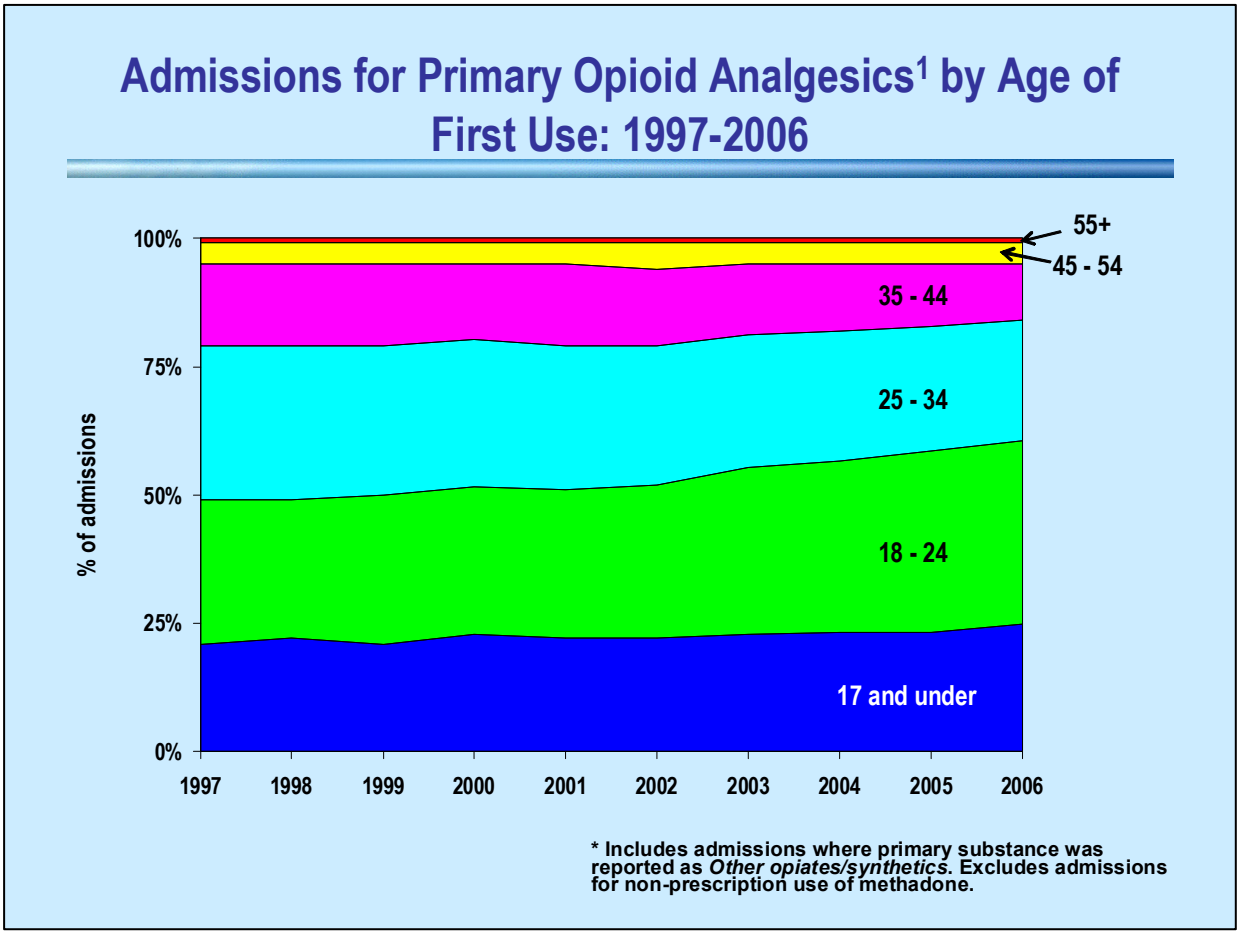
Characteristics of Opioid Analgesic[1] Admissions 1997 and 2006

	1997	2006
Male	56%	57%
White (non-Hispanic)	83%	88%
Less than 20 years of age	5%	11%
20 to 29 years	16%	37%
30 years or more	79%	52%
New users (3 yrs use or less)	20%	28%
Oral	78%	74%
Injected	14%	10%
Inhaled	3%	13%

[1] Includes admissions where primary, secondary, or tertiary substance was reported as *Other opiates/synthetics*. Excludes admissions for non-prescription use of methadone.

Figure 9

Figure 9 chart shows age at first use among primary opioid analgesic admissions between 1997 and 2006. Note that that age at first use for opioid analgesic admissions decreased during the time period, mainly driven by the increase in those initiating use between the ages of 18 and 24. Over the entire 10 year span, age of first use occurred before the age of 25 for at least half of all pain reliever admissions. Initiates over the age of 45 accounted for only 5 percent of all admissions. This suggests that the reason for initiation was other than legitimate medical use in a large proportion of cases. If reason for initiation was prescribed medical treatment of pain, we would expect age at first use to be more heavily concentrated in the older age groups.



Conclusions

- The number of treatment admissions for abuse of opioid analgesics has risen sharply since 1997, following the introduction of Oxycontin.
- In States identifying specific pain relievers, the increase in these admissions can be attributed almost entirely to oxycodone.
- The data suggest that propoxyphene accounts for a very small fraction of pain reliever admissions.
- The youngest opioid analgesic admissions are the most likely to inhale on inject the drug.
- First use of opioid analgesics by persons admitted to treatment for abuse of these drugs is more likely to occur before the age of 25 than after the age of 25.

References

Substance Abuse and Mental Health Services Administration, Office of Applied Studies, *Treatment Episode Data Set (teds): 1996-2006. National Admissions to Substance Abuse Treatment Services*, DASIS Series: S-43, DHHS Publication No. (SMA) 08-4347, Rockville, MD, 2008.

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee

January 30, 2009

Discussion Topics

Propoxyphene-containing products were first approved in 1957 and are currently widely prescribed. The efficacy of propoxyphene has been called into question, particularly whether there is any contribution to efficacy for combination products containing propoxyphene and acetaminophen.

There are also questions about the safety of propoxyphene based, in part, on nonclinical data that indicate propoxyphene is capable of prolonging cardiac conduction time.

The efficacy and safety of propoxyphene-containing products will be reviewed to assess the overall risk to benefit balance of these products. The committee will be asked to consider the benefits of continued marketing of these products or whether these products should no longer be marketed in the U.S. If the committee recommends continued marketing of these products, the need for modifications to the labeling will be discussed. If the committee recommends removal of propoxyphene from the U.S. market, further discussion will include what analgesics would be appropriate to fill the void.