

Testimony Before the Select Committee on Small Business,

United States Senate

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Studies involving Darvon and its combinations conducted at the Mayo Clinic have primarily involved treatment of the patient with advanced cancer. For these patients our single most overriding responsibility is relief of pain. Unfortunately in this vital area we as physicians frequently perform rather poorly. In our medical schools instruction in the practical use of drugs is often inadequate. Our judgment in prescribing drugs for pain is quite comparable to the public's judgment in purchasing over the counter drugs for pain. Both are largely governed by advertising. We as doctors are no less vulnerable than the public at large to the persuasive influence of Madison Avenue. For vivid evidence of this you only have to look at the Physicians Desk Reference. This is a manual distributed free of charge to all physicians each year by the Pharmaceutical Manufacturers Association. It lists all prescription drugs promoted by pharmaceutical companies. In the 1978 edition there were 149 drugs advertised for relief of pain by oral route of administration.

More than a decade ago, because we were disturbed by our ineptitude in the management of pain of the cancer patient, we initiated at the Mayo Clinic carefully controlled research studies to evaluate the relative effectiveness of the many medications for pain that were available to us. Our only vested interest was our patient in pain and these studies were not paid for by any drug company.

To insure that the results of these studies could not be in any way influenced by us or by any preconceived ideas of our patients, we double blinded the studies. By this I mean that all of the pain medications we gave to the patients looked exactly alike and were identified only by code number. Neither we nor the patients could tell which was which. The drugs were administered in randomized sequences and we only broke the code when the entire study was completed.

In our first study we looked at analgesic drugs in their pure form and this study compared nine different analgesics as well as placebo or sugar pill. It involved close to 600 drug evaluations. Our results with the four drugs that are pertinent to this hearing are displayed in Table 1. As in all studies, even with cancer pain, there will be a substantial number of patients who claim relief with sugar pills. Darvon showed some advantage over sugar pills, but this was small and not statistically significant - that is the difference could easily have occurred by accident. Acetaminophen or APAP - commonly marketed as Tylenol or Datril - showed a much more substantial degree of relief; and surprisingly, leading the pack, two simple aspirin tablets. The superiority of aspirin over Darvon was statistically significant - by that I mean that the odds are greater than 20 to 1 that this difference did not occur by chance alone. These results were quite startling to us because at that time Darvon led the market in prescription drug sales. (1)

It can reasonably be argued that although interesting, these results really aren't a fair evaluation of Darvon. Although

Darvon is sold in pure form, it is usually marketed in combination with aspirin or APAP or with APC as the so-called Darvon compound. In a second study we, therefore, looked at aspirin alone compared to aspirin plus a variety of other drugs that are commonly marketed in aspirin containing drug combinations. This study involved 100 patients in 1000 separate drug evaluations. In Table 2 you can see that again aspirin showed a significant advantage over placebo. The addition of a full dose of Darvon to aspirin, however, provided essentially no improvement in pain relief. You can also see that within this same study it was demonstrated that two prescription drugs did provide better relief than aspirin alone. These are the combinations of either Talwin (Pentazocine) or codeine with aspirin. The time honored codeine - aspirin combination also showed a statistically significant advantage to the Darvon - aspirin combination - again the odds better than 20 to 1 that this difference did not occur by accident.

Based on our results we would have to conclude that if Darvon alone has any pain relieving effect, this is trivial and simply doesn't match up to common, inexpensive over-the-counter drugs. We must also conclude that the combination of Darvon with aspirin holds no advantage to aspirin alone, and if a patient requires a stronger analgesic the physician should prescribe some other more effective drug regimen.

These, however, are just the results from a single institution; and although we feel our studies were of sound design and conducted meticulously and analyzed without bias, it is possible that there could be some unrecognized distorting quirk in our methodology or

that cancer pain is not representative of other types of pain. We only really feel comfortable with clinical experimental results when they are confirmed by others.

Over the remainder of my testimony I'd like to review all of the published medical literature of which I am aware that pertains to the clinical evaluation of Darvon as an analgesic agent. Here I'm only going to refer to the controlled, randomized, double-blind studies. When your endpoint of a study is as subjective as pain relief, these are the only kind of studies you can believe.

In all, we found 34 such studies involving various types of pain and these are listed in the bibliography which I have supplied. In Table 3 I've displayed the results of the 23 studies in which standard doses of Darvon alone were compared with placebo. You can see that none of the studies favored sugar pills. In four of the studies there was essentially no difference between Darvon and sugar pills. In seven the results favored Darvon but the difference was not statistically significant. Our first study is included in these. In 12 of the 20 studies Darvon was favored and the results were statistically significant. Based on these overall results it is reasonable to conclude that Darvon alone does have some analgesic activity although its not very striking. If, for example, aspirin alone had been tested in the 23 study populations of patients with relatively mild pain, it could be reasonably anticipated that aspirin would have been strongly favored in all 23.

In Table 4 I've displayed the results of 14 studies in which Darvon alone at standard doses was compared to common over the counter drugs - aspirin alone, acetaminophen or APAP alone, or APC.

Among this group there were no studies favoring Darvon, in one study there was no difference, and in the remaining 13 of the 14 studies the over-the-counter drugs were favored over Darvon. In seven of these the differences were statistically significant.

In Table 5, I've shown the studies involving standard doses of Darvon in combination with aspirin, APAP, or APC compound. The results of these combinations are compared to the results of the over-the-counter drugs used alone without the addition of Darvon. Three studies favored Darvon combinations, three favored the over-the-counter drugs used alone, and 6 of the 12 studies showed no difference. Its of interest that there are two other studies of this kind that have not appeared in the medical literature although they have been highly publicized in lay media. It seems that some ad men at a proprietary pharmaceutical company must have been looking at the overall Darvon literature and decided they could make a real good sales pitch by showing their over-the-counter analgesic was just as good as Darvon compound. So they proceeded to contract out for two clinical research studies and that is exactly what the studies showed. Perhaps you remember the subsequent ads that appeared on the media displaying an Anacin tablet side by side with a Darvon compound capsule and accompanied by the advertising claim that Anacin had been shown in two medical studies to provide just as much relief as the high priced prescription item.

In Table 6 I've shown the results of ten studies in which combinations of Darvon plus over the counter drugs were compared to combinations of codeine or Talwin (pentazocine) plus over-the-

2

counter drugs. Eight of the 10 comparisons favored either the codeine or the Talwin combinations.

In short, the results of our Mayo Clinic studies are entirely consistent with preponderance of the studies done by other investigators. It can be concluded that Darvon does have some pain relieving activity but this is very minor and does not match up to the safer and readily available over the counter drugs. Combinations of Darvon with aspirin, APAP or APC are not better than using the over-the-counter drugs alone. If the patient requires more pain relief than over-the-counter drugs can provide, the physician should not prescribe Darvon compound or Darvocet N because he has other more effective drug combinations available to him. The only real difference between the Darvon combinations and over-the-counter analgesics is the price. If you use 1978 Redbook average wholesale prices and add on a 30% markup for retail sales, the price for 100 tablets of Darvocet N plus aspirin is \$11.50 and for 100 tablets of Darvon N plus APAP is \$13.50. If you are a careful shopper you can go to your corner drug store or super-market and get 100 two tablet doses of APAP for about \$2.00 or 100 two tablet doses of aspirin for less than \$1.00.

To summarize, I will answer specifically the four questions addressed to me when I was invited to testify before this committee. The first question, from my knowledge and experience what is the relative efficacy of Darvon as compared to other analgesics? In my judgment Darvon is inferior to the commonly marketed aspirin, acetaminophen, or APC combinations. The second question, is it possible to treat patients for pain with analgesics other than Darvon? Absolutely. For patients with mild pain you can do just

as good a job, if not better, with aspirin or APAP alone, and you can do it at about one tenth of the price. With regard to the use of Darvon combinations for the treatment of moderate pain, you can achieve significantly superior pain relief using combinations of aspirin with codeine, aspirin with oxycodone, or aspirin with pentazocine or Talwin. 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. The third question, is it possible to maintain good medical practice without the use of Darvon? Yes. I would seriously question whether the use of Darvon is good medical practice at all. And the last question, what is the medical justification for using Darvon? I know of none.

3

See questions for the two MD's.

Table 1

Mayo Clinic Evaluation of Analgesics in Pure Form

<u>Agent</u>	<u>Patients</u>	<u>Percent Pain Relief</u>
Aspirin, 650 mg.	57	62
Acetaminophen (APAP, 650 mg)	57	50
Darvon HCl, 65 mg.	57	43
Placebo	57	32

Aspirin superior to Darvon, $p < 0.05$

Reference: 22

Table 2

Mayo Clinic Evaluation of Analgesic Combinations

<u>Regimen</u>	<u>Patients</u>	<u>Percent Pain Relief</u>
Codeine, 65 mg. + ASA	100	55
Talwin, 25 mg. + ASA	100	54
Darvon N, 100 mg. + ASA	100	41
Aspirin alone, 650 mg. (ASA)	100	39
Placebo	100	23

Codeine + ASA superior to Aspirin alone and to Darvon + ASA $p < 0.05$

Reference: 23

Table 3

Published Comparisons of Darvon* with Placebo

<u>Study Result</u>	<u>Number of Studies</u>
Strongly favoring Darvon	12
Favoring Darvon	7
No difference	4
Favoring placebo	0
Strongly favoring placebo	0

*Darvon at standard doses. Darvon HCl 32.5 to 65 mg;
Darvon N 100 mg.

References: 1,4,5,6,7,9,10,11,12,13,15,16,18,23,26,
28,31,32,33,34

Table 4

Published Comparisons of Darvon with
Over-the-counter (OTC) Analgesics
(Aspirin, Acetaminophen (APAP), or APC)

<u>Study Result</u>	<u>Number of Studies</u>
Strongly favoring Darvon	0
Favoring Darvon	0
No difference	1
Favoring OTC drugs	6
Strongly favoring OTC drugs	7

References: 5,12,13,15,16,19,20,21,23,26,29,33

Table 5

Published Comparisons of Darvon plus
OTC Drugs (Aspirin, APAP, APC) versus
OTC Drugs Used Alone

<u>Study Result</u>	<u>Number of Studies</u>
Strongly, favoring Darvon + OTC	2
Favoring Darvon + OTC	1
No difference	6
Favoring OTC alone	2
Strongly favoring OTC alone	1

References: 2,3,10,11,12,17,18,19,22,24,26,28

Table 6

Published Comparisons of Darvon plus OTC
Drugs versus Codeine or Talwin plus OTC Drugs

<u>Study Result</u>	<u>Number of Studies</u>
Strongly favoring Darvon + OTC	0
Favoring Darvon + OTC	0
No difference	2
Favoring Codeine or Talwin + OTC	4
Strongly favoring Codeine or Talwin + OTC	4

References: 5,6,10,12,22,23,25,26,27

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