

# **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*

**November 14, 2008**

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

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**M E M O R A N D U M**

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DATE: November 12, 2008

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 November 14, 2008 ALSDAC Meeting to Discuss NDA  
22-321 for Embeda (morphine sulfate extended release with sequestered  
naltrexone hydrochloride) Capsules

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On the second day of this session of the ALSDAC, we will be discussing another application for an extended-release potent opioid product intended to introduce modifications that would potentially reduce the abuse liability of the drug. This application, submitted by AlPharma Pharmaceuticals, is for a modified-release formulation of morphine.

As noted in my memo for the first day of our meeting, the abuse of prescription opioid products is a growing public health problem in the United States. While morphine has not shown a particularly high signal of abuse in recent years compared to the other potent opioids, it is clear that as we put more efforts into controlling the abuse of one opioid, abusers turn to other available products. Just to cite two examples, we have seen this phenomenon occur when heroin addicts turned to Talwin (before it was reformulated with an antagonist) when the heroin market dried up in the 1970s and more recently with the abuse of methadone increasing as more and more oversight of OxyContin prescribing has been instituted over the past eight years. Morphine itself has an established history of abuse resulting in addiction, overdose and death that goes back well over a century so it is essential as part of an overall abuse reduction program that we provide appropriate risk mitigation strategies, including the development of abuse-resistant formulations, for morphine products as we institute these changes for the other potent opioid products.

According to the sponsor:

EMBEDA™ is a capsule comprised of individual pellets containing morphine sulfate with a sequestered naltrexone hydrochloride inner core. If taken as prescribed, only morphine is liberated in an extended-release profile to provide relief of moderate to severe chronic pain for up to 24 hours. The opioid antagonist naltrexone is designed to remain sequestered in the core of each pellet. However, upon crushing, dissolving, or chewing of the pellets, both the morphine and naltrexone would be available and absorbed as an immediate-release dosage form. Uniquely, the released and absorbed naltrexone would:

- mitigate the liking and euphoric effects of the morphine
- deter drug tampering and diversion

During the second say of this ALSDAC session, we will again be asking you to address the adequacy of the abuse-resistant features of the product as described in the sponsor's application and to consider any increased risks that might be associated with the formulation for legitimate patients.

And, once again, we are most grateful for your time and efforts in assisting us with this important task.

## Modified-Release Oral Morphine Products AC Background

There are currently four approved modified-release oral morphine products on the market; MS Contin, Oramorph, Kadian, and Avinza. All are indicated for the management of moderate-to-severe pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time, except Oramorph, which is indicated for the relief of pain in patients who require opioid analgesics for more than a few days.

MS Contin (Purdue Pharma) was the first of the modified-release morphine products to be approved (May, 1987). It is available as 15mg, 30mg, 60mg, 100mg, and 200mg tablets for dosing every 12 hours. A major labeling change occurred in May, 2003 with the addition of a Boxed Warning which included restriction of the 100mg and 200mg doses to opioid-tolerant patients, as illustrated below.

**\*100 mg and 200 mg are for use in opioid-tolerant patients only**

### **WARNING:**

**MS CONTIN contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.**

**Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing MS CONTIN in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.**

**MS CONTIN Tablets are a controlled-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.**

**MS CONTIN Tablets are NOT intended for use as a prn analgesic.**

**MS CONTIN 100 and 200 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.**

**MS CONTIN TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, DISSOLVED, OR CRUSHED. TAKING BROKEN, CHEWED, DISSOLVED, OR CRUSHED MS CONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.**

Oramorph SR (Xanodyne) was approved in August, 1991. It is available as in 15mg, 30mg 60mg, and 100mg tablets for dosing every 8 to 12 hours. The label has not had any major changes since approval, and does not contain a Boxed Warning or restrictions regarding opioid-tolerant patients.

Kadian (Alpharma) was approved in July, 1996. Initially approved doses were 20mg, 50mg, and 100mg capsules. Since approval, 10mg, 30mg, 60mg, 80mg, and 200mg capsules have been added. The dosing for Kadian is every 12 to 24 hours. The capsules are to be swallowed whole or may be sprinkled on applesauce. A Boxed Warning with language restricting use of the 100mg and 200mg capsules to opioid-tolerant patients, similar to that for MS Contin (above), was added to the label in October, 2006.

The most recently approved modified-release morphine product is Avinza (Ligand), approved March, 2002. It is available as 30mg, 60mg, 90mg, and 120mg capsules for dosing every 24 hours. The capsules may be swallowed whole or sprinkled on applesauce. Unlike MS Contin, Oramorph SR, and Kadian which do not have a

maximum daily recommended dose, Avinza has a daily dose limited to 1600mg due to the presence of fumaric acid in the formulation.

#### Dose-dumping in the presence of alcohol

As a result of the finding in 2004 that Palladone (modified-release hydromorphone) exhibited dose-dumping *in vivo* when co-ingested with alcohol, which resulted in the withdrawal of Palladone from the market, Sponsors for all modified-release opioids were required to study the effect of alcohol on the dissolution of their product *in vitro*, followed by *in vivo* testing as needed. The dissolution of all modified-release opioids was assessed in the presence of 40% alcohol. Avinza and Kadian were also studied using 4% and 20% alcohol.

Avinza showed substantial release of drug within the first hour of dissolution. Kadian had complete drug release once it was placed in a buffer solution containing alcohol. MS Contin and Oramorph SR showed minimal effect of drug release in the presence of 40% alcohol.

Alpharma went on to conduct *in vivo* testing with alcohol, the results of which showed there was not an increase in drug release in the presence of alcohol. These results superseded those from the *in vitro* studies.

In October, 2005, language was added to the Avinza label regarding the *in vitro* alcohol interaction. Wording was added to the Pharmacokinetic section describing the *in vitro* studies and results, and the following language was added to the Box Warning and throughout the label.

“Patients must not consume alcoholic beverages while on Avinza therapy. Additionally, patients must not use prescription or non-prescription medications containing alcohol while on Avinza therapy. Consumption of alcohol while taking Avinza may result in the rapid release and absorption of a potentially fatal dose of morphine.”

Oramorph SR, Kadian, and MS Contin labels contain the standard wording regarding alcohol use stating that the drug may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

## History of Opioid-Antagonist Combination Products AC Background

Combination products comprised of an opioid plus an opioid antagonist are a special case of regulation 21CFR 300.50(a), which reads “Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effect...Special cases of this rule are where a component is added...To minimize the potential for abuse of the principle active ingredient.” There are currently two such oral products which have been approved; Talwin NX (pentazocine/naloxone) and Suboxone (buprenorphine/naloxone). Naloxone HCL was added to both products in order to deter intravenous abuse of the drugs.

Talwin (pentazocine HCL), an opioid agonist/antagonist was initially approved in 1969 for the relief of moderate-to-severe pain. An increasing frequency of cases of abuse, diversion, overdose and death were reported to the Agency through the late 1970’s. Reports included intravenous abuse of crushed tablets. Talwin was added to Schedule IV of the CSA in 1979. In 1981, a report to the Agency from NIDA discussed the ongoing increase in addiction to Talwin and the need to alter labeling to reflect the postmarketing experiences with addiction and to permit treatment with methadone. However, reports of abuse and diversion, particularly the crushing and injecting of the product continued in spite of the scheduling of Talwin and labeling changes. At the request of the Agency, the product was reformulated with naloxone in 1982 as Talwin NX (pentazocine 50mg/Naloxone 0.5mg). The original Talwin was withdrawn from the U.S. market in 1983. Naloxone, when administered orally at 0.5mg, was shown to have no pharmacologic activity, however when administered parenterally it is an antagonist to pentazocine and other narcotic analgesics.

Suboxone is a fixed-ratio combination drug consisting of buprenorphine HCL (a partial mu opioid agonist) and Naloxone HCL (a full opioid antagonist). It was approved in October, 2002 for the treatment of opioid dependence, along with Subutex, which is buprenorphine HCL without the addition of Naloxone. The two products are interchangeable in terms of the pharmacokinetics of buprenorphine.

Suboxone was designed to be administered sublingually, where the absorption of the Naloxone component caused no clinically significant effect although plasma levels were measurable. In clinical pharmacology studies, the Sponsor showed that, if Suboxone was improperly administered via the intravenous route, the naloxone component would become available and block the euphoric effects of the opioid component or precipitate opioid withdrawal.

No studies have ever been done to assess whether the addition of naloxone to these products has resulted in a decrease in abuse.



**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: October 15, 2008

To: Bob Rappaport, MD, Director  
Division of Analgesia, Anesthesia and Rheumatology  
Products

Through: Kellie Taylor, Pharm D, MPH, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Richard Abate, RPh, MS, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Medication Error Postmarketing Safety Review of the  
Manipulation of Oral Morphine Extended-Release Products

Drug Name(s): MS Contin (morphine sulfate extended-release) tablets  
Oramorph SR (morphine sulfate extended-release) tablets  
Kadian (morphine sulfate extended-release) capsules  
Avinza (morphine sulfate extended-release) capsules

Application  
Type/Number: MS Contin (NDA 19-516)  
Oramorph SR (NDA 19-977)  
Kadian (NDA 20-616)  
Avinza (NDA 21-260)

Sponsor: Purdue Pharma, LP (MS Contin)  
Xanodyne Pharmaceuticals (Oramorph SR)  
Alpharma Pharmaceuticals (Kadian)  
King Pharmaceuticals (Avinza)

OSE RCM #: RCM 2008-1515

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## **EXECUTIVE SUMMARY**

The Division of Medication Error Prevention and Analysis identified 22 cases of morphine sulfate extended-release products being manipulated prior to use (both misuse and abuse.) While not all of the cases of abuse indicated how the product was manipulated, all reports indicated the method of administration. Crushing was the most reported method of manipulation in cases of abuse (n=5), followed by chewing (n=3), and dissolving (n=2). Injection is the most commonly reported route of administration when these products are abused (n=11). We recommend consideration be given during review of the application as to whether these known methods of misuse and abuse will be impacted by the abuse deterrents in the Embeda formulation given the method of administration for abuse was injection rather than oral administration.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This post-marketing safety review of medication errors is written in response to a request from the Division of Analgesia, Anesthesia, and Rheumatology Products (DAARP) to evaluate medication error cases involving the manipulation of morphine sulfate extended-release from the Adverse Events Reporting System (AERS). This summary was requested in preparation for the November 14, 2008 Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) Meeting on an abuse-deterrent formulation of a product under review, Embeda (morphine sulfate extended-release with sequestered naltrexone hydrochloride) capsules (NDA #22-321).

### **1.2 REGULATORY HISTORY**

The oral morphine sulfate extended-release products have been marketed for more than 20 years.

The first extended-release morphine product, MS Contin (morphine sulfate extended-release) tablets (NDA # 19-516) was approved May 29, 1987. This approval was followed by Oramorph SR (morphine sulfate extended-release) tablets (NDA #19-977) approved August 15, 1991; Kadian (morphine sulfate extended-release) capsules (NDA #20-616) approved July 3, 1996, and, most recently Avinza (morphine sulfate extended-release) capsules (NDA #21-260) approved March 20, 2002.

The extended-release morphine products are not intended to be crushed or chewed. The professional labeling for all four marketed products contains a black box warning against chewing or crushing the tablet or the content of the capsules and repeats this warning in the Dosage and Administration section. In addition, the professional labeling of the capsule formulations (Kadian and Avinza) also include warnings against dissolving the contents of the capsules along side the warnings for chewing and crushing.

### **1.3 PRODUCT INFORMATION**

Embeda (morphine sulfate extended-release with sequestered naltrexone hydrochloride) capsules (NDA #22-321) are proposed to be indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an

extended period of time. The 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, and 100 mg strength capsules will be dosed as one capsule by mouth once or twice daily. The capsule strength is based on the morphine sulfate component of the product. The capsules may be swallowed whole or opened and the contents sprinkled over apple sauce prior to oral administration. The product, Embeda, is most similar to the existing morphine extended-release product, Kadian, as they have the same manufacturer, Alpharma Pharmaceuticals.

The amount of naltrexone in this product is not intended to block all or most of the effects of the morphine sulfate if the product is manipulated for abuse, but rather the naltrexone is intended to block enough of the morphine effects to reduce the euphoria drug abusers seek. The ratio of morphine to naltrexone contained within the capsules is 24 to 1. The design of the formulation of Embeda is intended to result in no clinical effects from the sequestered naltrexone hydrochloride when the product is taken as directed. However, crushing, dissolving, or chewing the extended-release pellets within the capsules in an attempt to misuse or abuse the product results in the rapid release and absorption of both the morphine sulfate and naltrexone hydrochloride when taken orally. The misuse and abuse of this product via injection has not been studied.

## **2 METHODS AND MATERIALS**

### **2.1 ADVERSE EVENTS REPORTING SYSTEM (AERS) SELECTION OF CASES**

The Division of Medication Error Prevention and Analysis searched the FDA AERS database on August 25, 2008 to identify post-marketing cases involving improper manipulation of Kadian and Avinza Capsules and on September 17, 2008 for cases involving MS Contin and Oramorph SR tablets. Only the tradenames, “Avinza,” “Kadian,” “MS Contin,” and “Oramorph SR” were used as search criteria to limit the cases to morphine sulfate extended-release formulations. No MedDRA reaction terms were included in the search in an attempt to obtain all cases associated with these products. Additionally, we searched the narratives of the retrieved cases for the following terms regarding methods of manipulation of these products: crack, crush, cut, grind, melt, snort, chew, inject, inhale, and dissolve.

Reports were reviewed for duplicates and grouped together as cases.

## **3 RESULTS**

### **3.1 ADVERSE EVENTS REPORTING SYSTEM (AERS) CASES**

Our initial searches of the AERS database identified a total of 2,063 cases involving extended-release morphine products. Among these cases, a narrative search of manipulation terms identified a total of 95 cases. Seventy-three cases were excluded from further analysis because the cases described manipulation of a concomitant medication rather than the extended-release morphine product, the search term described the route of administration of a concomitant medication or a product complaint regarding half-full capsules or undigested capsules. Thus, 22 cases involving improper manipulation of extended-release morphine products were evaluated (Appendix A).

Of these 22 cases, five cases involved medication errors in which healthcare professionals manipulated the extended-release morphine tablets for ease of

administration (e.g. crushing the tablets to administer through a G-tube or sprinkle over applesauce). One additional case involved a wrong technique medication error involving a patient who always crushes larger tablets prior to administration. This patient received a generic of MS Contin which was too large for her to swallow without crushing.

The remaining 16 cases involved the manipulation of morphine sulfate extended-release products for the purpose of abuse. The breakdown of manipulation terms of these 16 cases includes the following: five cases (n=5) including the term “crush;” five cases (n=5) including the term “inject;” three cases (n=3) including the term “chew;” two cases (n=2) including the term “dissolve;” and one case (n=1) including the term “snort.” Finally, two cases identified with term “inject” noted the method of manipulation prior to administration as heating or boiling.

When reviewing the narratives, the identified methods of administration in these 16 cases of abuse can be broken down as injected (n=11), swallowed or ingested (n=3), and inhaled through the nose or snorted (n=2).

#### **4 DISCUSSION**

Our analysis of the 22 cases of improper manipulation of morphine sulfate extended-release products suggests the majority of misuse is a result of intentional abuse. Five medication error cases indicate healthcare professionals are either unaware these are extended-release products or unaware of the consequences of crushing these products to ease patient administration. One case resulted from inappropriate prescribing of morphine sulfate extended-release tablets for a patient who routinely crushes large size medication prior to administration.

While not all of the abuse cases indicated how the product was manipulated, all noted the method of administration. When described in the report, the methods of manipulations included crushing, chewing, dissolving, and heating. The most prevalent method of manipulation was crushing (n=5).

Regardless of the method the manipulation, the route of administration of morphine sulfate extended-release products utilized most often by abusers in the identified cases was injection (n=11). This fact may be important to consider because Embeda is intended for oral administration, and the Applicant for Embeda has only tested the effects of administering manipulated products orally. Thus, it is unknown what the potential effects of injecting this product following manipulation.

#### **5 CONCLUSION**

The Division of Medication Error Prevention and Analysis identified cases of morphine sulfate extended-release product manipulation. Injection is the most commonly reported route of administration when these products are abused, and the most prevalent method of manipulation was crushing. Since the Applicant only tested the effects of manipulation orally, we recommend consideration be given during evaluation of the application as to whether these known methods of misuse and abuse are impacted by the abuse deterrents in Embeda.

## **6 REFERENCES**

### **6.1 ADVERSE EVENTS REPORTING SYSTEM (AERS)**

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers who have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). Furthermore, raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

## APPENDICES

### Appendix A: AERS cases

ISR number	Receipt date	Medication error/ abuse	Term	Route of Administration
4087931-X	4/2/2003	Abuse	Chew	Oral
4311135-6	3/2/2004	Abuse	Chew	Oral
4915868-X	2/14/2006	Abuse	Chew	Oral
4236314-8	11/14/2003	Abuse	Crush	Injected
4636784-7	4/14/2005	Abuse	Crush	Injected
4903419-5	2/3/2006	Abuse	Crush	Injected
5600261-7	1/23/2008	Abuse	Crush	Snorted
5835098-7	8/6/2008	Abuse	Crush	Injected
3066657-5	3/27/1998	Abuse	Dissolve	Injected
4307252-7	2/26/2004	Abuse	Dissolve	Injected
3493068-0	4/26/2000	Abuse	Inject	Injected
4270256-7	12/17/2003	Abuse	Inject	Injected
5228159-7	1/30/2007	Abuse	Inject	Injected
5577880-X	12/31/2007	Abuse	Inject	Injected
5750440-3	5/28/2008	Abuse	Inject	Injected
4309801-1	3/1/2004	Abuse	Snort	Snorted
3764841-6	7/24/2001	Medication Error	Crush	Oral
3937410-2	6/20/2002	Medication Error	Crush	Oral
3991887-5	10/10/2002	Medication Error	Crush	Oral
4021604-4	12/6/2002	Medication Error	Crush	Oral
4024757-7	12/10/2002	Medication Error	Crush	G-tube
4595709-3	2/24/2005	Medication Error	Crush	Oral

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/s/

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Richard Abate  
10/15/2008 09:34:55 AM  
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor  
10/15/2008 10:38:56 AM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
10/15/2008 10:44:25 AM  
DRUG SAFETY OFFICE REVIEWER



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**DATE:** October 15, 2008

**TO:** Bob Rappaport, M.D., Director  
Division of Anesthesia, Analgesia and Rheumatology Products  
(DAARP)

**THRU:** Michael Klein, Ph.D., Director  
Silvia Calderon, Ph.D., Team Leader

**FROM:** James M. Tolliver, Ph.D., Pharmacologist  
Controlled Substance Staff (CSS)

**Subject:** **Background Package for Advisory Committee** NDA 22-321  
EMBEDA (Morphine Sulfate Extended-Release with Sequestered  
Naltrexone Hydrochloride) – Capsules, 20, 30, 50, 60, 80 and 100 mg  
strengths  
**Indication:** Management of moderate to severe pain when a  
continuous, around-the-clock analgesic is needed for an extended period  
of time.  
**Company:** Alpharma Pharmaceuticals LLC

This memorandum provides comments to the Division of Anesthesia, Analgesia, and Rheumatology Products regarding abuse deterrent properties of EMBEDA™ (Morphine Sulfate Extended-Release with Sequestered Naltrexone Hydrochloride) Capsules.

**Summary:**

Alpharma Pharmaceuticals LLC has filed NDA 22-321 in support of EMBEDA™. The product constitutes individual pellets containing morphine sulfate and a sequestered naltrexone hydrochloride core. If taken as prescribed, morphine is released over a period of 12 hours providing around-the-clock relief of moderate to severe pain. The claim is made by the Sponsor that upon crushing or chewing the pellets, both morphine and naltrexone are released and absorbed as an immediate release dosage form. The released and absorbed naltrexone will abate the liking and euphoric effects of the morphine.

**Background:**

Data from the National Survey on Drug Use and Health (NSDUH) and the Drug Abuse Warning Network (DAWN) show that the nonmedical use or abuse of prescription opioids is a significant problem in the United States. This has resulted in increased rates

of opioid-related mortality and admissions to emergency room departments and publicly funded substance abuse treatment facilities. Information on routes of administration involved in the nonmedical use or abuse of prescription opioids is limited. A few literature articles report that oral administration is the main route by which prescription opioids are used nonmedically. However a small percentage of individuals abuse prescription opioids by injection following crushing of oral drug products.<sup>1</sup> As noted by the Sponsor, persons deliberately and habitually abusing opioids are likely to tamper with controlled-release formulations in hopes of obtaining a large dose at one time (dose dumping) and using the concentrated dose to induce an immediate euphoria.

CSS-CDER has reviewed the data provided by the Sponsor concerning the abuse resistant properties of EMBEDA™. However, specific details of the report are not included in this review because of confidential proprietary reasons related to the chemistry and properties (extraction and solubilization) of the proposed formulation.

**Conclusions:**

Studies by the Sponsor demonstrate that under selected conditions, morphine can be efficiently extracted in isolation from naltrexone from EMBEDA™ capsules. Once extracted, the morphine could be subject to abuse by various routes of administration.

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<sup>1</sup> Havens et al. (2007). Drug and Alcohol Dependence, 87: 98-102. and Rees Davis and Johnson (2008): Drug and Alcohol Dependence, 92: 267-276

## Discussion Points – Embeda

The committee will be asked to discuss how much impact on abuse and misuse might be expected from a modified-release opioid product formulated with a sequestered opioid antagonist. Discussion points will include: how effective might the presence of an antagonist be toward creating a less defeatable product, how should the ease of separation of the opioid and the antagonist be considered in the assessment of these products, and whether a minimum standard can be set for how readily releasable the antagonist should be upon physical manipulation. Additionally, the committee will be asked to discuss the potential safety implications for exposure of legitimate patients to low levels of the antagonist.

The committee will also be asked to discuss the available methods for assessing the impact of a novel formulation on abuse and misuse in the community once the product has been approved, and whether the applicant's proposed evaluation plan for assessing abusability of their reformulated product will provide the information necessary to make that type of determination. Finally, the committee will be asked to discuss how much information about the physical attributes of the new formulation should be included in the product label.

# **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*

**November 13 & 14, 2008**

**Common Materials**

### **Table of Contents**

#### Background Materials

1. Summary of National Survey on Drug Use and Health (NSDUH)
2. Summary of Drug Abuse Warning Network (DAWN) Data
3. Treatment Episode Data Set (TEDS)
4. Literature Overview: Relative Opioid Likeability

## Summary of National Survey on Drug Use and Health (NSDUH)

NSDUH is the primary source of statistical information on the use of illegal drugs by the U.S. population. Conducted by the Federal Government since 1971, the survey collects data by administering questionnaires to a representative sample of the population through face-to-face interviews at the respondent's place of residence. The survey is sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), U.S. Department of Health and Human Services, and is planned and managed by SAMHSA's Office of Applied Studies (OAS). Data collection is conducted under contract with RTI International, Research Triangle Park, North Carolina.<sup>1</sup>

NSDUH collects information from residents of households and noninstitutional group quarters (e.g., shelters, rooming houses, dormitories) and from civilians living on military bases. The survey excludes homeless persons who do not use shelters, military personnel on active duty, and residents of institutional group quarters, such as jails and hospitals.

Since 1999, the NSDUH interview has been carried out using computer-assisted interviewing (CAI). Most of the questions are administered with audio computer-assisted self-interviewing (ACASI). ACASI is designed to provide the respondent with a highly private and confidential means of responding to questions to increase the level of honest reporting of illicit drug use and other sensitive behaviors and problems. Less sensitive items are administered by interviewers using computer-assisted personal interviewing (CAPI).

In addition to questions about the use of tobacco and alcohol, the survey obtains information on nine different categories of illicit drug use: use of marijuana, cocaine, heroin, hallucinogens, and inhalants; and the nonmedical use of prescription-type pain relievers, tranquilizers, stimulants, and sedatives. In these categories, hashish is included with marijuana, and crack is considered a form of cocaine. Several drugs are grouped under the hallucinogens category, including LSD, PCP, peyote, mescaline, mushrooms, and "Ecstasy" (MDMA). Inhalants include a variety of substances, such as nitrous oxide, amyl nitrite, cleaning fluids, gasoline, spray paint, other aerosol sprays, and glue. The four categories of prescription-type drugs (pain relievers, tranquilizers, stimulants, and sedatives) cover numerous pharmaceutical drugs available by prescription and drugs within these groupings that may be manufactured illegally, such as methamphetamine, which is included under stimulants. Respondents are asked to report only "nonmedical" use of these drugs, defined as use without a prescription of the individual's own or simply for the experience or feeling the drugs caused. Within the pain reliever category, specific questions about nonmedical use of Oxycontin are asked. Use of over-the-counter drugs and legitimate use of prescription drugs are not included.

Questions assessing substance use disorders, based on DSM-IV criteria, are included, as well as items on treatment for substance use problems. Mental health status and treatment are also covered in NSDUH.

The 2006 NSDUH employed a State-based design with an independent, multistage area probability sample within each State and the District of Columbia. The eight States with the

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<sup>1</sup> RTI International is a trade name of Research Triangle Institute.

largest population (which together account for 48 percent of the total U.S. population aged 12 or older) were designated as large sample States (California, Florida, Illinois, Michigan, New York, Ohio, Pennsylvania, and Texas). For these States, the design provided a sample sufficient to support direct State estimates. For the remaining 42 States and the District of Columbia, smaller, but adequate, samples support State estimates using small area estimation (SAE) techniques. The design oversampled youths and young adults, so that each State's sample was approximately equally distributed among three age groups: 12 to 17 years, 18 to 25 years, and 26 years or older.

Nationally, 137,057 addresses were screened for the 2006 survey, and 67,802 completed interviews were obtained. The survey was conducted from January through December 2006. Weighted response rates for household screening and for interviewing were 90.6 and 74.2 percent, respectively.

Although the design of the 2002 through 2006 NSDUHs is similar to the design of the 1999 through 2001 surveys, there are important methodological differences that affect the comparability of the 2002-2006 estimates with estimates from prior surveys. In addition to the name change, each NSDUH respondent completing the interview is now given an incentive payment of \$30. These changes, implemented in 2002 and continued subsequently, resulted in an improvement in the response rate, but also affected respondents' reporting of items that are the basis of prevalence measures produced each year. Comparability also may be affected by improved data collection quality control procedures that were introduced beginning in 2001 and by the incorporation of new population data from the 2000 decennial census into NSDUH sample weighting procedures. Analyses of the effects of these factors on NSDUH estimates have shown that 2002 and later data should not be compared with 2001 and earlier data from the survey series to assess changes over time.

A comprehensive set of tables, referred to as "detailed tables," is available through the Internet at <http://www.oas.samhsa.gov>. The tables are organized into sections based primarily on the topic, and most tables are provided in several parts, showing population estimates (e.g., numbers of drug users), rates (e.g., percentages of population using drugs), and standard errors of all nonsuppressed estimates. Additional methodological information on NSDUH, including the questionnaire, is available electronically at the same Web address.

Annual summary reports, brief descriptive reports and in-depth analytic reports focusing on specific issues or population groups are produced by OAS. A complete listing of published reports from NSDUH and other data sources is available from OAS. Most of these reports also are available through the Internet (<http://www.oas.samhsa.gov>). In addition, OAS makes public use data files available to researchers through the Substance Abuse and Mental Health Data Archive (SAMHDA, 2007) at <http://www.icpsr.umich.edu/SAMHDA/index.html>. Currently, files are available from the 1979 to 2006 surveys. The 2007 NSDUH public use file will be available by the end of 2008.

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## 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<sup>1</sup> 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.

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<sup>1</sup> 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.

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## Treatment Episode Data Set

The Treatment Episode Data Set (TEDS) provides information on the demographic characteristics and substance abuse problems of clients admitted to treatment for abuse of alcohol and drugs in the United States. The information in TEDS is compiled from State administrative systems and is collected by the States from those treatment facilities that they monitor or fund. TEDS records represent admissions rather than individuals, as a person may be admitted to treatment more than once. Approximately 1.8 million admissions records are submitted to TEDS each year. TEDS is maintained by the Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA).

While TEDS does not represent the total national demand for substance abuse treatment, it does comprise a significant proportion (an estimated 80 percent) of all admissions to substance abuse treatment, and largely includes those admissions that are subsidized by public funds. Differences in State systems of licensure, certification, accreditation, and disbursement of public funds affect the scope of facilities included in TEDS. Treatment facilities that are operated by private for-profit agencies, hospitals, and State correctional systems, if not licensed through the State substance abuse agency, may be excluded from TEDS. TEDS does not include data on facilities operated by Federal agencies (the Bureau of Prisons, the Department of Defense, and the Veterans Administration).

TEDS data on treatment admissions include:

- demographic information
- primary secondary and tertiary substances of abuse, 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 methadone.

Among the substances of abuse collected in TEDS are opiates. This category is further broken down into three subcategories: heroin, non-prescription methadone, and other opiates/synthetics. "Other opiates" is comprised almost entirely of opioid analgesics. While admissions involving use of "other opiates" represent a very small proportion of total TEDS admissions (4.2% in 2006), in the past decade, there has been a dramatic increase in the admissions for drugs in this category. Most of this growth has occurred since 1997. From 1997-2006, total admissions increased 12%, admissions in which heroin was the primary substance of abuse increased 4% and admissions in which "other opiates" were the primary substance increased 367%.

	1997		2006	
	N	%	N	%
Total admissions	1,607,957	100.0	1,800,717	100.0
Heroin admissions	235,143	14.6	245,984	13.7
Other opiates	16,274	0.1	74,750	4.2

Admissions for “other opiates” are primarily white and somewhat more likely to be male than female (57% versus 43%). The increase in admissions for “other opiates” between 1997 and 2006 were greatest among the youngest age groups, especially 15-19 years and 20-24 years.

TEDS is an exceptionally large and powerful data set. Like all data sets, however, care must be taken that interpretation does not extend beyond the limitations of the data. Limitations fall into two broad categories: those related to the scope of the data collection system, and those related to the difficulties of aggregating data from the highly diverse State data collection systems. Limitations to be kept in mind while analyzing TEDS data include:

- TEDS is an admission-based system and TEDS admissions do not represent individuals. An individual admitted to treatment twice within a calendar year would be counted as two admissions. Many States cannot, for reasons of confidentiality, identify clients with a unique ID assigned at the State level. Consequently TEDS is unable to follow individual clients through a sequence of treatment episodes.
- TEDS attempts to enumerate treatment episodes by distinguishing the initial admission of a client from his/her subsequent transfer to a different service type (for example, from residential treatment to outpatient) within a single continuous treatment episode. However, States differ greatly in their ability to identify transfers; some can distinguish transfers within providers but not across providers. Some admission records may in fact represent transfers, and therefore the number of admissions reported probably overestimates the number of treatment episodes.
- The number and client mix of TEDS admissions does not represent the total national demand for substance abuse treatment, nor the prevalence of substance abuse in the general population.
- The primary, secondary, and tertiary substances of abuse reported to TEDS are those substances which led to the treatment episode, and not necessarily a complete enumeration of all drugs used at the time of admission.

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# Clinical Trial Data Related to Relative Opioid Likeability

## **Background:**

There are 15 approved full opioid-agonist moieties in the United States. The approved moieties include the true opiates, morphine sulfate and codeine, and the semi-synthetic and fully synthetic moieties, hydrocodone, hydromorphone, oxycodone, oxymorphone, meperidine, levorphanol, propoxyphene, fentanyl, sufentanil, alfentanil, remifentanil, tramadol, and methadone. Scientific data suggest that certain opioids have a higher abuse liability or are more likeable than others, a concept that is part of the decision-making process when the Drug Enforcement Administration (DEA) schedules the moiety.

Of the approved opioids, 12 moieties, morphine, hydromorphone, oxycodone, oxymorphone, buprenorphine, levorphanol, meperidine, fentanyl, sufentanil, alfentanil, remifentanil, and methadone are classified Schedule II. Despite belonging to the same DEA Schedule, anecdotal evidence and “conventional wisdom” support the notion that these 12 moieties may differ in likeability, that is, how desirable each drug is to abusers.

## **Research Methodology:**

A literature search was conducted to include the search terms “opioid/opiate likeability,” “relative opioid/opiate euphoria,” and “narcotic likeability.” The “related articles” function was used when a pertinent article was identified. In conducting these searches, three researchers, Donald Jasinski, James Zacny, and Sandra Comer appeared prominent in pertinent references so an additional search for these three authors’ work was added.

## Data Reviewed:

The literature search indicated that research in this area dates to at least 1966<sup>1</sup>. While the study of abuse liability has a long history, it appears to be a science in evolution. Study techniques have evolved over time but it tends to be difficult to draw strong conclusions from the available data. Reasons for this include:

- The relative potency of opioids as analgesics is not particularly well established.
- The relative potency of opioids with regard to analgesia may be different from the relative potency based on the outcomes measured in likeability studies.
- By definition, the pertinent outcome measures are subjective.
- Objective outcome measures to assess the pharmacodynamic effects of opioids (i.e. pupillometry) have not been conclusively correlated with analgesia or the effects measured in abuse liability studies.
- There is significant subject-to-subject variability with regard to pharmacodynamics and pharmacokinetics.

However, clinical trials in this area tend to be of a fairly standard design.

Objective: To determine the relative likeability of various doses of opioids

Design: Randomized, double-blind, placebo- and active-controlled, cross-over.

Population: These studies tend to use opioid-experienced, non-dependent, otherwise healthy volunteers or healthy volunteers who do not meet criteria for current or past substance abuse. Most of these studies enroll approximately 20 subjects.

Study Conduct:

- Screening usually consists of obtaining informed consent, a detailed medical, psychiatric, and substance abuse history, physical exam, and instruments designed to establish baseline measures designed to assess the risk of substance abuse.
- In a pre-dosing visit, subjects are re-screened and a toxicology screen is administered. Baseline testing [safety-related (e.g. vital signs), physiologic (e.g. pupillometry), and psychomotor (assessments of descriptors such as “being high”)] is conducted.
- Eligible subjects are admitted to the testing facility.
- Study drug is administered and questionnaires and other pharmacodynamic measurements are made. Subjects are monitored for safety.
- Following completion of the study (usually approximately 300 minutes post-dose), subjects are taken home by livery service.
- Following an appropriate washout period, subjects repeat the procedure with another treatment.

Treatment Groups:

Most studies use one or more doses of morphine sulfate (the most common active control), one or more doses of study drug(s), and placebo. Study drugs are administered via oral or parenteral routes.

Outcome Measures:

Usually, a large battery of surveys and tests are administered including measures of psychomotor and cognitive performance and physiological findings (vital signs, miosis). Listed and described are what appear to be the most pertinent outcome measure data collected.

1. Short form of the Addiction Research Center Inventory (ARCI), in particular the MGB subscale, often described as euphoria.
2. A visual analog scale for various descriptors. Descriptors of interest include:
  - a. Bad effect
  - b. Good effect
  - c. Nauseous
  - d. Sedated
  - e. Carefree

- f. High
  - g. Mellow
  - h. Dizzy
  - i. Itchy
  - j. Like
  - k. Quality
  - l. Social
  - m. Stimulated
  - n. Nodding
  - o. “Spaced out”
  - p. Having pleasant bodily sensations
  - q. Having unpleasant bodily sensations
  - r. Would pay for drug
3. Drug effect/drug liking/take again questionnaire or the Drug Effects Questionnaire
  4. Drug and money choices

The conditions studied in each trial are summarized in Table 1. In the abstracts, the authors tend to draw a final conclusion that the opioids studied were similar in the outcome measures studied. However, in the head-to-head studies where oxycodone was used, the data suggest that oxycodone is associated with more positive effects and/or fewer negative effects than the comparator drug(s), usually morphine. In the trials where oxycodone was studied, the authors note this as well, although they generally place such comments in the discussion section. In Table 1, the pertinent quotations from the discussion/conclusion sections are included.

**Table 1:** Summary of pertinent literature

Study	Population	Drugs Studied	Doses	Route of Administration	Excerpts from Discussion Section
Comer <sup>2</sup>	Morphine-maintained heroin addicts	Fentanyl Oxycodone Morphine Buprenorphine Heroin	0-250 mcg/70kg 0-50 mg/70kg 0-50 mg/70kg 0-8 mg/70kg 0-25 mg/70kg	IV	“Another important finding from the present study is that the abuse liability of oxycodone appears to be substantial. Oxycodone produced robust reinforcing effects, similar to those of morphine and heroin, and it produced some of the most robust increases in positive subjective ratings, but no increases in ratings of bad effects. Given that a balance of positive and negative subjective ratings is likely to influence the degree to which a drug is abused, the fact that oxycodone produced virtually no negative effects in heroin abusers is particularly concerning.”
Zacny (2003) <sup>3</sup>	Non-drug abusing volunteers	Oxycodone Morphine Lorazepam	0, 10, 20, 30 mg 40 mg 2 mg	PO	<ol style="list-style-type: none"> <li>1. “Oxycodone produced a number of subjective effects that could be considered abuse liability-related in nature. One of these effects was an increase in the MBG score of the ARCI. Peak MBG scores [related to euphoria] increased significantly after ingestion of 20 mg and 30 mg oxycodone. It should be noted that an increase in scores of the MBG scale is not typically observed in mu opioid studies with non-drug abusing volunteers.”</li> <li>2. “There were several other subjective effects measures used in this study that could be considered as being pleasant in nature and thus having face validity as being abuse liability-related that were increased by 20 mg and/or 30 mg oxycodone.”</li> <li>3. “However, it is important to note that oxycodone at the two higher doses produced subjective effects that could be considered as unpleasant in nature. [‘skin itchy,’ ‘difficulty concentrating,’ ‘heavy or sluggish feeling,’ etc.]”</li> </ol>
Zacny (2008) <sup>4</sup>	Non-drug abusing volunteers	Oxycodone Morphine	0, 10, 20 mg 30, 60 mg	PO	<ol style="list-style-type: none"> <li>1. “In the present study, we would tentatively conclude that on balance, OXY 20 mg had more abuse liability-related effects and fewer aversive effects than MOR 60 mg.”</li> <li>2. “...we can only point out the differences we found as being suggestive of a quicker onset of effect with oxycodone.”</li> <li>3. “Several clinical studies suggest potential differences in side-effect profiles between oral oxycodone and oral morphine...with oxycodone producing less severe side effects than morphine.”</li> </ol>
Hill <sup>5</sup>	Non-drug abusing volunteers	Hydromorphone Morphine	0-1.3 mg/70kg 5-10 mg/70kg	IV	“The subjective effects of morphine at putatively equianalgesic doses to those of hydromorphone were similar to those of hydromorphone, but in some cases of lesser magnitude.”
Jasinski <sup>6</sup>	Non-dependent, post-addict volunteers	Methadone Morphine Heroin	5-20 mg/70kg 5-20 mg/70kg 2.5-10 mg/70kg	IV	“In summary, our studies indicate that intravenously given heroin, methadone, and morphine are equally euphorogenic in opiate users.”

## **Conclusions:**

1. The study of the relative likeability of opioids is complex and definitive conclusions are difficult to make.
2. In most cases, the formal conclusion drawn by the investigators is that the opioids tested were not dissimilar with regard to outcome measures that predict abusability.
3. However, in every study that compared oxycodone to morphine +/- other opioids at relevant doses, subjects either found oxycodone to have more positive effects, fewer negative effects, or both. This was observed via the intravenous and oral route of administration and in substance abusers and non-abusers. Therefore, the preponderance of the data suggests that oxycodone is more "likeable" than morphine.
4. It is important to note that one study suggested that hydromorphone may be more likeable than morphine as well. However, a study to be published<sup>7</sup> compared oral oxycodone, hydrocodone, and hydromorphone in recreational drug abusers. The study showed similar drug effects across groups.
5. One study suggested that morphine and methadone are roughly equivalent with regard to euphoria.
6. Buprenorphine is probably less likeable than other opioids.

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<sup>3</sup>Zacny JP, Gutierrez S. Characterizing the subjective, psychomotor, and physiological effects of oral oxycodone in non-drug abusing volunteers. *Psychopharmacology* 2003;170:242-54.

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