# Journal of Opioid Management™

*A medical journal for proper and adequate use*

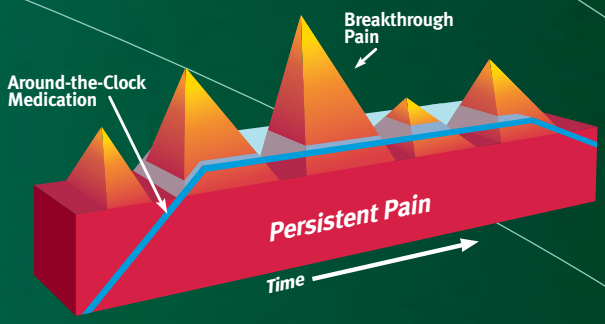
Volume 3, Number 3 | MAY/JUNE 2007 | ISSN 1551-7489

Official Journal of Opioid Management Society

## CONTENTS

# Optimize onset with *FENTORA*

## For the sudden strike of breakthrough pain (BTP) in patients with cancer,




## *FENTORA* optimizes onset of relief

**FENTORA**™
fentanyl buccal tablet
optimize onset

Serious adverse events associated with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. All patients should be followed for symptoms of respiratory depression.

The most common (≥10%) adverse events observed in all *FENTORA* clinical trials were nausea, dizziness, vomiting, fatigue, headache, constipation, somnolence, anemia, dehydration, and application site abnormalities. Application site reactions tended to occur early in treatment, were self-limited, and resulted in treatment discontinuation for only 2% of patients. Most side effects were mild to moderate in severity. No attempt was made to correct for concomitant use of around-the-clock opioids or cancer-related symptoms.

PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

***FENTORA* contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. *FENTORA* can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing *FENTORA* in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.**

***FENTORA* is indicated for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine/day, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

Because life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients, *FENTORA* is **contraindicated** in the management of acute or postoperative pain. **This product is not indicated for use in opioid non-tolerant patients.**

**Patients and their caregivers must be instructed that *FENTORA* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. (See Information for Patients and Their Caregivers for disposal instructions.)**

**Due to the higher bioavailability of fentanyl in *FENTORA*, when converting patients from other oral fentanyl products, including oral transmucosal fentanyl citrate (OTFC and Actiq®), to *FENTORA*, do not substitute *FENTORA* on a mcg per mcg basis. Adjust doses as appropriate. (See DOSAGE AND ADMINISTRATION.)**

***FENTORA* is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.**

**For more information about *FENTORA*, please call Cephalon Professional Services and Medical Information at 1-800-896-5855 or visit www.*FENTORA*.com**

Please see boxed warning and brief summary of prescribing information on adjacent pages.

Cephalon
deliver more

# *FENTORA*® (fentanyl buccal tablet) C-II

**BRIEF SUMMARY:** Please see full prescribing information.

**PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.**

***FENTORA*** **contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.** ***FENTORA*** **can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing** ***FENTORA*** **in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.**

***FENTORA*** **is indicated for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine/day, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

Because life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients, *FENTORA* is **contraindicated** in the management of acute or postoperative pain. **This product is not indicated for use in opioid non-tolerant patients.**

**Patients and their caregivers must be instructed that** ***FENTORA*** **contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. (See Information for Patients and Their Caregivers for disposal instructions.)**

**Due to the higher bioavailability of fentanyl in** ***FENTORA*****, when converting patients from other oral fentanyl products, including oral transmucosal fentanyl citrate (OTFC and Actiq®), to** ***FENTORA*****, do not substitute** ***FENTORA*** **on a mcg per mcg basis. Adjust doses as appropriate. (See DOSAGE AND ADMINISTRATION.)**

***FENTORA*** **is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.**

**INDICATIONS AND USAGE** (See **BOXED WARNING** and **CONTRAINDICATIONS)**

*FENTORA* is indicated for the management of breakthrough pain in patients with cancer who are **already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine/day, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer. This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation could occur at any dose in patients not on a chronic regimen of opiates. For this reason, *FENTORA* is contraindicated in the management of acute or postoperative pain. *FENTORA* is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

**CONTRAINDICATIONS**

Because life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients, *FENTORA* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients. *FENTORA* is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

**WARNINGS** (See **BOXED WARNING)**

The concomitant use of other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, potent inhibitors of cytochrome P450 3A4 isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors), and alcoholic beverages may produce increased depressant effects. Hypoventilation, hypotension, and profound sedation may occur. *FENTORA* is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

**Pediatric Use:** The safety and efficacy of *FENTORA* have not been established in pediatric patients below the age of 18 years. **Patients and their caregivers must be instructed that** ***FENTORA*** **contains a medicine in an amount which can be fatal to a child.** Patients and their caregivers must be instructed to keep tablets out of the reach of children. (See **SAFETY AND HANDLING**, **PRECAUTIONS**, and **Medication Guide** for specific patient instructions.)

**Drug Abuse, Addiction and Diversion of Opioids:** *FENTORA* contains fentanyl, a mu-opioid agonist and a Schedule II controlled substance with high potential for abuse similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Fentanyl can be abused and is subject to misuse, and criminal diversion. Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers. Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Since *FENTORA* tablets may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised. Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs. *FENTORA* should be handled appropriately to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

**Physical Dependence and Withdrawal:** The administration of *FENTORA* should be guided by the response of the patient. Physical dependence, per se, is not ordinarily a concern when one is treating a patient with cancer and chronic pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain. Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine). Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

**Respiratory Depression:** Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in *FENTORA*. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

**PRECAUTIONS**

**General:** The extent of fentanyl absorption with different formulations of transmucosal delivery systems can be substantially different; therefore, the same dose of fentanyl in two different formulations should not be viewed as equivalent. Therefore, caution must be exercised when switching patients from one product to another (see **DOSAGE AND ADMINISTRATION**). For patients not previously using oral transmucosal fentanyl citrate, the initial dose of *FENTORA* should be 100 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects. Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Patients taking *FENTORA* should be warned of these dangers and should be counseled accordingly. The use of concomitant CNS active drugs requires special patient care and observation (see **WARNINGS**).

**Chronic Pulmonary Disease:** Because potent opioids can cause respiratory depression, *FENTORA* should be titrated with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to respiratory depression. In such patients, even normal therapeutic doses of *FENTORA* may further decrease respiratory drive to the point of respiratory failure.

**Head Injuries and Increased Intracranial Pressure:** *FENTORA* should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of $CO_2$ retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

**Application Site Reactions:** In clinical trials, 10% of all patients exposed to *FENTORA* reported application site reactions. These reactions ranged from paresthesia to ulceration and bleeding. Application site reactions occurring in ≥1% of patients were pain (4%), ulcer (3%), and irritation (3%). Application site reactions tended to occur early in treatment, were self-limited and only resulted in treatment discontinuation for 2% of patients.

**Cardiac Disease:** Intravenous fentanyl may produce bradycardia. Therefore, *FENTORA* should be used with caution in patients with bradyarrhythmias.

**Hepatic or Renal Disease:** Insufficient information exists to make recommendations regarding the use of *FENTORA* in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system and mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

**Information for Patients and Their Caregivers**

1. **Patients and their caregivers must be instructed that children, especially small children, exposed to** ***FENTORA*** **are at high risk of FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep *FENTORA* tablets out of the reach of children. (See **SAFETY AND HANDLING, WARNINGS**, and **Medication Guide** for specific patient instructions).
2. Patients and their caregivers should be provided a Medication Guide each time *FENTORA* is dispensed because new information may be available.
3. Patients should be aware that *FENTORA* contains fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
4. Patients should be instructed that the active ingredient in *FENTORA*, fentanyl, is a drug that some people abuse. *FENTORA* should be taken only by the patient it was prescribed for, and it should be protected from theft or misuse in the work or home environment.
5. Patients should be instructed that *FENTORA* tablets are not to be swallowed whole; this will reduce the effectiveness of the medication. They are to be placed between the cheek and gum above a molar tooth and allowed to dissolve. After 30 minutes if remnants of the tablet still remain, patients may swallow it with a glass of water.
6. Patients should be cautioned to talk to their doctor if breakthrough pain is not alleviated or worsens after taking *FENTORA*.
7. Patients should be cautioned that *FENTORA* can affect a person's ability to perform activities that require a high level of attention (such as driving or using heavy machinery). Patients taking *FENTORA* should be warned of these dangers and counseled accordingly.
8. Patients should be warned to not combine *FENTORA* with alcohol, sleep aids, or tranquilizers except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
9. Female patients should be informed that if they become pregnant or plan to become pregnant during treatment with *FENTORA*, they should ask their doctor about the effects that *FENTORA* (or any medicine) may have on them and their unborn children.
10. Patients and caregivers should be advised that if they have been receiving treatment with *FENTORA* and the medicine is no longer needed they should contact Cephalon at 1-800-896-5855 or flush any remaining product down the toilet.

**Disposal of Unopened** ***FENTORA*** **Blister Packages When No Longer Needed:** Patients and members of their household must be advised to dispose of any unopened blister packages remaining from a prescription as soon as they are no longer needed. To dispose of unused *FENTORA*, remove *FENTORA* tablets from blister packages and flush down the toilet. Do not flush the *FENTORA* blister packages or cartons down the toilet. (See **SAFETY AND HANDLING.**) Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of *FENTORA* are provided in the *FENTORA* Medication Guide. Patients should be encouraged to read this information in its entirety and be given an opportunity to have their questions answered. In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, they should be instructed to call the toll-free number (1-800-896-5855) or seek assistance from their local DEA office.

**Laboratory Tests:** The effects of *FENTORA* on laboratory tests have not been evaluated.

**Drug Interactions:** See **WARNINGS.** Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4), therefore potential interactions may occur when *FENTORA* is given concurrently with agents that affect CYP3A4 activity. Coadministration with agents that induce 3A4 activity may reduce the efficacy of *FENTORA*. The concomitant use of *FENTORA* with ritonavir or other strong 3A4 inhibitors such as ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazadone may result in a potentially dangerous increase in fentanyl plasma concentrations. The concomitant use of moderate CYP3A4 inhibitors such as amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil may also result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving *FENTORA* and potent and moderate CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage increase should be done conservatively. **(See PHARMACOKINETICS: Drug Interactions and DOSAGE AND ADMINISTRATION.)**

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate the carcinogenic potential of fentanyl. Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay in *S. tymphimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay. Fentanyl citrate was not clastogenic in the *in vivo* mouse micronucleus assay. Fentanyl impairs fertility in rats at doses of 30 mcg/kg IV and 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for *FENTORA*.

**Pregnancy - Category C:** There are no adequate and well-controlled studies in pregnant women. *FENTORA* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported. Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures characteristic of neonatal abstinence syndrome in newborn infants. Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl. Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl. Fentanyl is embryocidal as evidenced by increased resorptions in pregnant rats at doses of 30 mcg/kg IV or 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for *FENTORA*. Fentanyl citrate was not teratogenic when administered to pregnant animals. Published studies demonstrated that administration of fentanyl (10, 100, or 500 mcg/kg/day) to pregnant rats from day 7 to 21, of their 21 day gestation, via implanted microosmotic minipumps was not teratogenic (the high dose was approximately 3-times the human dose of 1600 mcg per pain episode on a mg/m$^2$ basis). Intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant female rats from gestation day 6 to 18, was embryo or fetal toxic, and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but was not teratogenic.

**Labor and Delivery:** Fentanyl readily passes across the placenta to the fetus; therefore *FENTORA* is not recommended for analgesia during labor and delivery.

**Nursing Mothers:** Fentanyl is excreted in human milk; therefore *FENTORA* should not be used in nursing women because of the possibility of sedation and/or respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using *FENTORA*.

**Pediatric Use:** See **WARNINGS.**

**Geriatric Use:** Of the 304 patients with cancer in clinical studies of *FENTORA*, 69 (23%) were 65 years of age and older. Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients. Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating *FENTORA* in elderly patients to provide adequate efficacy while minimizing risk.

**ADVERSE REACTIONS**

Pre-Marketing Clinical Trial Experience: The safety of *FENTORA* has been evaluated in 304 opioid tolerant cancer patients with breakthrough pain. The average duration of therapy was 76 days with some patients being treated for over 12 months. The most commonly observed adverse events seen with *FENTORA* are typical of opioid side effects. Opioid side effects should be expected and managed accordingly. The clinical trials of *FENTORA* were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent pain. The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received *FENTORA* for breakthrough pain along with a concomitant opioid for persistent pain. There has been no attempt to correct for concomitant use of other opioids, duration of *FENTORA* therapy or cancer-related symptoms. Table 5 lists, by maximum dose received, adverse events with an overall frequency of 5% or greater within the total population that occurred during titration. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies.

**Table 5. Adverse Events Which Occurred During Titration at a Frequency of ≥ 5%**

| System Organ Class MeDRA preferred term, n (%) | 100 mcg (N=45) | 200 mcg (N=34) | 400 mcg (N=53) | 600 mcg (N=56) | 800 mcg (N=113) | Total (N=304)* |
|---|---|---|---|---|---|---|
| **Gastrointestinal disorders** | | | | | | |
| Nausea | 4 (9) | 5 (15) | 10 (19) | 13 (23) | 18 (16) | 50 (17) |
| Vomiting | 0 | 2 (6) | 2 (4) | 7 (13) | 3 (3) | 14 (5) |
| **General disorders and administration site conditions** | | | | | | |
| Fatigue | 3 (7) | 1 (3) | 9 (17) | 1 (2) | 5 (4) | 19 (6) |
| **Nervous system disorders** | | | | | | |
| Dizziness | 5 (11) | 2 (6) | 12 (23) | 18 (32) | 21 (19) | 58 (19) |
| Somnolence | 2 (4) | 2 (6) | 6 (12) | 7 (13) | 3 (3) | 20 (7) |
| Headache | 1 (2) | 3 (9) | 4 (8) | 8 (14) | 10 (9) | 26 (9) |

* Three hundred and two (302) patients were included in the safety analysis.

Table 6 lists, by successful dose, adverse events with an overall frequency of ≥5% within the total population that occurred after a successful dose had been determined.

**Table 6. Adverse Events Which Occurred During Long-Term Treatment at a Frequency of ≥ 5%**

| System Organ ClassMeDRA preferred term, n (%) | 100 mcg (N=19) | 200 mcg (N=31) | 400 mcg (N=44) | 600 mcg (N=48) | 800 mcg (N=58) | Total (N=200) |
|---|---|---|---|---|---|---|
| **Blood and lymphatic system disorders** | | | | | | |
| Anemia | 6 (32) | 4 (13) | 4 (9) | 5 (10) | 7 (13) | 26 (13) |
| Neutropenia | 0 | 2 (6) | 1 (2) | 4 (8) | 4 (7) | 11 (6) |
| **Gastrointestinal disorders** | | | | | | |
| Nausea | 8 (42) | 5 (16) | 14 (32) | 13 (27) | 17 (31) | 57 (29) |
| Vomiting | 7 (37) | 5 (16) | 9 (20) | 8 (17) | 11 (20) | 40 (20) |
| Constipation | 5 (26) | 4 (13) | 5 (11) | 4 (8) | 6 (11) | 24 (12) |
| Diarrhea | 3 (16) | 0 | 4 (9) | 3 (6) | 5 (9) | 15 (8) |
| Abdominal pain | 2 (11) | 1 (3) | 4 (9) | 7 (15) | 4 (7) | 18 (9) |
| **General disorders and administration site conditions** | | | | | | |
| Edema peripheral | 6 (32) | 5 (16) | 4 (9) | 5 (10) | 3 (5) | 23 (12) |
| Asthenia | 3 (16) | 5 (16) | 2 (5) | 3 (6) | 8 (15) | 21 (11) |
| Fatigue | 3 (16) | 3 (10) | 9 (20) | 9 (19) | 8 (15) | 32 (16) |
| **Infections and infestations** | | | | | | |
| Pneumonia | 1 (5) | 5 (16) | 1 (2) | 1 (2) | 4 (7) | 12 (6) |
| **Investigations** | | | | | | |
| Weight decreased | 1 (5) | 1 (3) | 3 (7) | 2 (4) | 6 (11) | 13 (7) |
| **Metabolism and nutrition disorders** | | | | | | |
| Dehydration | 4 (21) | 0 | 4 (9) | 6 (13) | 7 (13) | 21 (11) |
| Anorexia | 1 (5) | 2 (6) | 4 (9) | 3 (6) | 6 (11) | 16 (8) |
| Hypokalemia | 0 | 2 (6) | 0 | 1 (2) | 8 (15) | 11 (6) |
| **Musculoskeletal and connective tissue disorders** | | | | | | |
| Back pain | 2 (11) | 0 | 2 (5) | 3 (6) | 2 (4) | 9 (5) |
| Arthralgia | 0 | 1 (3) | 3 (7) | 4 (8) | 3 (5) | 11 (6) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | | | | | | |
| Cancer pain | 3 (16) | 1 (3) | 3 (7) | 2 (4) | 1 (2) | 10 (5) |
| **Nervous system disorders** | | | | | | |
| Dizziness | 5 (26) | 3 (10) | 5 (11) | 6 (13) | 6 (11) | 25 (13) |
| Headache | 2 (11) | 1 (3) | 4 (9) | 5 (10) | 8 (15) | 20 (10) |
| Somnolence | 0 | 1 (3) | 4 (9) | 4 (8) | 8 (15) | 17 (9) |
| **Psychiatric disorders** | | | | | | |
| Confusional state | 3 (16) | 1 (3) | 2 (5) | 3 (6) | 5 (9) | 14 (7) |
| Depression | 2 (11) | 1 (3) | 4 (9) | 3 (6) | 5 (9) | 15 (8) |
| Insomnia | 2 (11) | 1 (3) | 3 (7) | 2 (4) | 4 (7) | 12 (6) |
| **Respiratory, thoracic, and mediastinal disorders** | | | | | | |
| Cough | 1 (5) | 1 (3) | 2 (5) | 4 (8) | 5 (9) | 13 (7) |
| Dyspnea | 1 (5) | 6 (19) | 0 | 7 (15) | 4 (7) | 18 (9) |

In addition, a small number of patients (n=11) with Grade 1 mucositis were included in clinical trials designed to support the safety of *FENTORA*. There was no evidence of excess toxicity in this subset of patients. The duration of exposure to *FENTORA* varied greatly, and included open-label and double-blind studies. The frequencies listed below represent ≥1% of patients from 3 clinical trials who experienced that event while receiving *FENTORA*.

**Adverse Events (≥1%): Blood and Lymphatic System Disorders:** Anemia, Neutropenia, Thrombocytopenia, Leukopenia; **Cardiac Disorders:** Tachycardia; **Gastrointestinal Disorders:** Nausea, Vomiting, Constipation, Abdominal Pain, Diarrhea, Stomatitis, Dry Mouth, Dyspepsia, Upper Abdominal Pain, Abdominal Distension, Dysphagia, Gingival Pain, Stomach Discomfort, Gastroesophageal Reflux Disease, Glossodynia, Mouth Ulceration; **General Disorders and Administration Site Conditions:** Fatigue, Edema Peripheral, Asthenia, Pyrexia, Application Site Pain, Application Site Ulcer, Chest Pain, Chills, Application Site Irritation, Edema, Mucosal Inflammation, Pain; **Hepatobiliary Disorders:** Jaundice; **Infections and Infestations:** Pneumonia, Oral Candidiasis, Urinary Tract Infection, Cellulitis, Nasopharyngitis, Sinusitis, Upper Respiratory Tract Infection, Influenza, Tooth Abscess; **Injury, Poisoning and Procedural Complications:** Fall, Spinal Compression Fracture; **Investigations:** Decreased Weight, Decreased Hemoglobin, Increased Blood Glucose, Decreased Hematocrit, Decreased Platelet Count; **Metabolism and Nutrition Disorders:** Dehydration, Anorexia, Hypokalemia, Decreased Appetite, Hypoalbuminemia, Hypercalcemia, Hypomagnesemia, Hyponatremia, Reduced Oral Intake; **Musculoskeletal and Connective Tissue Disorders:** Arthralgia, Back Pain, Pain in Extremity, Myalgia, Chest Wall Pain, Muscle Spasms, Neck Pain, Shoulder Pain; **Nervous System Disorders:** Dizziness, Headache, Somnolence, Hypoesthesia, Dysgeusia, Lethargy, Peripheral Neuropathy, Paresthesia, Balance Disorder, Migraine, Neuropathy; **Psychiatric Disorders:** Confusional State, Depression, Insomnia, Anxiety, Disorientation, Euphoric Mood, Hallucination, Nervousness; **Renal and Urinary Disorders:** Renal Failure; **Respiratory, Thoracic and Mediastinal Disorders:** Dyspnea, Cough, Pharyngolaryngeal Pain, Exertional Dyspnea, Pleural Effusion, Decreased Breathing Sounds, Wheezing; Skin and Subcutaneous Tissue Disorders: Pruritus, Rash, Hyperhidrosis, Cold Sweat; **Vascular Disorders:** Hypertension, Hypotension, Pallor, Deep Vein Thrombosis

**OVERDOSAGE**

**Clinical Presentation:** The manifestations of *FENTORA* overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being hypoventilation.

**General:** Immediate management of opioid overdose includes removal of the *FENTORA* tablet, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, as well as ventilatory and circulatory status.

**Treatment of Overdosage in the Opioid Non-Tolerant Person:** Ventilatory support should be provided, intravenous access obtained, and naloxone or other opioid antagonists should be employed as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the package insert of the individual opioid antagonist for details about such use.

**Treatment of Overdose in Opioid-Tolerant Patients:** Ventilatory support should be provided and intravenous access obtained as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

**General Considerations for Overdose:** Management of severe *FENTORA* overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated. Patients with overdose should be carefully observed and appropriately managed until their clinical condition is well controlled. Although muscle rigidity interfering with respiration has not been seen following the use of *FENTORA*, this is possible with fentanyl and other opioids. If it occurs, it should be managed by the use of assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

**DOSAGE AND ADMINISTRATION**

Physicians should individualize treatment using a progressive plan of pain management. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring. (See **BOXED WARNING** and **Dose Titration**.)

**Patients with hepatic and/or renal impairment:** Caution should be exercised for patients with hepatic and/or renal impairment, and the lowest possible dose should be used in these patients. (See **PRECAUTIONS**.)

**Patients receiving CYP3A4 inhibitors:** Particular caution should be exercised for patients receiving CYP3A4 inhibitors, and the lowest possible dose should be used in these patients. (See **PRECAUTIONS**.)

**Patients with mucositis:** No dose adjustment appears necessary in patients with Grade 1 mucositis. The safety and efficacy of *FENTORA* when used in patients with mucositis more severe than Grade 1 have not been studied.

**Administration of *FENTORA*: Dose Titration:** Patients should be titrated to a dose of *FENTORA* that provides adequate analgesia with tolerable side effects. **Starting Dose:** The initial dose of *FENTORA* should be 100 mcg. For patients switching from oral transmucosal fentanyl citrate to *FENTORA*, the starting dose of *FENTORA* should be initiated as shown in Table 7 below. (See **PHARMACOKINETICS, Absorption**.)

**Table 7. Dosing Conversion Recommendations**

| Current Actiq (OTFC) Dose (mcg) | Initial *FENTORA* Dose (mcg) |
|---|---|
| 200, 400 | 100 |
| 600, 800 | 200 |
| 1200, 1600 | 400 |

**Re-dosing Patients Within a Single Episode:** Dosing may be repeated once during a single episode of breakthrough pain if pain is not adequately relieved by one *FENTORA* dose. Re-dosing may occur 30 minutes after the start of administration of *FENTORA* and the same dosage strength should be used. **Increasing the Dose:** From an initial dose, patients should be closely followed and the dosage strength changed until the patient reaches a dose that provides adequate analgesia with tolerable side effects using a single *FENTORA* tablet. Patients should record their use of *FENTORA* over several episodes of breakthrough pain and discuss their experience with their physician to determine if a dosage adjustment is warranted. Titration should be initiated using multiples of the 100 mcg *FENTORA* tablet. Patients needing to titrate above 100 mcg can be instructed to use two 100 mcg tablets (one on each side of the mouth in the buccal cavity). If this dose is not successful in controlling the breakthrough pain episode, the patient may be instructed to place two 100 mcg tablets on each side of the mouth in the buccal cavity (total of four 100 mcg tablets). Although not bioequivalent, four 100 mcg *FENTORA* tablets were found to deliver approximately 12% and 13% higher values for $C_{max}$ and $AUC_{0-\infty}$, respectively, compared to one 400 mcg *FENTORA* tablet. Consequently, patients converting from four 100 mcg tablets to one 400 mcg *FENTORA* tablet would be expected to experience a decrease in plasma concentration. The impact of this decrease on pain relief has not been evaluated clinically. Titrate above 400 mcg by 200 mcg increments bearing in mind (1) Using more than 4 tablets simultaneously has not been studied and (2) It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose. To reduce the risk of overdose during titration, patients should have only one strength *FENTORA* tablet available at any one time. Patients should be strongly encouraged to use all of their *FENTORA* tablets of one strength prior to being prescribed the next strength. If this is not practical, unused *FENTORA* should be disposed of safely. (See **DISPOSAL OF *FENTORA***.) Once a successful dose has been established, if the patient experiences greater than four breakthrough pain episodes per day, the dose of the maintenance (around-the-clock) opioid used for persistent pain should be re-evaluated. **Dosage Adjustment:** Dosage adjustment of both *FENTORA* and the maintenance (around-the-clock) opioid analgesic may be required in some patients in order to continue to provide adequate relief of breakthrough pain. Generally, the *FENTORA* dose should be increased when patients require more than one dose per breakthrough pain episode for several consecutive episodes.

**Opening the Blister Package:** Patients should be instructed not to open the blister until ready to administer. A single blister unit should be separated from the blister card by tearing it apart at the perforations. The blister unit should then be bent along the line where indicated. The blister backing should then be peeled back to expose the tablet. **Patients should NOT attempt to push the tablet through the blister as this may cause damage to the tablet.** The tablet should not be stored once it has been removed from the blister package as the tablet integrity may be compromised and because this increases the risk of accidental exposure to the tablet.

**Tablet Administration:** Patients should remove the tablet from the blister unit and **immediately** place the entire *FENTORA* tablet in the buccal cavity (above a rear molar, between the upper cheek and gum). **Patients should not attempt to split the tablet.** The *FENTORA* tablet should not be sucked, chewed or swallowed, as this will result in lower plasma concentrations than when taken as directed. The *FENTORA* tablet should be left between the cheek and gum until it has disintegrated, which usually takes approximately 14-25 minutes. After 30 minutes, if remnants from the *FENTORA* tablet remain, they may be swallowed with a glass of water. Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl.

**SAFETY AND HANDLING**

*FENTORA* is supplied in individually sealed, child-resistant blister packages. The amount of fentanyl contained in *FENTORA* can be fatal to a child. **Patients and their caregivers must be instructed to keep *FENTORA* out of the reach of children.** (See **BOXED WARNING, WARNINGS, PRECAUTIONS,** and **MEDICATION GUIDE**.) Store at 20-25ºC (68-77ºF) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use. (See USP Controlled Room Temperature.) *FENTORA* should be protected from freezing and moisture. Do not use if the blister package has been tampered with.

**DISPOSAL OF *FENTORA***

**Patients and members of their household must be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed.** Instructions are included in **Information for Patients and Their Caregivers** and in the Medication Guide. If additional assistance is required, referral to the *FENTORA* 800# (1-800-896-5855) should be made.

**HOW SUPPLIED**

Each carton contains 7 blister cards with 4 tablets in each card. The blisters are child resistant, encased in peelable foil, and provide protection from moisture. Each dosage strength is uniquely identified by the debossing on the tablet. The dosage strength of each tablet is marked on the tablet, the blister package and the carton. See blister package and carton for product information. **Note: Colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.**

Manufactured for:
Cephalon, Inc.
Frazer, PA 19355

By:
CIMA LABS, INC.®
10000 Valley View Road
**Eden Prairie**, MN 55344

and

Cephalon, Inc.
4745 Wiley Post Way
**Salt Lake City**, UT 84116

U. S. Patent No. 6,200,604 and 6,974,590
Printed in USA

FENT 085a

# Journal of Opioid Management™

*A medical journal for proper and adequate use*

470 Boston Post Road • Weston, MA 02493
781-899-2702 • Fax: 781-899-4900
E-mail: jom@pnpco.com

# Journal of Opioid Management™

*A medical journal for proper and adequate use*

Published bimonthly by Prime National Publishing Corporation
470 Boston Post Rd., Weston, MA 02493 • 781-899-2702, Fax: 781-899-4900
www.opioidmanagement.com
E-mail: jom@pnpco.com



## Subscription Rates: (All rates in US dollars)

**Individual:** US $322; Canada $349; Foreign $392
**Institution:** US $430; Canada $457; Foreign $500
**Library:** US $494; Canada $517; Foreign $522
**Single issues:** US $85; Canada $100; Foreign $125

## Subscription Information

Submit your complete name, address and zip code, attention: ***Journal of Opioid Management***, Subscription Department, 470 Boston Post Road, Weston, MA 02493. Please enclose check, purchase order or credit card number and expiration date with authorization signature. Subscribers notifying the publication of an address change must submit an old mailing label and their new address, including zip code. No claims for copies lost in the mail may be allowed unless they are received within 90 days of the date of issue. Claims for issues lost as a result of insufficient notice of change of address will not be honored.

## Manuscript Submittal/Author Information

**(See Call for manuscripts)**

## Quotations and Reprints

Quotations from ***Journal of Opioid Management*** may be used for purposes of review without applying for permission as long as the extract does not exceed 500 words of text, and appropriate credit is given to the Journal. Authorization to photocopy items for internal use of specific clients, is granted by Prime National Publishing Corp., provided the appropriate fee is paid directly to: Copyright Clearance Center (CCC), 222 Rosewood Drive, Danvers, MA 01923, USA (978) 750-8400. CCC should also be contacted prior to photocopying items for educational classroom use. Multiple reprints of material published in ***Journal of Opioid Management*** can be obtained by filling out the reprint order form in the publication or by calling 781-899-2702.



## Postal Information

Postmaster: Send address changes and form 3579 to: ***Journal of Opioid Management***, 470 Boston Post Road, Weston, MA 02493.



Since 2005, this journal has been printed on acid-free paper that meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).

12576 1/22/07 Rev. h

# Journal of Opioid Management™

*A medical journal for proper and adequate use*



***Editor-in-Chief, Robert E. Enck, MD***

*Professor of Medicine, Assistant Division Chief for Clinical Activities, Division of Medical Oncology, Thomas Jefferson University, Philadelphia, Pennsylvania.*


## *Editorial Review Board*

GUEST EDITORIAL

# Fentanyl: Are we paying too high a price?

Vincenzo Fodale, MD
Manuela Romeo, MD
Federica Mafrica, MD

## INTRODUCTION

Fentanyl is an analgesic opioid that was introduced into medical practice in the 1960s. It has been commonly used for decades in anesthesia, sedation, and pain management. Along with nitrous oxide and thiopental, fentanyl is one of the anesthesiological drugs with the longest history of use. In fact, after about 50 years, it is still administered daily to millions of adult and pediatric patients. However, an increasing number of papers report that the use of fentanyl is correlated to unpleasant effects both in and out of clinical scenarios. Recently, *The Lancet* has focused on the drug's use and effects, not only in patients but also in healthcare professionals, offering evidence of its increasingly prevalent role as a drug of abuse and overdose. In fact, the drug has become so strongly associated with abuse in recent years that it has earned the new moniker of "killer fentanyl."[1,2]

Given the large number of patients receiving the drug, as well as of physicians administering it (anesthesiologists, intensive care specialists, pain professionals, etc.), queries about the validity of these accusations are both warranted and expected.

## ABUSE AND OVERDOSE: A GLOBAL PROBLEM

The prevalence of overdose deaths attributed to opioids is increasing throughout the world. Heroin is still the predominant illicit opioid of interest for toxicology laboratories because of its widespread availability and its ability to elicit respiratory depression and coma,[3] but today, new, totally synthetic drugs are becoming an increasingly important subset of abused substances. Fentanyls, a family of very potent narcotic analgesics, are of particular concern. They first appeared on the streets in California in 1979 under the name "China White," sold as heroin substitutes or used to lace street drugs.

It is likely that as efforts to restrict the importation of natural opiates and prevent diversion of pharmaceuticals have become more effective, fentanyls have become increasingly important drugs of abuse.[4] The effects of fentanyl are indistinguishable from those produced by nasal inhalation of street heroin. In light of this, and because of its very low production costs, fentanyl is very attractive for the narcotics market.[2]

Health workers began to notice a spike in fentanyl overdoses and deaths late last year, thanks to new, sophisticated toxicology and autopsy tests.[1] At least 112 overdose deaths have been associated with the drug. No preexisting medical conditions were identified as possible risk factors in any of these recorded deaths. Although most of the fentanyl victims had a prior history of intravenous drug use, drugs such as morphine or codeine were not commonly found in their systems, which suggests that the victims had little or no opiate tolerance. It is probable that the general availability of the drug, rather than the potency of any particular analog, determined the incidence of overdose deaths.[5] More than 20 years ago, in California, increased fentanyl use was detected as a new trend in drug use in a sample population of young users.[6] In early 1992, the Office of the Chief Medical Examiner of the State of Maryland encountered 30 cases in which fentanyl was identified in postmortem examinations of victims.[7]

Increases in fentanyl abuse are therefore a growing public health problem, with the risk that within a few years, fentanyl abuse could evolve into a problem of global epidemic proportions.[2]

## CLINICAL ASPECTS

As with other opioids, fentanyl use can induce opioid tolerance, physical dependence, and addiction. These consequences limit its applications for appropriate long-term use.

Cases of withdrawal syndrome related to fentanyl have been observed in both adult and pediatric patients in intensive care units (ICUs). There is an elevated incidence of abstinence syndrome in children in the pediatric ICU, owing to the interruption of fentanyl infusion and midazolam; this syndrome is related to fentanyl dose and time of use.[8] Symptoms include systemic convulsions

with loss of consciousness.[9] Acute withdrawal syndrome related to the administration of analgesic and sedative medications has also been observed in adult ICU patients, particularly in mechanically ventilated patients receiving extended ICU care (≥ seven days).[10]

Thanks to its highly lipophilic nature, fentanyl can be administered in the form of a transdermal patch to control pain. From 1997 to 2000, the Los Angeles County coroner's toxicology laboratory encountered 25 cases involving fentanyl patches. Causes of death included 15 accidental, five natural, three suicidal, and two undetermined.[11]

The number of fentanyl-related deaths increased between 2000 and 2002, and 19 out of 23 deaths attributed to fentanyl misuse or abuse were related to transdermal patches. Routes of administration included transdermal, transmucosal/oral, intravenous, and a combination of routes, suggesting that fentanyl is rapidly becoming a desirable opioid for street users, similar to oxycodone and methadone.[12]

Pharmacogenomics—the study of genetic contributions to drug action—may aid in certifying fentanyl toxicity. As suggested in 92 percent of fentanyl-related deaths, toxicity may be partially due to cytochrome P450 (CYP) 3A4*1B and 3A5*3 variant alleles, resulting in variable fentanyl metabolism. In fact, postmortem/in vivo data have provided scientific evidence that CYP3A5 is involved in fentanyl metabolism, and that homozygous CYP3A5*3 causes impaired metabolism of fentanyl.[13]

Large-dose fentanyl anesthesia induces prolonged suppression of natural killer (NK) cell cytotoxicity in patients undergoing abdominal surgery, and this increases the risk of tumor metastasis. In fact, suppression of NK cells at the time of surgery may induce tumor dissemination and the spread of metastases.[14]

There are numerous problems for patients and healthcare providers regarding use, abuse, or overdose of fentanyl in anesthesia, intensive care, and pain therapy; these are summarized below. The quantity of related international research published in the last few decades is quite impressive.

Problems for patients include the following:

- dependence and withdrawal syndromes after long-term infusion in adults and children;[15,16]
- muscle rigidity (increased large-trunk-muscle tone with decreased thoracic compliance);[17,18]
- respiratory depression (inhibition of brain stem respiratory center);[19-21]
- glottic closure (effects on vagal motor neurons with tonic vocal-fold closure and pharyngeal obstruction of airflow);[22-25]
- nausea and vomiting (stimulation of brain stem chemoreceptor trigger zone);[26,27]
- misperceptions of sexual abuse by critically ill patients;[28]
- analgesic abuse;[29,30] and
- improper intravenous injection of fentanyl derived from transdermal systems.[31,32]

Problems in healthcare providers include the following:

- high risk of addiction for medical staff working with these drugs;[33]
- dependence in anesthesia providers;[34]
- substance abuse by anesthesiologists;[35] and
- increased mortality resulting from overdose and abuse by healthcare professionals.[36]

## FENTANYL ADDICTION

Risk of addiction through occupational exposure to drugs of abuse is an important but relatively neglected public health problem. It is well known that secondhand inhalation of vapors from crack cocaine can be quite dangerous, but rarely has the alarm been raised about exposing anesthesiologists to secondhand fentanyl.[37] To explain the high incidence of this problem, it has been hypothesized that aerosolization of anesthetics administered intravenously to patients in the operating room may be an unintended source of exposure for physicians.[38]

Fentanyl has been detected in the air of cardiovascular operating rooms, and the highest concentrations were close to the patient's mouth, where anesthesiologists sometimes work for hours.[39] As with tobacco, secondhand exposure to opioids can inadvertently sensitize, increasing the risk of developing addiction, and brain changes may occur, leading to abuse, dependence, and behavioral disorders; these problems are more likely among anesthesiologists and surgeons.[39] Moreover, there are many risk factors, such as psychiatric stress and a family history of substance use disorders, that are implicated in fentanyl addiction in healthcare professionals and anesthesiologists.[40] Additionally, chemical impairment may be more common than usually thought in anesthesiologists, perhaps in part because of drug availability.[41] This may contribute to the overrepresentation of certain specialties among physicians with addiction.[38] The ends to which an individual motivated by an addicted

brain will go to obtain drugs to quench his or her chemical addiction has been described in fascinating detail.[42]

## CONCLUSION

The introduction of a new drug into clinical practice is welcomed when it helps our efforts at improving a patient's clinical course or the medical practice as a whole. Fentanyl's entrance into the anesthesiological setting, about 50 years ago, contributed greatly to the evolution of our science.

Half a century has passed since then, and clinical practice has undergone substantial evolution. Anesthesiology has witnessed rapid, continuous changes in anesthetic drugs, as well as inhalational and neuromuscular blocking drugs. But its very low price has made fentanyl an "evergreen," and in today's climate of cost consciousness, hospital administrations still push its use and avoid promoting newer and more specific opioids.[2] Military units' interest in the toxic effects of fentanyl is also increasing, as suggested by the Dubrovka theater incident of 2002. The Russian military pumped a fentanyl-related compound into the theater two and a half days after it was seized by armed Chechen militants, who were holding 850 occupants hostage. Because of respiratory depression induced by the compound, all of the militants were killed—along with over 100 hostages.[43]

Fentanyl is implicated in complications, toxicity, addiction, abuse, overdose, and death in patients and healthcare professionals. The "gentlemanly" face of fentanyl has changed, and it is now becoming viewed as a potential killer. In light of its potentially fatal side effects and growing popularity as a street drug, maybe the widespread use of fentanyl should be reconsidered. Since legally related problems should also be taken into consideration, recommendations by various institutions for the limitation of fentanyl use could be devised.

*Vincenzo Fodale, MD, Aggregate Professor of Anesthesiology and Intensive Care, Department of Neuroscience, Psychiatric and Anesthesiological Sciences, University of Messina School of Medicine, Messina, Italy.*

*Manuela Romeo, MD, School of Medicine and Surgery, University of Messina, Messina, Italy.*

*Federica Mafrica, MD, Research Residents Program, Anesthesia Intensive Care, Department of Neuroscience, Psychiatric and Anesthesiological Sciences, University of Messina School of Medicine, Messina, Italy.*

## REFERENCES

1. Boddiger D: Fentanyl-laced street drugs "kill hundreds." *Lancet.* 2006; 368(9535): 569-570.
2. Fodale V, Mafrica F, Santamaria LB: Killer fentanyl: A lesson from anaesthesiology. *Lancet.* 2006; 368(9543): 1237-1238.
3. Drummer OH: Recent trends in narcotic deaths. *Ther Drug Monit.* 2005; 27(6): 738-740.
4. Henderson GL: Designer drugs: Past history and future prospects. *J Forensic Sci.* 1988; 33(2): 569-575.
5. Henderson GL: Fentanyl-related deaths: Demographics, circumstances, and toxicology of 112 cases. *J Forensic Sci.* 1991; 36(2): 422-433.
6. Siegel RK: New trends in drug use among youth in California. *Bull Narc.* 1985; 37(2-3): 7-17.
7. Smialek JE, Levine B, Chin L, et al.: A fentanyl epidemic in Maryland 1992. *J Forensic Sci.* 1994; 39(1): 159-164.
8. Bicudo JN, de Souza N, Mangia CM, et al.: Withdrawal syndrome associated with cessation of fentanyl and midazolam in pediatrics. *Rev Assoc Med Bras.* 1999; 45(1): 15-18.
9. Takara I, Tomiyama H, Tokumine J, et al.: [Withdrawal syndrome in a critically ill child after sedation with midazolam and fentanyl]. *Masui.* 2004; 53(7): 791-794.
10. Cammarano WB, Pittet JF, Weitz S, et al.: Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. *Crit Care Med.* 1998; 26(4): 676-684.
11. Anderson DT, Muto JJ: Duragesic transdermal patch: Postmortem tissue distribution of fentanyl in 25 cases. *J Anal Toxicol.* 2000; 24(7): 627-634.
12. Kuhlman JJ Jr, McCaulley R, Valouch TJ, et al.: Fentanyl use, misuse, and abuse: A summary of 23 postmortem cases. *J Anal Toxicol.* 2003; 27(7): 499-504.
13. Jin M, Gock SB, Jannetto PJ, et al.: Pharmacogenomics as molecular autopsy for forensic toxicology: Genotyping cytochrome P450 3A4*1B and 3A5*3 for 25 fentanyl cases. *J Anal Toxicol.* 2005; 29(7): 590-598.
14. Shavit Y, Ben-Eliyahu S, Zeidel A, et al.: Effects of fentanyl on natural killer cell activity and on resistance to tumor metastasis in rats. Dose and timing study. *Neuroimmunomodulation.* 2004; 11(4): 255-260.
15. Franck LS, Naughton I, Winter I: Opioid and benzodiazepine withdrawal symptoms in paediatric intensive care patients. *Intensive Crit Care Nurs.* 2004; 20(6): 344-351.
16. Taha J, Favre J, Janszen M, et al.: Correlation between withdrawal symptoms and medication pump residual volume in patients with implantable Synchro Med pumps. *Neurosurgery.* 2004; 55: 390-393.
17. Jackson FW: Fentanyl and the wooden chest. *Gastroenterology.* 1994; 106(3): 820-821.
18. Viscomi CM, Bailey PL: Opioid-induced rigidity after intravenous fentanyl. *Obstet Gynecol.* 1997; 89(5 Pt 2): 822-824.
19. Bouillon T, Bruhn J, Roepcke H, et al.: Opioid-induced respiratory depression is associated with increased tidal volume variability. *Eur J Anaesthesiol.* 2003; 20(2): 127-133.
20. Clark JD, Edwards T: Severe respiratory depression in a patient with gastroparesis while receiving opioids for pain. *Clin J Pain.* 1999; 15(4): 321-323.
21. McLoughlin R, McQuillan R: Transdermal fentanyl and respiratory depression. *Palliat Med.* 1997; 11(5): 419.
22. Tsou CH, Luk HN: Fentanyl-induced coughing and airway hyperresponsiveness. *Acta Anaesthesiol Sin.* 2002; 40(4): 165-172.
23. Ananthanarayan C: Tussive effect of fentanyl. *Anaesthesia.* 1990; 45(7): 595.
24. Arandia HY, Patil VU: Glottic closure following large doses of fentanyl. *Anaesthesiology.* 1987; 66(4): 574-575.
25. Gin T, Chui PT: Coughing after fentanyl. *Can J Anaesth.* 1992; 39(4): 406.
26. Yu SY, Sun Y, Wu YL, et al.: [Transdermal fentanyl for the management of cancer pain: A survey of 4492 patients]. *Zhonghua Zhong Liu Za Zhi.* 2005; 27(6): 369-372.
27. Okamura K, Sanuki M, Kinoshita H, et al.: [Study of nausea

and vomiting accompanying intravenous patient-controlled analgesia with fentanyl after cervical spine surgery]. *Masui.* 2003; 52(11): 1181-1185.
28. Hansen-Flaschen J, Adler BS: Allegations of sexual abuse in an intensive care unit. *Crit Care Med.* 1999; 27(2): 437-440.
29. Nevin J: Drug update: Fentanyl patch abuse. *Emerg Med Serv.* 2004; 33(7): 24-25.
30. Compton WM, Volkow ND: Abuse of prescription drugs and the risk of addiction. *Drug Alcohol Depend.* 2006; 83 Suppl 1: S4-S7.
31. Lilleng PK, Mehlum LI, Bachs L, et al.: Deaths after intravenous misuse of transdermal fentanyl. *J Forensic Sci.* 2004; 49(6): 1364-1366.
32. Jost U, Wolter E, Bohrer H: [Repeated improper intravenous injection of fentanyl from a transdermal system]. *Dtsch Med Wochenschr.* 2004; 129(7): 313-314.
33. Holth LS, Friesen R, Green C, et al.: A simple method for quantifying fentanyl, sufentanil, or morphine in discard syringes from anesthesia procedures. *Ther Drug Monit.* 2002; 24(5): 665-669.
34. Moore NN, Bostwick JM: Ketamine dependence in anaesthesia providers. *Psychosomatics.* 1999; 40(4): 356-359.
35. Kintz P, Villain M, Dumestre V, et al.: Evidence of addiction by anesthesiologists as documented by hair analysis. *Forensic Sci Int.* 2005; 153(1): 81-84.
36. Schwartz JG, Garriott JC, Somerset JS, et al.: Measurements of fentanyl and sufentanil in blood and urine after surgical application. Implication in detection of abuse. *Am J Forensic Med Pathol.* 1994; 15(3): 236-241.
37. Gold MS, Byars JA, Frost-Pineda K: Occupational exposure and addictions for physicians: Case studies and theoretical implications. *Psychiatr Clin North Am.* 2004; 27(4): 745-753.
38. McAuliffe PF, Gold MS, Bajpai L, et al.: Second-hand exposure to aerosolized intravenous anesthetics propofol and fentanyl may cause sensitization and subsequent opiate addiction among anesthesiologists and surgeons. *Med Hypotheses.* 2006; 66(5): 874-882.
39. Gold MS, Melker RJ, Dennis DM, et al.: Fentanyl abuse and dependence: Further evidence for second hand exposure hypothesis. *J Addict Dis.* 2006; 25(1): 15-21.
40. Domino KB, Hornbein TF, Polissar NL, et al.: Risk factors for relapse in health care professionals with substance use disorders. *JAMA.* 2005; 293(12): 1513-1515.
41. Ward CF, Ward GC, Saidman LJ: Drug abuse in anesthesia training programs. A survey: 1970 through 1980. *JAMA.* 1983; 250(7): 922-925.
42. Thompson ES: Where is the fentanyl? *Anesthesiology.* 2004; 101(1): 265.
43. Skulska A, Kala M, Parczewski A: Fentanyl and its analogues in clinical and forensic toxicology. *Prz Lek.* 2005; 62(6): 581-584.

ORIGINAL ARTICLE

# Prevalence of opioid dependence in spine surgery patients and correlation with length of stay

Mohammad Sami Walid, MD, PhD
Leon Hyer, PhD
Mohammed Ajjan, MD
Aaron C. M. Barth
Joe Sam Robinson, Jr., MD

## ABSTRACT

***Objective:*** *We addressed the prevalence of opioid dependence (OD) in spine surgery patients and its correlation with length of stay (LOS) as the most important determinant of hospital cost.*

***Methods:*** *The study took place at Georgia Neurosurgical Institute and the Medical Center of Central Georgia between March 2006 and January 2007. A prospective convenience sample of 150 spine surgery patients (48 lumbar diskectomy, 60 cervical decompression and fusion, and 42 lumbar decompression and fusion [LDF]) was assembled. Patients were interviewed before surgery using a questionnaire designed in accordance with the World Health Organization and DSM-IV-TR criteria for the diagnosis of OD. The prevalence of OD was calculated based on questionnaire results. Pain intensity was quantified during admission using a 0-to-10 pain scale. We used pain intensity multiplied by duration of pain in months (WR index) as a new parameter. Lengths of stay were collected following patients' discharge from hospital. Pearson correlation and regression analysis were performed using SPSS software.*

***Results:*** *Thirty (20.00 percent) patients were opioid dependent. The prevalence was highest among LDF patients (23.81 percent), females (22.78 percent), and, to a lesser degree, Caucasians (20.87 percent). There was no correlation between OD and age ($r = 0.08$, $p > 0.1$) or between OD and LOS ($r = 0.09$, $p > 0.1$). This study proved a very significant positive correlation between OD and pain intensity ($r = 0.24$, $p < 0.01$) and between OD and the WR index ($r = 0.30$, $p < 0.01$). On the other hand, there was a significant positive correlation between LOS and age ($r = 0.42$, $p < 0.01$), between LOS and the number of previous spine surgeries ($r = 0.28$, $p < 0.01$), and between LOS and duration of pain ($r = 0.18$, $p < 0.05$). Regression analysis showed that age, ethnicity, and type of surgery were the main determinants of LOS.*

***Conclusions:*** *Chronic pain and prolonged use of opioids raise the prevalence of OD in spine surgery patients to 20 percent. The lack of effect of OD on LOS after surgical intervention means that efforts to decrease LOS by trying to satisfy patients' craving for opioids will not be fruitful. Older, African-American LDF patients with a lengthy history of pain and multiple spine surgeries in the past are the most likely to stay longer in hospital.*

*Key words: opioid, dependence, spine surgery, length of stay, WR index*

## INTRODUCTION

> The first thing they told us in medical school is that no one has ever died from pain, but plenty of physicians have had their careers destroyed trying to help people who are in pain.
>
> —Comment from an emergency room physician requesting anonymity (2001)

Chronic pain and addiction to prescription painkillers are two growing national problems. In 1999, it was estimated that over 86 million Americans suffered from ongoing chronic pain caused by back injuries, arthritis, and other noncancer conditions. Over 66 million individuals were partially or totally disabled due to back pain, and 8 million were permanently disabled. By 2003 the numbers had increased, with approximately 117 million American adults suffering from chronic pain conditions.[1] The director of the National Institute on Drug Abuse, Nora Volkow,[2] stated in 2005 that if opiates are given for pain, an estimated 5 to 15 percent of patients receiving them will become addicted. When opiates are prescribed for short-term use (one to two weeks), there is little likelihood of addiction, but there is an increased risk of addiction with long-term opiate use.

Fishbain et al.[3] reviewed prevalence percentages for addiction in patients with chronic pain. They reported that different authors utilized different definitions and criteria. Overall, the prevalence of drug abuse/dependence/addiction for patients with chronic pain was in the range of 3.2 to 18.9 percent. Other studies have directly or indirectly explored this issue. Hoffmann et al.[4] found an addiction rate of 23.4 percent, Chabal et al.[5] found a rate of 34 percent, and Kouyanou et al.[6] reported a rate of 12 percent. There has also been one report relating to chronic pain populations at a US Veterans' Affairs (VA) facility and in a primary care setting. In this study, Reid et al.[7] found that prescription opioid abusive behavior was recorded in 24 percent of the VA patients and 31 percent of the primary care patients. As "opioid abusive behavior" does not necessarily translate into addiction, there is some uncertainty as to how to interpret these results and their implications.

Patients with back pain are among those with high potential for prescription-painkiller abuse. The prevalence of opioid dependence (OD) in back pain patients admitted for spine surgery has not been studied before, and its association with length of stay (LOS) in the hospital has not been determined. Therefore, in this article we address two issues: 1) the prevalence of OD in spine surgery patients, and 2) the correlations between different opioid-, pain-, and LOS-related parameters. Our hypothesis was that patients classified as opioid dependent would stay in the hospital for longer periods than those not meeting OD criteria. The study protocol was approved by the Institutional Review Board of the Medical Center of Central Georgia.

## METHODS

We prospectively studied 150 preoperative spine surgery patients at Georgia Neurosurgical Institute between March 2006 and January 2007. All eligible patients were using an opioid for pain relief (convenience sample). These participants were between 24 and 78 years of age; 52.67 percent were female and 76.67 percent were Caucasian, and all were diagnosed with either herniated nucleus pulposus in the cervical or lumbar segments or spinal stenosis.

The World Health Organization (WHO) and the fourth revision of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) both require three or more of the following six criteria for a diagnosis of dependence:

1. a strong desire or sense of compulsion to take the drug in question;

2. difficulties controlling drug-taking behavior in terms of its onset, termination, or levels of use;

3. a physiological withdrawal state when drug use is stopped or reduced, as evidenced by the characteristic withdrawal syndrome for the substance or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;

4. evidence of tolerance such that increased doses of the drug are required in order to achieve effects originally produced by lower doses;

5. progressive neglect of alternative pleasures or interests because of drug use, as well as increased amounts of time necessary to obtain or take the drug or to recover from its effects; and

6. persisting with drug use despite clear evidence of overtly harmful consequences, such as harm to the liver, depressive mood states, or impairment of cognitive functioning.[8,9]

The Walid-Robinson Opioid-Dependence (WROD) Questionnaire was designed based on the above mentioned criteria:

1. Which of your drugs helps you most to ease the pain? Which do you desire to continue using?

2. Do you now experience lengthy periods of use or binge patterns of use?

3. Do you have tremors and use substances to relieve withdrawal symptoms?

4. Are you able to take more of the drug without easing the pain?

5. Do you neglect food, hygiene, or healthcare?

6. Do you continue to use the drug despite knowledge of problems caused or exacerbated by it?

The prevalence of OD in our convenience sample was calculated based on the results of this questionnaire. Pain intensity was quantified during admission using a 0-to-10 pain scale. We used pain intensity multiplied by duration of pain suffering in months (Walid-Robinson [WR] index) as a new parameter. Lengths of stay were collected following patients' discharge from hospital (after being able to stand and walk in the absence of complications). Pearson correlation and regression analysis were performed using SPSS software.

Counseling and Pharmacotherapy...

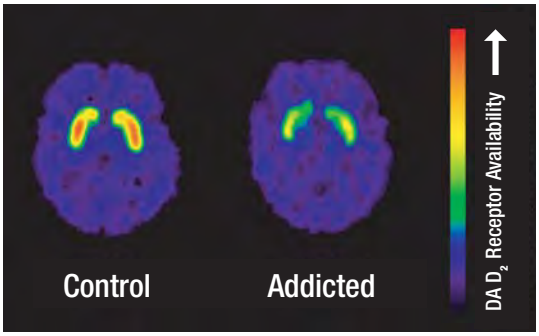
# Help Enhance the Recovery Plan for Your Opioid-Dependent Patients

As a counselor, you may often see patients with opioid dependence who come to you for help and are ready to take the next step toward recovery. Many of them may be taken off course by withdrawal symptoms or drug cravings, and ultimately relapse. Some patients feel like they have failed themselves, and you might feel challenged in your efforts to help.

While psychosocial counseling is a cornerstone to successful opioid-dependence treatment, these patients may be candidates for medical treatment as an adjunct to counseling. A treatment option is available to address the biological basis of this disease within the privacy of a physician's office.

## *Evolving Evidence: Opioid Dependence Is a Biological Brain Disease*

Studies document that continued drug use causes neurological and molecular changes in the brain. In fact, these alterations in brain structure and function persist long after drug use has ceased[1,2]—perpetuating the cycle of drug-seeking behavior and withdrawal avoidance.




PET scans confirm the biological differences between the brain of a healthy volunteer and that of an opioid-dependent individual.[3]

## *Implementing an Integrated Treatment Program: Improving Patients' Outcomes*

Pharmacotherapy plays an important role in helping control the biological effects of dependency—specifically, withdrawal symptoms and cravings. These are often the driving forces that lead individuals to continued opioid use, despite ongoing counseling. Addressing these symptoms with pharmacotherapy may allow your patients to have a more focused approach, positive attitude, and greater receptivity to counseling.

In fact, studies have shown that treatment using a combined strategy improved outcomes for many patients, including[4]:

- Increase in therapy retention
- Improvement in personal relationships and employment
- Decrease in illicit drug use

**For more information about pharmacotherapy that can help you get the results you're seeking, please visit opioiddependence.com, or call 1-877-782-6966.**

**References:**

**1.** Camí J, Farré M. Mechanisms of disease: drug addiction. *N Engl J Med.* 2003;349:975-986.
**2.** Leshner AI. Addiction is a brain disease, and it matters. *Science.* 1997;278:45-47.
**3.** Wang G-J, Volkow ND, Fowler JS, et al. Dopamine $D_2$ receptor availability in opiate-dependent subjects before and after naloxone-precipitated withdrawal. *Neuropsychopharmacology.* 1997;16:174-182.
**4.** McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. The effects of psychosocial services in substance abuse treatment. *JAMA.* 1993;269:1953-1959.

RECKITT BENCKISER HEALTHCARE


TF06023 9/06 Printed in USA

## RESULTS

Out of 150 preoperative spine surgery patients (48 lumbar diskectomy [LMD], 60 cervical decompression and fusion [CDF], and 42 lumbar decompression and fusion [LDF]) on opioids (hydrocodone, acetaminophen plus hydrocodone, acetaminophen plus oxycodone, tramadol, hydromophone), 30 (20.00 percent) met the criteria for a diagnosis of OD.

Focusing on type of surgery (Figure 1), the percentage of OD was highest among LDF patients (23.81 percent), followed by CDF (21.67 percent) and LMD (14.58 percent). After categorizing the sample according to age (Figure 2), the graph seemed to indicate increased prevalence of OD with age. However, SPSS showed no correlation ($r = 0.08$, $p > 0.1$) between OD and age. Considering gender and ethnicity (Figure 3), rates were higher among females (22.78 percent, n = 79) than males (16.90 percent, n = 71) and, to a lesser degree, among Caucasians (20.87 percent, n = 115) than African Americans (17.14 percent, n = 35).

When taking LOS into consideration (Figure 4), we found no significant correlation with OD ($r = 0.09$, $p > 0.1$). Obviously, factors other than drug problems were determining LOS. The correlation coefficients between OD and LOS for each type of surgery were $r = 0.09$, $p > 0.1$ for LMD (n = 48); $r = 0.07$, $p > 0.1$ for CDF (n = 60); and $r = -0.08$, $p > 0.1$ for LDF (n = 42). The average hospital stays for OD patients compared to nondependent patients were as follows: 0.14 (n = 7) versus 0.07 (n = 41) for LMD, 2.08 (n = 13) versus 1.73 (n = 47) for CDF, and 4.00 (n = 10) versus 4.00 (n = 32) for LDF.

This study showed no correlation between OD and LOS ($r = 0.09$, $p > 0.1$) or between OD and age ($r = 0.08$, $p > 0.1$). However, it revealed a very significant correlation between OD and pain intensity ($r = 0.24$, $p < 0.01$) and between OD and the WR index ($r = 0.30$, $p < 0.01$) (Table 1). There were also significant positive correlations between LOS and age ($r = 0.42$, $p < 0.01$), LOS and the number of previous spine surgeries ($r = 0.28$, $p < 0.01$), and LOS and duration of pain ($r = 0.18$, $p < 0.05$) (Table 2).

Regression analysis showed that type of surgery ($p = 0.000$), age ($p = 0.016$), and ethnicity ($p = 0.032$) were the most significant variables affecting LOS (Figure 5). OD ($p = 0.911$) was the least significant factor among all studied variables.

## DISCUSSION

Before the 1960s, it was fairly common to ascribe elements of criminality, character deficit, immorality, and weakness of will to drug addiction. Because these attributes were not objective or scientifically based and carried various negative social connotations, the WHO, in 1964, recommended that the term "drug addiction" be replaced with "drug dependence" in an effort to define this problem more precisely.[10,11]

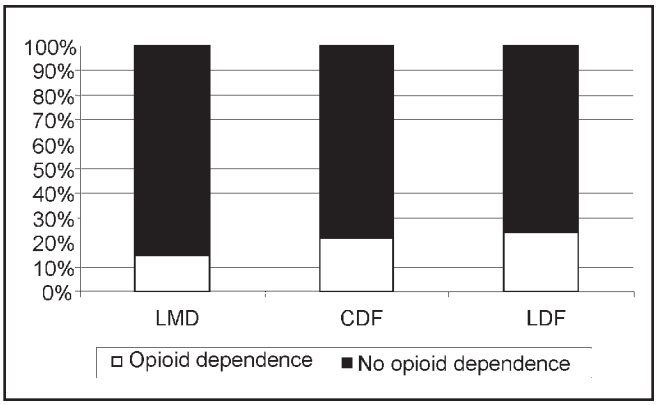



**Figure 1. OD prevalence by type of spine surgery. The percentage of OD was highest among LDF patients (23.81 percent), followed by CDF (21.67 percent) and LMD (14.58 percent).**

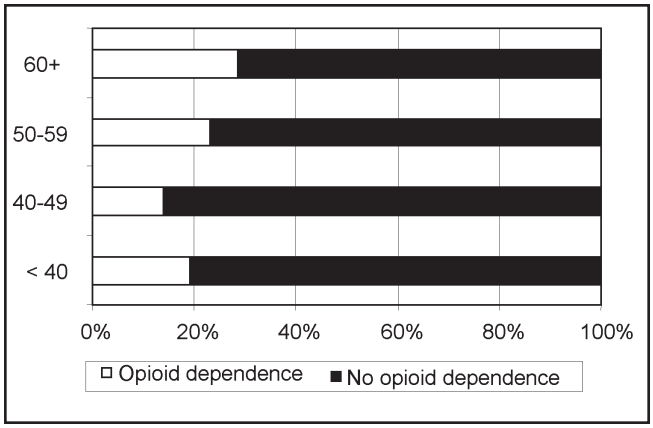



**Figure 2. OD prevalence by age group; no correlation between OD and age ($r = 0.08$, $p > 0.1$).**

In 1964, the WHO Expert Committee on Drug Dependence introduced "dependence" as "a cluster of physiological, behavioural and cognitive phenomena of variable intensity, in which the use of a psychoactive drug (or drugs) takes on a high priority. The necessary descriptive characteristics are preoccupation with a desire to obtain and take the drug and persistent drug-seeking behaviour. Determinants and problematic consequences of drug dependence may be biological, psychological or social, and usually interact."[10] The core concept of the WHO definition of drug dependence requires the presence of a strong desire or sense of compulsion to take the drug, and the WHO and DSM-IV-TR clinical guidelines for a definite diagnosis of dependence require that three or more of the six previously described characteristic features be experienced or exhibited.

Our questionnaire revealed that one-fifth (20.00 percent) of spine surgery patients were opioid dependent. This is likely because opioids are commonly prescribed

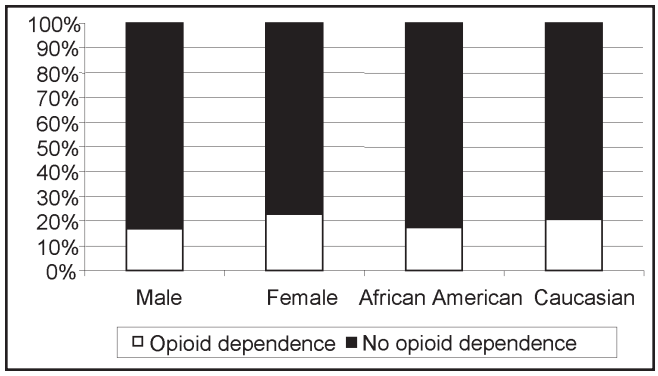



**Figure 3. OD prevalence by gender and ethnicity. OD rates were higher among females (22.78 percent) than males (16.90 percent) and, to a lesser degree, among Caucasians (20.87 percent) than African Americans (17.14 percent).**

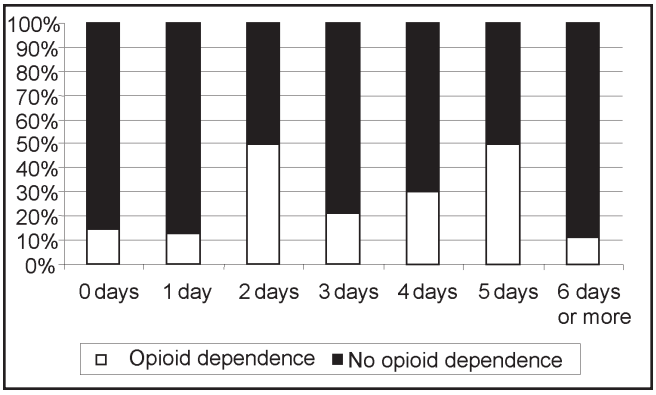



**Figure 4. OD prevalence by LOS; no correlation between OD and LOS (r = 0.09, p > 0.1).**

to patients with disk hernia and spinal stenosis. The high percentage of OD in LDF patients (24.39 percent) may be due to their long history of chronic pain accompanied by prolonged use of opioids. That the percentage of OD was higher among female patients (22.37 percent) than males agrees with the observation that women are more likely to be prescribed an abusable prescription drug.[12]

Hospital LOS is dependent on many medical, social, psychological, and institutional factors. In this study, age, number of previous spine surgeries, and duration of pain suffering were correlated with LOS but not OD. The older the patient, the more health problems he or she has, and the more time he or she will need to recover. In addition,

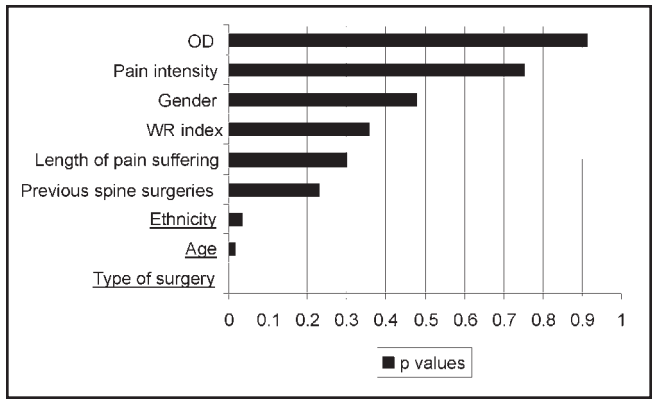



**Figure 5. Variables affecting LOS; underlined variables are statistically significant.**

elderly patients have more comorbidities, as well as altered drug pharmacokinetics and pharmacodynamics. They are also more likely to be prescribed long-term and multiple medications, which can interact and increase side effects.[12] Regression analysis proved that age, ethnicity, and type of surgery were the main determinants of LOS. Combining results, we concluded that older, African-American LDF patients with a long duration of pain and a history of multiple spine surgeries were the most likely to stay longer in hospital. The role of ethnicity is unclear and requires further investigation. The lack of effect of OD on LOS after surgical intervention was surprising and proved our hypothesis wrong, as we originally anticipated a higher LOS for patients with OD.

Fear of addiction continues to be a barrier to adequate pain control. Patients, families, the public, and healthcare professionals have numerous misconceptions regarding addiction and the use of opioids to control pain. The media continually highlights negative uses of opioids, and this only enhances misconceptions concerning addiction. Unfortunately, relief of back pain is rarely featured in the media as an appropriate and beneficial use for opioids. In 1999, the American Pain Society surveyed 805 people with chronic pain regarding the adequacy of treatment received from their physicians. Only 26 percent of those respondents who had "very severe" pain reported taking opioids at the time of the survey.[13] In 2005, Mahowald et al.[14] studied opioid use in an orthopedic spine clinic and challenged the concept that opioid treatment is inappropriate for chronic nonmalignant pain. They provided clinical evidence to support and protect

**Table 1. OD correlations**

| | | Age | LOS | Number of previous spine surgeries | Pain intensity | Duration of pain | WR index | OD |
|---|---|---|---|---|---|---|---|---|
| OD | Pearson correlation | 0.077 | 0.085 | 0.027 | 0.236** | 0.218* | 0.296** | 1 |
| | Significance (two-tailed) | 0.348 | 0.299 | 0.743 | 0.006 | 0.012 | 0.000 | 0 |
| | n | 150 | 150 | 149 | 132 | 132 | 150 | 150 |

* Correlation is significant at the 0.05 level; ** Correlation is significant at the 0.01 level.

| Table 2. LOS correlations | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Age | LOS | Number of previous spine surgeries | Pain intensity | Duration of pain | WR index | OD |
| LOS | Pearson correlation | 0.418** | 1 | 0.284** | -0.008 | 0.182* | 0.175* | 0.085 |
| | Significance (two-tailed) | 0.000 | 0 | 0.000 | 0.930 | 0.036 | 0.033 | 0.299 |
| | n | 150 | 150 | 149 | 132 | 132 | 150 | 150 |
| * Correlation is significant at the 0.05 level; ** Correlation is significant at the 0.01 level. | | | | | | | | |

physicians treating patients with chronic musculoskeletal diseases, who may be reluctant to prescribe opioids because of possible sanctions from regulatory agencies. Additionally, the International Narcotics Control Board has called attention to the inadequate treatment of pain, due in part to overly restrictive laws and regulations that impede the adequate availability and medical use of opioids.[15]

Our study showed that spine surgery patients continue to suffer from severe pain despite opioid use. Chronic pain and prolonged use of opioids raise the risk of OD, as was proven by the very significant correlation between OD and the WR index ($r = 0.30$, $p < 0.01$). Further probing of the WR index is important, as it may prove to be a marker of OD in spine surgery patients. The average value of the WR index for OD patients was 660.

## CONCLUSIONS

The significant prevalence of OD among spine surgery patients merits attention. Chronic pain and prolonged use of opioids raise the prevalence of OD in spine surgery patients to 20 percent. The lack of effect of OD on LOS after surgical intervention means that efforts to decrease LOS by trying to satisfy patients' craving for opioids will not be fruitful. Older, African-American LDF patients with a long history of pain and multiple spine surgeries in the past are the most likely to stay longer in hospital.

Drug abuse and undertreated pain are both serious public health issues, but finding solutions for one need not undermine the other. Knowledgeable pain practitioners need to educate patients, families, the public, and other healthcare professionals about the differences between addiction, dependence, and tolerance, and the benefit of safely using opioids to relieve back pain.

*Mohammad Sami Walid, MD, PhD, Research Fellow, Medical Center of Central Georgia, Macon, Georgia.*

*Leon Hyer, PhD, Psychologist, Georgia Neurosurgical Institute, PC, Macon, Georgia.*

*Mohammed Ajjan, MD, Internist, Georgia Neurosurgical Institute, PC, Macon, Georgia.*

*Aaron C. M. Barth, Decision-Making Analyst, Medical Center of Central Georgia, Macon, Georgia.*

*Joe Sam Robinson, Jr., MD, Professor and Chairman, Georgia Neurosurgical Institute, PC, Macon, Georgia.*

## REFERENCES

1. Grinstead SF: *War on Drugs—War on Pain Management.* Addiction Free Pain Management Web site. Available at *www.addiction-free.com/chronic_pain_management_&_addiction_war_on_drugs.htm.* Accessed April 27, 2007.
2. Volkow N: What do we know and what don't we know about opiate analgesic abuse? Keynote address, Wednesday, March 30, 2005. Program and abstracts of the 24th Annual Scientific Meeting of the American Pain Society, March 30 through April 2, 2005, Boston, MA.
3. Fishbain DA, Rosomoff HL, Rosomoff RS: Drug abuse, dependence, and addiction in chronic pain patients. *Clin J Pain.* 1992; 8(2): 77-85.
4. Hoffmann NG, Olofsson O, Salen B, et al.: Prevalence of abuse and dependency in chronic pain patients. *Int J Addict.* 1995; 30(8): 919-927.
5. Chabal C, Erjavec MK, Jacobson L, et al.: Prescription opiate abuse in chronic pain patients: Clinical criteria, incidence, and predictors. *Clin J Pain.* 1997; 13(2): 150-155.
6. Kouyanou K, Pither CE, Wessely S: Medication misuse, abuse and dependence in chronic pain patients. *J Psychosom Res.* 1997; 43(5): 497-504.
7. Reid MC, Engles-Horton LL, Weber MB, et al.: Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med.* 2002; 17(3): 173-179.
8. World Health Organization: *Narcotic & Psychotropic Drugs: Achieving Balance in National Opioids Control Policy.* World Health Organization, 2000. Available at *www.painpolicy.wisc.edu/publicat/00whoabi/00whoabi.pdf.* Accessed April 27, 2007.
9. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR Fourth Edition (Text Revision).* Arlington, VA: American Psychiatric Publishing, 2000.
10. WHO Expert Committee on Addiction-Producing Drugs: *Thirteenth Report.* World Health Organization Technical Report Series No. 273. Geneva: World Health Organization, 1964.
11. World Health Organization: *5th Review of Psychoactive Substances for International Control.* Geneva: World Health Organization, 1981.
12. National Institute on Drug Abuse: *Trends in prescription drug abuse.* National Institute on Drug Abuse Web site. Available at *www.drugabuse.gov/ResearchReports/Prescription/prescription5.html.* Accessed April 27, 2007.
13. Portenoy RK: What should we tell the public to do. *APS Bulletin.* 1999; 9(5). Available at *www.ampainsoc.org/pub/bulletin/sep99/president.htm.*
14. Mahowald ML, Singh JA, Majeski P: Opioid use by patients in an orthopedics spine clinic. *Arthritis Rheum.* 2005; 52(1): 6-10.
15. International Narcotics Control Board: *Use of Essential Narcotic Drugs to Treat Pain is Inadequate, Especially in Developing Countries.* INCB Annual Report, Press Release No. 6. Vienna: United Nations Information Service, 2004.

ORIGINAL ARTICLE

# Oral naltrexone to enhance analgesia in patients receiving continuous intrathecal morphine for chronic pain: A randomized, double-blind, prospective pilot study

Scott Hamann, PhD, MD
Paul Sloan, MD

## ABSTRACT

***Background:*** *Years' worth of observations suggest that morphine has both inhibitory and excitatory actions, and that selective blockade of excitatory effects by low doses of opioid antagonists (e.g., naltrexone) may paradoxically enhance morphine analgesia. The purpose of this pilot study was to evaluate and compare the analgesic efficacy and safety of two different low doses of oral naltrexone given in addition to chronic intrathecal morphine infusions in patients with chronic nonmalignant pain (CNMP).*

***Methods:*** *After institutional review board approval, 15 patients with CNMP receiving continuous intrathecal morphine were admitted into a prospective, randomized, double-blind, placebo-controlled, seven-day pilot study. Patients were randomized into three treatment groups based on oral naltrexone dose: 100 μg (Group A, n = 3), 10 μg (Group B, n = 7), or placebo (Group C, n = 5). All patients continued with their constant intrathecal morphine infusion, and in addition they received one capsule of study medication every 12 hours for seven days. Other analgesics or coanalgesics were kept at a constant dose level throughout the study. Patients rated pain scores (visual analogue score [VAS]; 0 = no pain, 10 = worst pain imaginable) and side effects three times daily throughout the study period. Efficacy measures included pain intensity difference (PID) scores, constructed so that positive scores indicate a reduction in pain intensity and negative scores indicate a worsening of pain.*

***Results:*** *Fifteen patients (six male, nine female) with a mean (SD) age of 55 (10) years and weight of 81 (21) kg completed the study. The mean (SD) baseline VAS pain intensity rating was similar in all three groups (6.8 [1.5]). Baseline pain VAS score minus the lowest daily pain VAS score yielded the peak PID score. The peak PID score from Day 1 was statistically ($p < 0.05$) highest (median PID score: 5.9) in Group A compared with Group C. There was a trend in PID scores across Days 2 through 7, with median PID scores higher (i.e., greater pain relief; $p = 0.07$) in Group A. In the daily global pain assessments, the pain scores across Days 2 through 7 approached significance (least pain) in Group A compared to Group C ($p = 0.07$) or B ($p = 0.08$). Side effects were common (93 percent of patients), minor (headache, nausea, sedation, dry mouth), and similar across treatment groups. No serious adverse events were observed, and no evidence of opioid withdrawal was seen.*

***Conclusions:*** *1) Patients with chronic pain who received oral naltrexone 100 μg BID in addition to their chronic intrathecal morphine infusions demonstrated the greatest improvement ($p = 0.07$) in their daily pain scores. Because of the small sample size, the results did not reach traditional levels of significance. 2) Side effects were common, minor, and similar across treatment groups. 3) No serious adverse events were recorded. 4) No evidence of opioid antagonist toxicity or opioid withdrawal was observed.*

*Key words: chronic pain, opioid agonists, opioid antagonists, intrathecal analgesics, analgesia*

## INTRODUCTION

Morphine and other opioids have been prescribed for many years for the treatment of cancer pain and have been found to be effective for the relief of moderate to severe pain.[1] In the last decade, chronic oral or transdermal opioids have gained acceptance as treatments for chronic nonmalignant pain (CNMP).[2] For CNMP patients who do not achieve adequate analgesia with chronic oral opioids or who experience intolerable side effects from opioids, other forms of treatment, such as spinal analgesics, are often used.[3]

Opioids interact with stereospecific, saturable receptors in the brain, spinal cord, and other tissues, with a principal therapeutic effect of analgesia.[4] Morphine binding to inhibitory opioid receptors on nerve cells results in inhibition of the transmission of pain signals into the

brain. It has been observed, however, that while the dominant effect of opioids in their usual clinical doses is to inhibit opioid receptors, opioid agonists simultaneously activate excitatory opioid receptors on sensory nerve cells.[5] This paradoxical excitatory action can weaken opioid-induced analgesia and contribute to dependence and tolerance-related opioid-therapy failures.[5-7] Therefore, medications able to selectively block this excitatory effect on opioid receptors could theoretically enhance opioid analgesia.

The antiexcitatory actions of low-dose opioid antagonists and their potential as possible adjuncts for the enhancement of opioid agonist analgesia have been evaluated through basic and clinical research. Selective antagonism of excitatory opioid receptor function has been shown to enhance the inhibitory potency of opioid agonists in dorsal root ganglion cultures.[8] In rodent nociceptive paradigms, opioid antagonists not only exhibit biphasic dose-response curves[9,10] but also markedly enhance the analgesic potency of morphine when coadministered in remarkably low doses.[11,12]

Several clinical studies and case reports published over the years provide further evidence of this enhancement of opioid analgesia via concurrent use of low doses of opioid antagonists. Levine[13] examined the analgesic actions of naloxone in patients with postoperative dental pain in a controlled, double-blind trial and found that naloxone 400 and 1,000 μg potentiated the analgesic effect of oral pentazocine. A more recent case report demonstrated the opioid-analgesic-enhancing effect of naltrexone when added to chronic methadone therapy in a patient with chronic and refractory painful diabetic neuropathy. For this patient, the addition of naltrexone in the ultra-low dose of 1 μg twice daily not only improved pain relief but also allowed for a modest reduction in methadone dose.[14]

Naltrexone is a pure opioid antagonist that blocks the subjective effects of intravenously administered opioids. It has few, if any, intrinsic actions aside from its opioid-blocking properties. Based on the hypothesis that selective antagonism of opioid excitatory actions may enhance the analgesic potency of opioid agonists, we designed a study to evaluate the safety and efficacy of combined intrathecal morphine and low-dose naltrexone in the treatment of CNMP. Intrathecal opioid therapy delivers low doses of opioids close to the site of action and is often effective in treating CNMP syndromes. However, complete pain relief is not always achieved in all patients, and additional therapies are needed to control chronic pain in the refractory population.[15] Thus, the addition of a low-dose opioid antagonist (i.e., naltrexone) was proposed to enhance analgesia in patients experiencing incomplete pain relief while receiving chronic intrathecal opioids for CNMP. The purpose of this pilot study was to evaluate and compare the analgesic efficacy and safety of two different low doses of oral naltrexone when added to chronic intrathecal morphine therapy in patients with CNMP.

## METHODS

### Study design

This was a prospective, randomized, double-blind, single-center, placebo-controlled pilot study of the effects of low-dose oral naltrexone on pain relief produced by chronic intrathecal morphine administration. Oral naltrexone was chosen over intrathecal antagonists because of concerns about the unapproved nature of intrathecal naloxone use and the potential for neurotoxicity.

Written informed consent was obtained from all patients. The protocol and informed consent form were reviewed and approved by the Institutional Review Board at the University of Kentucky. The study was conducted in accordance with the provisions of the Declaration of Helsinki and its amendments, and with the International Conference on Harmonization Good Clinical Practice as adopted by the US Food and Drug Administration.[16]

### Patients

Adult patients with a history of incompletely relieved CNMP who were using indwelling intrathecal morphine delivery systems were eligible for enrollment. Eligible patients were those with chronic refractory pain and a history of inadequate pain relief following prior use of at least two different opioid analgesic medications. Patients had a baseline visual analogue pain score (VAS) of at least 5 (0 = no pain, 10 = unbearable pain). Premenopausal women testing negative on a serum pregnancy test within seven days of enrollment and either practicing abstinence or using a medically accepted contraception method were eligible for enrollment. Patients had to be willing and able to complete the necessary patient evaluations. Exclusion criteria included any condition that might interfere with the absorption of study medications (e.g., intractable nausea and vomiting, inability to take oral medication, certain gastrointestinal disorders); a history of clinically significant intolerance or hypersensitivity to study medications; a history of (or anticipated) procedures that might confound quantification of analgesia; chronic respiratory insufficiency; severe hepatic or renal impairment; unstable seizure disorder; and any other physical, mental, or psychological condition that might interfere with the study or the interpretation of its results. Patients were not eligible for the study if adjuvant analgesics (e.g., anticonvulsants, antidepressants, NSAIDs) or oral opioids had been started or discontinued within four weeks of study entry.

### Study procedures

Fifteen patients were recruited and randomly assigned to one of three naltrexone treatment groups: naltrexone 100 µg (Group A, n = 3), naltrexone 10 µg (Group B, n = 7), or placebo (Group C, n = 5). Oral study medication was provided in the form of identical hard, opaque gelatin capsules. The inactive ingredients were microcrystalline cellulose and magnesium stearate. Both patients and researchers were blinded to the dose of study medication. All bottles, used or unused, were saved for final disposition.

All patients continued their constant intrathecal morphine infusion at the same dose throughout the seven-day study period. Patients receiving adjuvant analgesics continued their medications without change throughout the study period. Prior to administration of oral study drug, baseline assessments were performed, including vital signs, VAS (0 = no pain, 10 = unbearable pain), and evaluation of side effects (sedation, dry mouth, headache, itching, difficulty urinating, constipation, nausea, and vomiting) on a 4-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Patients recorded VAS ratings and assessed side effects three times daily throughout the seven-day study period. In addition, patients made a global 24-hour assessment of pain using a VAS scale (0 = no pain, 10 = worst possible pain) once daily. Pain evaluations on Day 1 were made prior to taking study drug, 30 minutes after taking study drug, and hourly post-dose over eight hours.

Patients took study medication every 12 hours throughout the seven-day trial. Acetaminophen was allowed as rescue medication.

### Safety and efficacy

Patients recorded their assessments of analgesia, nausea, and sedation, as well as the use of regularly scheduled medications and/or rescue medication. Compliance was determined by review of patient diaries and counts of returned medication. Vital signs, including respiratory rate, heart rate, blood pressure, blood oxygen saturation, and oral temperature, were taken prior to administration of study medication, hourly on the first study day, and once on Day 8 during the patient's exit evaluation. Adverse events were coded using standard methods and recorded in terms of severity and relationship to study drug.

Drug efficacy was estimated via evaluation of pain intensity difference (PID) score, which is the baseline VAS pain intensity rating minus the current pain intensity score. A positive PID score indicates a reduction in pain intensity, and a negative score indicates worsening of pain intensity.[17-19]

### Statistical analysis

Results from all enrolled patients were included in the analysis of efficacy data. Statistical evaluation of overall treatment effects was assessed using the exact Kruskal-Wallis procedure. Pairwise comparisons were made using the exact two-sample Wilcoxon procedure. Treatment differences were considered significant at $p < 0.05$. Pairwise testing was considered only if the overall treatment differences were found to be statistically significant ($p < 0.05$) or demonstrated a trend ($p < 0.05$ to $p < 0.10$).

## RESULTS

This investigation was considered a Phase I pilot study, intended to capture treatment information to be used in the design of future trials. While all 15 patients completed the study, the resultant uneven numbers of patients between treatment groups made it difficult to generate highly significant statistical results. Nonetheless, several interesting trends were observed in the study data.

Fifteen patients (nine females and six males) completed the protocol (Table 1) and complied with all drug-dosing schedules. The mean (SD) age was 55 (10) years, with a mean (SD) weight of 81 (21) kg. All patients had failed to achieve sustained pain relief on previous oral opioid analgesics, all patients had been previously treated with injective steroid therapy such as epidural or facet injections, and six patients had a history of previous back surgery for pain (one patient in Group A, four patients in Group B, and one patient in Group C). The pain diagnosis, daily intrathecal morphine dose, and concomitant analgesic use for each patient are listed in Table 2.

Mean (SD) baseline oxygen saturations (95.3 percent [3.2]), heart rates (75 bpm [17]), respiratory rate (19 bpm [3.4]), systolic blood pressure (127 mmHg [15.7]), diastolic blood pressure (78 mmHg [12]), and oral temperatures (98.4°F [0.6]) were all unremarkable and exhibited no statistically significant or clinically important changes during the study period.

The mean (SD) baseline VAS pain intensity rating of 6.8 (1.5) was similar in all three groups. Peak PID score was calculated by subtracting the lowest daily pain VAS score from the baseline pain VAS score. Differences in PID scores between all the treatment groups approached statistical significance ($p < 0.07$). The peak PID score from Day 1 was statistically ($p < 0.05$) highest (median PID score: 5.9) in Group A compared with Groups C and B (Figure 1). No difference in reported PID scores was found across time between Groups B and C. The PID scores through eight hours post-dose approached statistical significance ($p < 0.08$), as the median PID scores tended to be highest (i.e., greatest reduction in pain) in Group A and lowest (i.e., least reduction in pain) in Group B.

After Day 1, pain evaluations were made three times daily through Day 7. PID scores were then calculated for

| Table 1. Patient demographics | | | | |
|---|---|---|---|---|
| **Characteristic** | **Naltrexone 100 µg** | **Naltrexone 10 µg** | **Placebo** | **Total** |
| Number of patients | 3 | 7 | 5 | 15 |
| Age | | | | |
| Mean | 58.0 | 53.4 | 55.4 | 55.0 |
| Median | 51.0 | 52.0 | 52.0 | 52.0 |
| Range | 48 to 75 | 49 to 65 | 42 to 74 | 42 to 75 |
| Sex | | | | |
| Males | 1 (33 percent) | 3 (43 percent) | 2 (40 percent) | 6 (40 percent) |
| Females | 2 (67 percent) | 4 (57 percent) | 3 (60 percent) | 9 (60 percent) |
| Height (in) | | | | |
| Mean | 65.8 | 64.3 | 64.5 | 64.6 |
| Median | 64.0 | 61.5 | 65.0 | 64.0 |
| Range | 62 to 72 | 58 to 73 | 56 to 72 | 56 to 73 |
| Weight (kg) | | | | |
| Mean | 83.8 | 78.2 | 81.8 | 80.5 |
| Median | 90.7 | 79.4 | 88.4 | 80.7 |
| Range | 54 to 107 | 47 to 113 | 57 to 106 | 47 to 113 |

each time point in terms of change from Day 1 baseline evaluation (Figure 2). There was a statistically significant difference found among the treatment groups on the afternoon of Day 2 ($p < 0.05$), when Group A had significantly higher PID scores than Groups B and C ($p < 0.05$). A statistically significant difference was also found among the treatment groups on the evening of Day 3, when Group A had higher scores than either Group B or C ($p < 0.05$). The PID scores from Day 2 through Day 7 approached statistical significance ($p < 0.07$), as the median PID scores were higher in Group A than in Group B or C at all pain measurements for Days 2 through 7.

There were no deaths or serious adverse events reported during the one-week study. Side effects related to the gastrointestinal and/or nervous system were most commonly reported, with 14 of 15 patients reporting one or more events in those categories. The most commonly reported adverse events were headache (11 patients), dry mouth (11 patients), sedation (10 patients), and nausea (nine patients). Other side effects included constipation (six patients), pruritus (one patient), and vomiting (two patients). Interestingly, the highest number of reported adverse events per patient (five) occurred in the placebo group. Twenty-five events were reported by the five placebo patients, while 26 events were reported by the seven patients in Group B and seven events were reported by the three patients in Group A.

## DISCUSSION

Oral opioids have been recommended recently for the treatment of CNMP such as osteoarthritis and chronic low back pain.[20] This analgesic treatment is often successful, but some patients experience intolerable side effects or inadequate pain relief. For this subset of CNMP patients, spinal analgesics administered via implantable intrathecal pumps are frequently tried.[21] While many patients gain

| Table 2. Patient pain diagnosis and analgesic use | | | | |
|---|---|---|---|---|
| **Group** | **Patient** | **Pain diagnosis** | **Intrathecal morphine daily dose (mg/d)** | **Concomitant analgesics** |
| A | 1 | DJD lumbar spine | 8.0 | imipramine |
| | 2 | Postlaminectomy syndrome | 2.7 | oxycodone |
| | 3 | Chronic low back pain; bilateral hip pain | 6.5 | hydrocodone |
| B | 1 | Postlaminectomy syndrome | 2.3 | methadone |
| | 2 | Postlaminectomy syndrome | 7.0 | gabapentin |
| | 3 | Postlaminectomy syndrome | 4.5 | gabapentin |
| | 4 | DJD cervical spine | 12.7 | oxycodone |
| | 5 | DJD cervical spine | 1.8 | methadone |
| | 6 | DDD lumbar spine | 4.4 | amitriptyline |
| | 7 | Postlaminectomy syndrome | 2.5 | doxepin |
| C | 1 | DJD lumbar spine | 23.5 | methadone |
| | 2 | Postlaminectomy syndrome | 3.2 | oxycodone |
| | 3 | Flank pain (renal stones) | 7.5 | acetaminophen |
| | 4 | Lumbar spondylosis | 5.5 | NSAID |
| | 5 | DJD lumbar spine | 9.0 | NSAID |

DJD = degenerative joint disease; DDD = degenerative disc disease; NSAID = nonsteroidal anti-inflammatory drug.

excellent pain relief from intrathecal analgesics, some do not achieve adequate pain relief, and the occasional patient experiences serious adverse events such as paraplegia and respiratory depression.[22,23] Clearly, additional pain therapies are needed to control chronic pain among patients refractory to oral analgesics and invasive pain treatments. Ultra-low-dose opioid antagonists have occasionally been added to opioid therapy to paradoxically enhance opioid analgesia.[6] With this pilot study, we have reported the first use of oral naltrexone to enhance the analgesia of patients with chronic pain receiving intrathecal morphine.

In this study, patients with chronic pain who received oral naltrexone 100 μg twice daily as an adjunct to chronic intrathecal morphine infusions tended to experience the greatest improvement in their daily pain scores. On the first day of treatment, the highest peak PID scores (greatest pain relief) were seen in the group receiving naltrexone 100 μg BID. Throughout the first day of treatment, there was a trend in the PID scores indicating that the naltrexone 100 μg group tended to have the greatest reduction in pain, with the placebo and naltrexone 10 μg groups experiencing less pain relief. Although these data did not achieve statistical significance, we believe that this trend, even among this small number of patients, is important. Clearly, a larger prospective study needs to be completed to test more fully the hypothesis that oral naltrexone can enhance opioid analgesia among patients with CNMP.

This pilot study is limited chiefly by its small sample size. Because of the small patient numbers, the results did not always reach traditional levels of significance and frequently only suggested a trend. A larger, double-blind, prospective clinical trial is necessary to determine

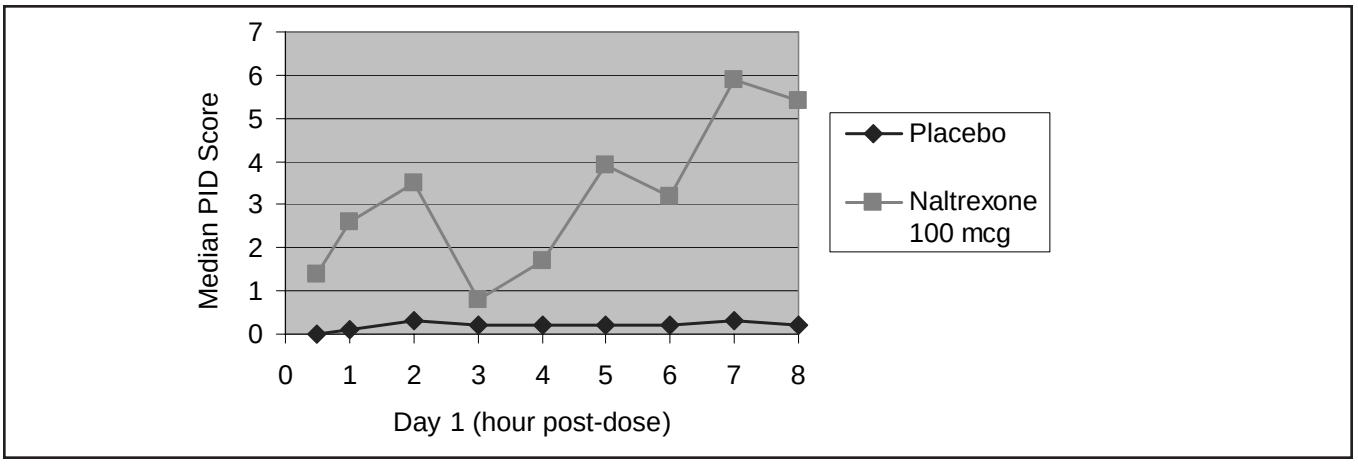



**Figure 1. Median pain intensity difference scores over the first eight hours post-dose, with Group A showing higher scores (i.e., greater analgesia) compared with Group C.**

whether the efficacy of naltrexone in enhancing intrathecal opioid analgesia can be verified.

The pharmacologic antagonism of excitatory (hyperalgesic), but not inhibitory (analgesic), central nociceptive systems offers a new therapeutic option for anesthesiology, psychiatry, pain management, and palliative medicine. The paradoxical analgesic actions of low doses of opioid antagonists have been demonstrated in both animals and humans.[6,7,11-14] This paradoxical ability of low-dose opioid antagonists to enhance opioid analgesia is not new; in the early 1950s, researchers at Massachusetts General Hospital were already attempting to combine an opioid analgesic with an opioid antagonist in order to enhance morphine analgesia without side effects.[6] Over the next 50 years, various case reports and clinical trials demonstrated that low doses of opioid antagonists enhance opioid analgesia, while large doses of opioid antagonists provide the expected antagonism of opioid effects. Our results indicate that naltrexone's enhancement of intrathecal morphine analgesia may be dose dependent, since only the 100 μg treatment group experienced improved pain relief. Since this pilot study was the first of its kind, the most useful dose of naltrexone was unknown, and our study dose was based on estimations from available animal and human data. Future clinical trials should better define the therapeutic range for naltrexone's analgesic enhancement actions by comparing effects of slightly higher and slightly lower doses of naltrexone to the 200 μg/d shown to be most effective in this pilot trial.

More recent case reports and clinical trials demonstrate the possible usefulness of this new analgesic treatment (naltrexone) in patients with refractory chronic pain.[6] One such case report involves a diabetic patient with painful peripheral neuropathy refractory to methadone 240 mg/d.[14] The patient rated his pain as 9/10 on the VAS scale, in spite of gabapentin adjuvant analgesic therapy, and methylphenidate was necessary in order to combat opioid-related sedation. The patient was given naltrexone 2 μg/d and reported a significant drop in pain score on Day 1, to 3/10. His pain remained controlled with this addition of low-dose naltrexone, and his methadone dose was reduced to 200 mg/d. Our patients responded to a higher—though still classified as low—dose of naltrexone (200 μg/d). This difference may be related to the pain etiology (none of our patients had painful diabetic neuropathy) and to the different route of opioid administration, with all patients in our trial receiving intrathecal opioid analgesics. Since this is the first report of naltrexone enhancing the analgesic effect of intrathecal opioids, the most useful oral dose of naltrexone for enhancing analgesia in CNMP patients remains speculative.

Two clinical trials have been completed using a commercial preparation of oxycodone combined with oral low-dose naltrexone. The first prospective, double-blind, placebo-controlled clinical trial compared the analgesic effect of oxycodone alone versus oxycodone with naltrexone 1 μg among patients with osteoarthritis and chronic pain.[24] Oxycodone combined with low-dose naltrexone gave better pain relief compared with placebo or oxycodone alone over the course of the four-week clinical trial. Another recent clinical trial compared an oxycodone-naltrexone oral preparation with oxycodone alone in patients with chronic nonmalignant low back pain.[25] Patients were allowed to titrate their own opioid doses to achieve adequate pain relief. Both oxycodone-naltrexone and oxycodone alone provided similar analgesia; however, the daily dose of oxycodone was lower in the oxycodone-naltrexone group, suggesting that the naltrexone enhanced opioid analgesia.[20] Furthermore, there were no significant side effects or adverse reactions in the low-dose naltrexone group. Correlation of our pilot study results with these larger clinical trials is difficult, since we added low-dose oral naltrexone to intrathecal morphine analgesia.

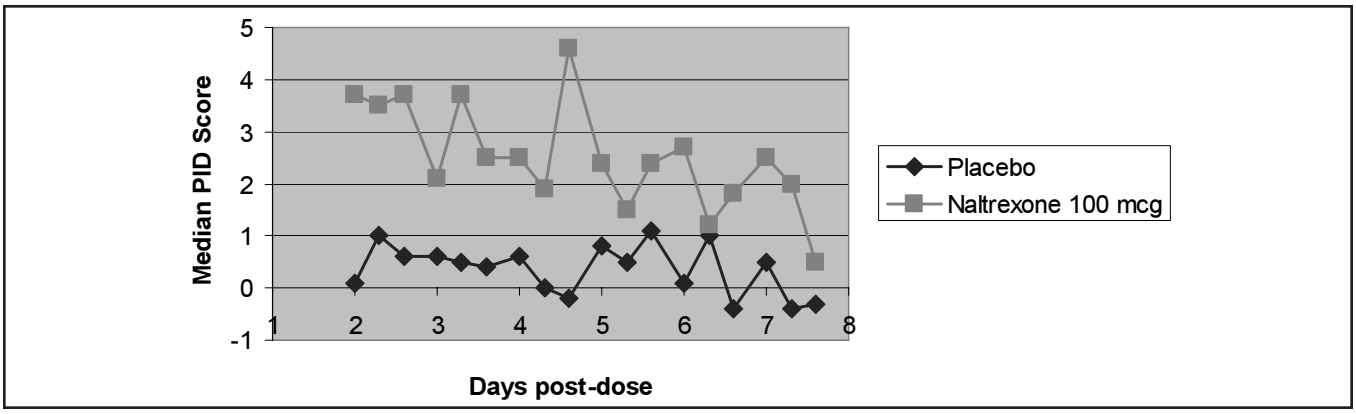



**Figure 2. Median pain intensity difference scores over the seven-day pilot study, with Group A showing higher scores (i.e., greater analgesia) compared with Group C.**

No deaths or serious adverse events were reported during this pilot study. Side effects were common but minor, with the highest rate of side effects occurring in the placebo group. These are important observations, as the addition of an opioid antagonist to chronic opioid analgesic therapy is potentially harmful.[6] There is always a possibility of precipitating opioid withdrawal, even when using low doses of naltrexone. Also, the opioid-enhancing effect of naltrexone could have precipitated opioid side effects such as sedation or respiratory depression. None of these serious side effects occurred during this clinical trial, however, and no evidence of opioid antagonist toxicity or opioid withdrawal was observed.

In summary, patients with CNMP who received oral naltrexone 100 µg twice daily in conjunction with continuous intrathecal morphine infusions tended to demonstrate the greatest improvement in daily pain scores as compared to patients receiving placebo or naltrexone 10 µg twice daily. We have presented the first pilot study in which low-dose oral naltrexone appears to enhance chronic intrathecal opioid analgesia among patients with chronic pain. Side effects were common, minor, and similar across treatment groups, with no serious adverse events (including opioid withdrawal) observed. While this pilot study involved a small number of patients, it employed rigorous methodology utilizing a prospective, double-blind, placebo-controlled trial design. Future trials need to explore the dose-response character of naltrexone's analgesia-enhancing effects and expand clinical application to patients receiving chronic oral opioids.

*Scott Hamann, PhD, MD, Department of Anesthesiology, University of Kentucky Medical Center, Lexington, Kentucky.*

*Paul Sloan, MD, Department of Anesthesiology, University of Kentucky Medical Center, Lexington, Kentucky.*

## ACKNOWLEDGMENTS

*The authors gratefully acknowledge the contributions made to this research study by Dr. W. Witt and Dr. E. Wala. The project was supported by Pain Therapeutics, Inc.*

## REFERENCES

1. Sloan PA, Slatkin NE, Ahdieh H: Effectiveness and safety of oral extended-release oxymorphone for the treatment of cancer pain: A pilot study. *Support Care Cancer.* 2005; 13(1): 57-65.
2. Sloan PA, Babul N: Extended-release opioids for the management of chronic non-malignant pain. *Expert Opin Drug Deliv.* 2006; 3(4): 489-497.
3. Sloan PA: The evolving role of interventional pain management in oncology. *J Support Oncol.* 2004; 2(6): 491-500, 503.
4. McDonnell FJ, Sloan JW, Hamann SR: Advances in cancer pain management. *Curr Oncol Rep.* 2000; 2(4): 351-357.
5. Crain SM, Shen KF: Opioids can evoke direct receptor-mediated excitatory effects on sensory neurons. *Trends Pharmacol Sci.* 1990; 11(2): 77-81.
6. Sloan PA, Hamann SR: Ultra-low-dose opioid antagonists to enhance opioid analgesia. *J Opioid Manag.* 2006; 2(5): 295-304.
7. Shen KF, Crain SM: Ultra-low doses of naltrexone or etorphine increase morphine's antinociceptive potency and attenuate tolerance/dependence in mice. *Brain Res.* 1997; 757(2): 176-190.
8. Shen KF, Crain SM: Dual opioid modulation of the action potential duration of mouse dorsal root ganglion neurons in culture. *Brain Res.* 1989; 491(2): 1227-1242.
9. Kayser V, Guilbaud G: Dose-dependent analgesic and hyperalgesic effects of systemic naloxone in arthritic rats. *Brain Res.* 1981; 226(1-2): 344-348.
10. Hamann SR, Martin WR: Hyperalgesic and analgesic actions of morphine, U50-488, naltrexone, and (-)-lobeline in the rat brainstem. *Pharmacol Biochem Behav.* 1994; 47(1): 197-201.
11. Crain SM, Shen KF: Antagonists of excitatory opioid receptor functions enhance morphine's analgesic potency and attenuate opioid tolerance/dependence liability. *Pain.* 2000; 84(2-3): 121-131.
12. Hamann SR, Malik H, Sloan JW, et al.: Interactions of "ultra-low" doses of naltrexone and morphine in mature and young male and female rats. *Receptors Channels.* 2004; 10(2): 73-81.
13. Levine JD, Gordon NC, Taiwo YO, et al.: Potentiation of pentazocine analgesia by low-dose naloxone. *J Clin Invest.* 1988; 82(5): 1574-1577.

14. Cruciani RA, Lussier D, Miller-Saultz D, et al.: Ultra-low dose oral naltrexone decreases side effects and potentiates the effect of methadone. *J Pain Symptom Manage.* 2003; 25(6): 491-500.
15. Sloan PA, Hodes J, John W: Radiosurgical pituitary ablation for cancer pain. *J Palliat Care.* 1996; 12(2): 51-53.
16. Food and Drug Administration (FDA): *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guideline.* US Department of Health and Human Services. FDA Web site. Available at *www.fda.gov/cder/guidance/959fnl.pdf.* Accessed April 24, 2007.
17. Zhou TJ, Tang J, White PF: Propacetamol versus ketorolac for treatment of acute postoperative pain after total hip or knee replacement. *Anesth Analg.* 2001; 92(6): 1569-1575.
18. Gimbel JS, Walker D, Ma T, et al.: Efficacy and safety of oxymorphone immediate release for the treatment of mild to moderate pain after ambulatory orthopedic surgery: Results of a randomized, double-blind, placebo-controlled trial. *Arch Phys Med Rehabil.* 2005; 86(12): 2284-2289.
19. Fricke JR Jr, Karim R, Jordan D, et al.: A double-blind, single-dose comparison of the analgesic efficacy of tramadol/ acetaminophen combination tablets, hydrocodone/acetaminophen combination tablets, and placebo after oral surgery. *Clin Ther.* 2002; 24(6): 953-968.
20. Cousins MJ, Brennan F, Carr DB: Pain relief: A universal human right. *Pain.* 2004; 112(1-2): 1-4.
21. Du Pen S, Du Pen A, Hillyer J: Intrathecal hydromorphone for intractable nonmalignant pain: A retrospective study. *Pain Med.* 2006; 7(1): 10-15.
22. Levin GZ, Tabor DR: Paraplegia secondary to progressive necrotic myelopathy in a patient with an implanted morphine pump. *Am J Phys Med Rehabil.* 2005; 84(3): 193-196.
23. Scherens A, Kagel T, Zenz M, et al.: Long-term respiratory depression induced by intrathecal morphine treatment for chronic neuropathic pain. *Anesthesiology.* 2006; 105(2): 431-433.
24. Chindalore VL, Craven RA, Yu KP, et al.: Adding ultralow-dose naltrexone to oxycodone enhances and prolongs analgesia: A randomized, controlled trial of Oxytrex. *J Pain.* 2005; 6(6): 392-399.
25. Webster LR, Butera PG, Moran LV, et al.: Oxytrex minimized physical dependence while providing effective analgesia: A randomized controlled trial in low back pain. *J Pain.* 2006; 7(12):937-946.

ORIGINAL ARTICLE

# Sleep improves when patients with chronic OA pain are managed with morning dosing of once a day extended-release morphine sulfate (AVINZA®): Findings from a pilot study

Murray Rosenthal, DO
Polly Moore, PhD
Eric Groves, MD, PhD
Tad Iwan, BA
Lisa Greenberg Schlosser, MS
Zofia Dziewanowska, MD, PhD
Andres Negro-Vilar, MD, PhD

## ABSTRACT

***Study objective:*** *To investigate the effect of once-a-day extended release of morphine sulfate AVINZA® (A-MQD) on polysomnographic measures of sleep in a population of chronic osteoarthritic pain patients with sleep difficulties.*

***Design:*** *Single-center, single-blind, placebo-lead-in, 30 mg or 60 mg. Patients' sleep and neurocognition were objectively measured at a sleep laboratory, and patients self-rated their pain, sleep, and other functions.*

***Participants:*** *Thirty-four participants (26 to 75 years old) complaining of sleep difficulties and chronic, stable pain secondary to hip or knee osteoarthritis.*

***Interventions:*** *Participants had a screening visit on current pain medication and then, following a single-blind placebo run-in period, received 30 mg/d of A-MQD for six days. At day 6, doses for participants with incomplete pain relief on the Brief-Pain-Inventory (BPI) pain scale were increased to 60 mg/d. Treatment continued for another eight days at the new dose level (14 days for a subgroup at 60 mg/d). Sleep was objectively measured by all-night polysomnography (PSG) at screening while on the participants' current pain therapy, at baseline following a placebo run-in and at the end of treatment while on A-MQD.*

***Outcome measures:*** *PSG parameters evaluated included Total-Sleep-Time (TST), Wake-timeafter-Sleep-Onset (WASO), Sleep-Efficiency (SE), Latency-to-Persistent Sleep (LPS), Latency-to-REM-sleep, the Number-of-Awakenings (NAW), the time spent in each stage of sleep, and REM-sleep-latency. Subjective evaluations included participants' estimations of sleep time and sleep quality, the Epworth-Sleepiness-Scale (ESS), the BPI, and participant acceptance of and relief due to current therapy. Assessments of neurocognitive function were also made.*

***Results:*** *Sleep initiation and maintenance tended to improve with A-MQD as demonstrated by the increases in TST and SE and decreases in WASO and NAW as compared with placebo-baseline values. Sleep architecture was preserved by the study drug and some increases in stage 2 and 3/4 sleep were seen compared with placebo baseline. Subjective ratings of sleep quality and sleep time were significantly improved with treatment, as were BPI scores and ratings of medication acceptance and pain relief. A-MQD was generally well tolerated.*

***Conclusions:*** *A-MQD was an effective treatment for pain, and this study treatment was associated with improvement of both objective and subjective sleep parameters in participants with chronic osteoarthritic pain.*

*Key words: sleep, sleep quality, chronic pain, polysomnography, AVINZA® capsules*

## INTRODUCTION

Chronic pain is highly correlated with sleep disturbance.[1-3] The incidence of disturbed sleep in participants with arthritis is estimated at nearly 60 percent.[4-6] Importantly, baseline pain levels may even be predictive of sleep difficulties up to two years in the future.[4] Furthermore, the relationship between disturbed sleep and pain appears to be bidirectional: pain worsens sleep difficulties and poor sleep heightens the perception of pain.[7-9] Increasing pain levels may be correlated with an increasing risk for insomnia,[2] and recurrent poor sleep may be linked to muscular pain, tenderness, and fatigue.[7,8]

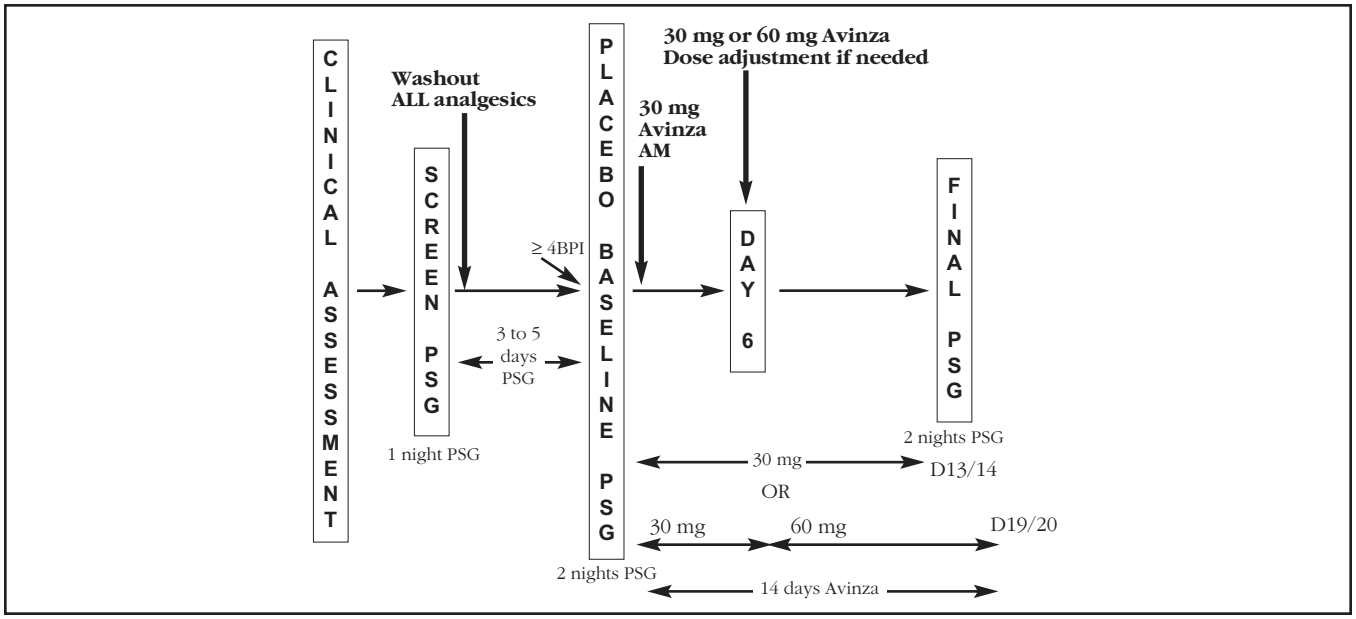



**Figure 1. Study schema for analyzed subgroups.**

Opioids are a commonly used pharmacological tool for the management of chronic to moderate to severe pain. Yet, there have been relatively few studies using objective sleep measurements to evaluate the effects of these medications on any participants, much less chronic pain participants. A publication of a limited study suggests that acute nighttime (presleep time) administration of opioids may suppress rapid eye movement (REM) sleep and slow wave sleep and may unexpectedly increase wakefulness.[10] On the basis of this limited experience related to acute administration, it might be speculated that in chronic pain participants opioid medications given to alleviate pain could in fact be disruptive to sleep and could contribute to the participant's sleep disturbance, rather than ameliorating it. Studies by Caldwell et al.,[11] Rauck et al.,[12] and Panjabi et al.[13,14] are in contrast to this, where osteoarthritis participants stated, in self-administered questionnaires, that pain relief with opiates improved the quality of their sleep.

The use of sustained release opioids (SROs) may be responsible for the improvements in sleep as found by Caldwell, Rauck, and Punjabi. The pharmacokinetics and analgesic properties of a given SRO are highly dependent on the release profile of the drug delivery system. Therefore, two different modified-release formulations of the same opioid may yield significantly different profiles, even when administered in a similar manner.

Release of morphine sulfate (A-MQD) is a morphine-based SRO with a novel modified-release formulation specifically designed for once-daily dosing.[11] The present exploratory study was designed to determine whether alleviation of chronic pain in osteoarthritic participants via A-MQD would produce concurrent improvements in polysomnographic (PSG) sleep measures in addition to confirming prior reports of subjective sleep improvement. Correlation of PSG findings with measures of neurocognition as well as quality of life measures was also assessed.

## METHODS

### Study design

This single-center, placebo-lead-in, single-treatment, single-blind study was conducted at a US site. Two doses (30 mg, titrated to 60 mg as needed for a subset of the population) of A-MQD were evaluated in participants with documented osteoarthritis complaining of sleep disturbances secondary to their osteoarthritic pain. The protocol for this study was approved by an institutional review board, and the study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Participant selection involved three screening steps (Figure 1). First, potential participants underwent a clinical assessment visit. Second, participants returned for a polysomnographic screening visit (screening) while continuing the participants' then current pain therapy. Third, participants who continued to be eligible were then withdrawn from their current pain and sleep medication during a five-day single-blind placebo-washout period that concluded with two nights of PSG evaluation (baseline). Subjective and neurocognitive evaluations were performed prior to discharge on the second morning (baseline for these evaluations). At this point, to continue to be eligible, participants had to have a score of ≥ 4 on the Brief-Pain-Inventory (BPI).

Participants who passed these three screening evaluations were formally entered into the study and were then

provided with 14 days of active treatment (30 mg/d A-MQD). Participants returned to the clinic on the sixth day of active treatment to repeat the series of subjective and neurocognitive tests performed at placebo baseline. At this visit, the dose of A-MQD was increased to 60 mg/d for participants reporting inadequately responsive pain. Participants returned to the clinic on the thirteenth- and fourteenth-day of treatment for a final two nights of PSG evaluation (day 13/14). Again, the subjective and neurocognitive batteries were repeated and final safety evaluations were performed prior to the final discharge on day 15.

As this was a pilot study, part way through the study, an interim analysis was conducted to examine the internal consistency of the data. This analysis suggested (see discussion section) that the two treatment arms (30 mg/d for 14 days vs 30 mg/d for six days followed by eight days at 60 mg/d) did not represent comparable exposure to constant doses of study drug. At this point, participants whose dosage had been increased to 60 mg/d were provided with treatment at this dose level for a further full 14 days, thus spending a total of 20 days on study treatment. Participants in this last group did not repeat the day 6 assessments after six days at the new dose level and engaged in the final PSG evaluations on day 19 and 20 (equivalent to day 13/14 for the other groups) and the final subjective assessments on day 21 (equivalent to day 15 for the other groups).

Regardless of treatment arm, concomitant medication was restricted. Both prescription and OTC pain and sleep medications were prohibited. In addition, the use of any form of steroids and viscosupplementation in osteoarthritic joints was not allowed. Rescue medications for either pain or sleep were not allowed.

## Subject recruitment and selection

Male and female participants with osteoarthritis at a hip and/or knee joint, aged 18 to 80, in relatively good health were recruited for this study through local physicians and newspaper advertisements. Participants were eligible if they reported sleep disturbances secondary to their osteoarthritic pain and had been taking NSAIDs, acetaminophen, and/or a prn analgesic containing an opioid (maximum of 30 mg/d in morphine equivalents) for at least three months. Participants were further required to 1) not have a diagnosis of any chronic pain syndrome that would interfere with the assessment of osteoarthritis symptoms, 2) not have prior replacement surgery or other clinically significant disease at the affected joint(s), 3) not have a history of substance abuse or dependence, and 4) not receive any steroids within 30 days prior to baseline assessments, intra-articular steroids in within 60 days prior to study baseline, or intra-articular viscosupplementation at the affected joint(s) within six months of the start of the study.

After signing an informed consent statement, prospective study participants underwent a screening process that included a physical examination, clinical laboratory tests, and a 12-lead ECG. Qualified participants were invited to undergo a PSG screening night while continuing their current pain therapy. Participants who met the screening criteria for other sleep disorders (i.e., sleep apnea, periodic limb movement disorder) during the PSG screening night were no longer eligible for participation.

Next, eligible participants underwent a five-day placebo washout from all pain and sleep medications. At this point (placebo baseline), participants were finally invited to enter into a single-blind treatment if they had an average pain rating of ≥ 4 on the BPI scale.

## Study procedures

**Study drug.** A-MQD (30 and 60 mg/d) was evaluated in this study. Medication (30 mg/d) was dispensed to participants after a single-blind placebo-baseline PSG night followed by next-morning neurocognitive, subjective pain, and sleep assessments. Participants were educated on the possible side effects of the study medication and cautioned about drowsiness while driving. They were then instructed to swallow one capsule of study medication in the morning each day for the next 14 days. Participants complaining of inadequate pain relief were titrated to 60 mg/d at the day 6 visit.

**Polysomnography.** PSG recordings were performed by experienced technicians and were scored according to the methodology of Rechtschaffen and Kales[15] by a single registered polysomnographic technologist. Scoring was later confirmed by a blinded external, accredited polysomnographer. Recordings were taken in the sleep laboratory at screening (day -6, -5), baseline (day -2, -1), and during treatment (day 13, 14) for a period of 480 minutes with lights out beginning at the participant's habitual bedtime. PSG values are the mean of each two-night period.

**Subjective assessments.** Participants completed several subjective assessments of their sleep and pain. These evaluations were completed at screening (day -5), baseline (day 0), and during treatment (day 6, 15) and included the Epworth Sleepiness Scale (ESS), a *sleep quality* questionnaire, the Brief Pain Inventory (BPI), and ratings of the *acceptability of* and *relief* provided by their current therapy. The ESS is an eight-question instrument that assesses the participant's subjective sense of the likelihood of falling asleep in various real-life situations. Each question is rated on a scale of 0 ("would never doze") to 3 ("high chance of dozing"). The *sleep quality* questionnaire asked participants to rate their quality of sleep on a VAS scale of 0 to 100 and to estimate the *average number of hours of sleep* they were getting per night. The BPI is a

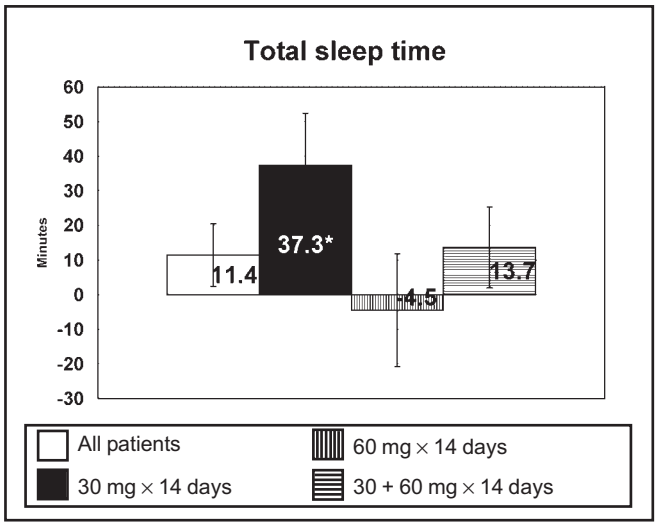



**Figure 2. Total sleep time, mean change from baseline at day 14. Increase = more time asleep; * p < 0.05.**

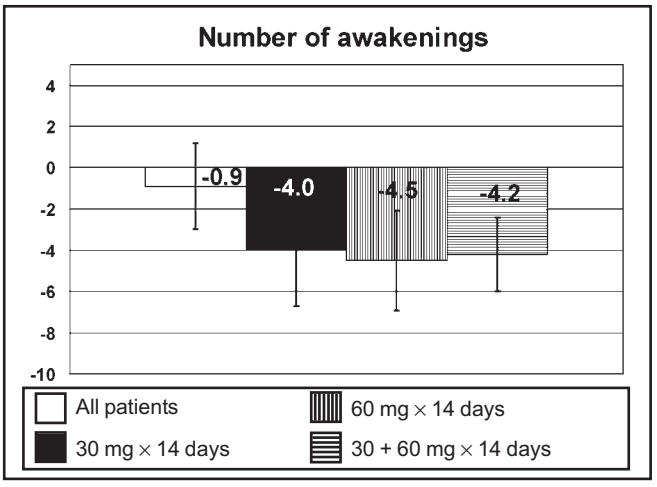



**Figure 3. Number of awakenings, mean change from baseline at day 14. Decrease = less awakenings.**

series of questions in which participants rate their pain on a scale of 0 ("no pain") to 10 ("pain as bad as you can imagine"). Participants used a five-point scale to rate their *acceptance of their current therapy*. This scale was anchored at 0, "none" and 4, "excellent." Finally, participants used a five-point scale anchored at 0, "none" and 4, "complete" to indicate the *pain relief* provided by their current therapy.

**Neurocognitive battery.** The neurocognitive battery was performed by a psychologist (SB) at screening (day -5), baseline (day 0), and during treatment (day 6, 15). A standardized neurocognitive battery was administered to participants. Alternative forms were employed where appropriate. The following cognitive domains with corresponding tests were administered: attention (*Trails Making A, Digit Symbol Substitution Test*: DSST), memory (*Rey Auditory Verbal Learning Test, Immediate and Delayed Condition Recognition*: RAVLT), motor-speed (*Finger Tapping Speed Test*), and executive function (*Letter-Number Sequencing, Trails Making B*).

**Compliance.** At each visit, participants were monitored for drug compliance and had to have taken at least 85 percent of the prescribed doses to be considered compliant. During the first week of treatment, if a participant missed ≥ one day of dosing or took > seven capsules during any seven-day period, he or she was instructed on the proper dosing and the importance of maintaining the dosing schedule. If the participant continued to be noncompliant, he or she was dropped from the study.

### Safety evaluations

Vital signs were recorded at screening and at each visit during treatment. A physical examination along with chemistry and hematology was performed at screening and prior to discharge at the last study visit. A 12-lead ECG was also obtained at screening. Adverse event information was collected at each visit.

### Data analysis

The efficacy endpoints were analyzed for compliant study participants who completed at least the day 6 evaluations (e.g., the evaluable population). The safety analysis was performed for all participants who were exposed to at least one dose of study medication. Parameters measured on more than one day (e.g., days 13 and day 14) during the screening, baseline, or treatment periods were defined as the average of the values obtained at each measurement period. Changes from baseline values were calculated both as a percent-change-from-baseline and as an absolute-change-from-baseline. Changes from screening were calculated as an absolute-change-from-baseline only. Nonparametric statistical methods (e.g., Wilcoxon tests) were used. Hypothesis testing was two-sided and claims of significance were based on two-sided p-values of p-values of 0.05 or less.

## RESULTS

### Demographics

A total of 127 participants were screened. Of these, 93 did not progress to treatment because they failed the inclusion/exclusion criteria. No participant dropped out of the screening process because of inadequately controlled pain during the placebo washout period. Thus, 34 progressed to receive treatment (e.g., intent-to-treat population) and 31 participated for long enough to be considered evaluable. The demographics of the participants who completed the study include a mean age of 53.7 (range 26 to 75), majority female (27 [79 percent] vs 7 [21 percent]), majority Caucasian (21 [62 percent]), but with

| Table 1. PSG results | | | | | |
|---|---|---|---|---|---|
| **PSG measure** | **Time point** | **All evaluable (n = 31)** | **30 mg × 14 d (n = 10)** | **60 mg × 8 d (n = 9)** | **60 mg × 14 d (n = 12)** |
| **Sleep continuity** | | | | | |
| Sleep efficiency, (percent) | Screening | 76.5 | 72.1 | 79.3 | 78.0 |
| | Baseline | 81.8 | 80.3 | 81.7 | 83.2 |
| | Day 13/14 | 83.8* | 88.0 | 82.8 | 81.3 |
| Total sleep time, (minutes) | Screening | 367.0 | 346.0 | 380.7 | 374.4 |
| | Baseline | 391.1 | 385.6 | 392.1 | 395.0 |
| | Day 13/14 | 402.5* | 422.9*† | 397.4 | 390.5 |
| Number of awakenings, (minutes) | Screening | 27.1 | 24.8 | 27.0 | 29.1 |
| | Baseline | 28.8 | 27.6 | 26.9 | 31.3 |
| | Day 13/14 | 27.9 | 23.6 | 34.6 | 26.8 |
| Latency to persistent sleep, (minutes) | Screening | 43.2 | 79.2 | 26.8 | 25.6 |
| | Baseline | 24.7 | 21.1 | 18.4 | 32.3 |
| | Day 13/14 | 23.9 | 16.3* | 24.1 | 29.4 |
| Wake time after sleep onset, (minutes) | Screening | 72.6 | 62.5 | 69.1 | 83.6 |
| | Baseline | 62.9 | 68.9 | 67.6 | 54.7 |
| | Day 13/14 | 59.1 | 42.0 | 65.6 | 67.7 |
| **Sleep architecture** | | | | | |
| REM sleep latency, (minutes) | Screening | 113.9 | 131.9 | 110.0 | 101.8 |
| | Baseline | 84.1 | 74.8 | 75.5 | 98.3 |
| | Day 13/14 | 68.5*† | 58.4 | 60.8 | 81.1 |
| REM sleep, (minutes) | Screening | 68.0 | 58.7 | 69.7 | 74.5 |
| | Baseline | 83.8 | 75.6 | 83.7 | 90.8 |
| | Day 13/14 | 77.9 | 79.3* | 74.6 | 78.9 |
| Stage 2 sleep, (minutes) | Screening | 245.2 | 223.7 | 253.5 | 257.0 |
| | Baseline | 262.1 | 260.5 | 257.7 | 266.8 |
| | Day 13/14 | 279.8 | 296.7*† | 267.4 | 275.3 |
| Stage 3/4 sleep, (minutes) | Screening | 13.5 | 11.1 | 13.9 | 15.4 |
| | Baseline | 18.9 | 13.8 | 11.7 | 13.1 |
| | Day 13/14 | 18.8 | 31.6 | 13.4 | 12.6 |

*Change from screening (former analgesic) where $p \leq 0.05$; †Change from placebo baseline where $p \leq 0.05$.

substantial African–American (10 [29 percent]) percentage and lesser percentages of Hispanic (2 [6 percent]) or other (1 [3 percent]).

Participants who received 30 mg/d of A-MQD for the entire study period will be referred to as the "30 mg × 14 day group," participants whose dosage was increased to 60 mg/d after the first six days of treatment will be referred to as the "60 mg × 8 day group," and participants whose dosage was increased to 60 mg/d and who continued with treatment for a full 14 days at this level will be referred to as the "60 mg × 14 day group." Day 13/14 and day 15 values refer to day 19/20 and day 21 values, respectively, for this latter group.

As mentioned earlier, the interim analysis suggested that the study results for the 30 mg × 14 day group and the 60 mg × 8 day group would not represent comparable periods of uniform exposure to study drug. Thus, the rest of this document will largely focus on the results for the 30 mg × 14 day group and the 60 mg × 14 day group. The results for the 60 mg × 8 day group are included in the appropriate tables, but will not be discussed further.

## Polysomnography

Given the relatively small size of the study population, measures of sleep continuity initiation, maintenance, and architecture are presented for the participant population as a whole and as a function of dose groups (Table 1 and Figures 2 to 4).

Compared with normal sleepers, the sleep architecture of the study population at screening reflected their sleep disturbances (increased sleep stage 1 [data not shown]; diminished sleep stages 2 and 3/4; longer REM latency), even while stable on prior pain therapy. At baseline, subsequent to the withdrawal of all pain medications, some of these differences were attenuated suggesting that the participants' previous therapies were negatively affecting their sleep (Table 1). Overall, compared with baseline, treatment with A-MQD preserved sleep architecture and tended to increase stage 2 and stage 3/4 sleep and reduce REM latency.

At study end, REM sleep duration was slightly depressed, dropping to 77.9 minutes vs 83.8 minutes at placebo-baseline. This effect was largely due to a decrease of 11.0 minutes in the 60 mg × 14 day group. In contrast, the 30 mg × 14 day group saw an increase of 3.7 minutes of REM sleep over this period.

For the total study population, PSG sleep parameters were consistently improved by A-MQD compared with measures obtained at screening while on prior therapy. Both Total Sleep Time (TST) and Sleep Efficiency (SE) were significantly increased by study drug while Latency to Persistent Sleep (LPS) and Wake-time-after-Sleep-Onset (WASO) both trended downward (Table 1). However, although some trends did emerge, A-MQD did not significantly impact PSG measures of sleep initiation and maintenance as compared with placebo baseline. Specifically, TST and SE increased while WASO and the Number of Awakenings (NAW) both decreased (Table 1).

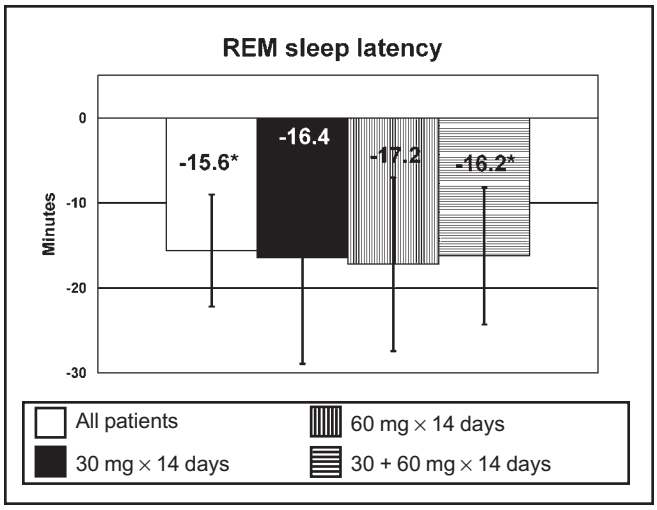



**Figure 4. REM sleep latency, mean change from baseline at day 14. Decrease = Less time to REM sleep; * p < 0.05.**

The treatment subgroups demonstrated varying results on PSG outcome measures. The 30 mg × 14 day group was consistently improved relative to placebo baseline in all aspects of sleep: LPS, WASO, NAW, and REM sleep latency were reduced while SE and TST were increased (Figures 2 to 4). Less consistent results for these measures were seen in 60 mg × 14 day group.

## Subjective assessments

Subjective participant assessments of nighttime sleep indicated significant improvement with A-MQD (Table 2 and Figure 5). The entire participant population showed significant improvements in subjective sleep quality at both day 6 and day 15 ($p = 0.0001$, $p \leq 0.0001$) relative to placebo-baseline values. Significance was maintained at day 6 for the 30 mg × 14 day group ($p = 0.0254$) and at day 15 for the 60 mg × 14 day groups ($p = 0.0010$). The study population reported sleeping for a mean of 30 minutes longer than at baseline at both the day 6 ($p = 0.0691$) and day 15 ($p = 0.0286$) time points. This increase in self-rated Number of Hours of Sleep was significant for the 30 mg × 14 day group (1.1 hours, $p = 0.0313$) and approached significance for the 60 mg × 14 day group (0.8 hours, $p = 0.0625$) at day 15.

Daytime alertness, as measured by the ESS, was impacted to a small, but significant degree for the study population as a whole at both day 6 ($p = 0.015$) and day 15 ($p = 0.0150$) (Table 2), but no treatment group showed significant reduction in alertness as compared with placebo baseline.

Participants' assessments of their pain severity and

| Table 2. Subjective measures of sleep | | | | | |
|---|---|---|---|---|---|
| **Subjective measure** | **Time point** | **All evaluable (n = 31)** | **30 mg × 14 d (n = 10)** | **60 mg × 8 d (n = 9)** | **60 mg × 14 d (n = 12)** |
| Epworth sleepiness score (< 8, normal; higher score indicates more sleepiness) | Screening | 5.3 | 4.4 | 6.3 | 5.3 |
| | Baseline | 4.7 | 3.7 | 5.3 | 5.0 |
| | Day 6 | 5.4* | 4.5 | 6.7 | 5.2 |
| | Day 14 | 6.6* | 5.4 | 7.5 | 6.8 |
| Number of hours of sleep | Screening | 5.9 | 5.9 | 5.7 | 6.0 |
| | Baseline | 6.1 | 6.3 | 6.0 | 6.0 |
| | Day 6 | 6.6 | 7.2 | 5.9 | 6.5 |
| | Day 14 | 6.6*† | 7.4*† | 5.3 | 6.8† |
| Overall quality of sleep (0, poor sleep; 100, best sleep; increase, better sleep) | Screening | 33.3 | 27.3 | 35.9 | 36.3 |
| | Baseline | 40.9 | 46.1 | 43.4 | 34.7 |
| | Day 6 | 57.9* | 64.7* | 55.0* | 54.5 |
| | Day 14 | 64.3*† | 61.8† | 61.4*† | 68.3*† |

*Change from placebo baseline where $p < 0.05$; †Change from screening (former analgesic) where $p \leq 0.05$.

their acceptance of, and relief provided by, the study drug indicate that A-MQD was an effective treatment for osteoarthritis pain (Table 3). Relative to placebo-baseline values, the BPI Average Pain scores were significantly improved for the total population (day 6, $p = 0.0016$; day 15, $p \leq 0.0001$), the 30 mg × 14 day group (day 6, $p = 0.0098$; day 15, $p = 0.0078$) and the 60 mg × 14 day group (day 15, $p = 0.0039$) (Table 3). The study population as a whole showed a significant increase in Acceptance of Current Therapy at day 6 ($p = 0.0011$) and day 15 ($p = 0.0006$) and indicated experiencing a significant improvement in Relief from Current Therapy (day 6 and day 15, $p \leq 0.001$) relative to placebo-baseline values.

## Neurocognitive battery

Treatment with A-MQD significantly enhanced cognition as compared with performance on prior analgesics and after a wash-out phase. When all treatment groups were combined (n = 31) significant improvement from screening (prior analgesics) was observed at day 15 for Letter Number Sequencing, Trails Making A&B, DSST, and RAVLT Immediate and Delayed Condition tests ($p = 0.0237$, $p = 0.0004$, $p = 0.0039$, $p = 0.0231$, $p < 0.0001$, and $p < 0.0001$, respectively). Trend improvement or no change was observed for other measures.

Significant improvements were also seen relative to placebo baseline on the RAVLT ($p = 0.0136$) and Trail Making part A ($p = 0.0045$) evaluations. Trend improvement or no change was observed for other measures. A thorough presentation of these results will be reported elsewhere.

## Safety

A-MQD was generally safe and well tolerated. Side effects did not appear to exhibit a dose effect. Twenty-two patients experienced one or more adverse events, most of which were mild to moderate in severity. The most common adverse events (occurring in > 10 percent of all treated participants) were nausea (n = 10, 29 percent), sedation (n = 5, 15 percent), constipation (n = 5, 15 percent), vomiting (n = 4, 12 percent), and pruritus (n = 4, 12 percent). All of these events were consistent with the known effects of the study drug and had been observed in previous clinical trials.

Serious adverse events (SAEs) occurred in one participant (3 percent) while receiving 60 mg/d for eight days. The SAEs (experienced simultaneously) were severe sedation and unresponsiveness in this participant who was subsequently found to have previously undiagnosed hypothyroidism. The participant subsequently recovered from these adverse events.

| Table 3. Subjective measures of pain therapy | | | | | |
|---|---|---|---|---|---|
| **Subjective measure** | **Time point** | **All evaluable (n = 31)** | **30 mg × 14 d (n = 10)** | **60 mg × 8 d (n = 9)** | **60 mg × 14 d (n = 12)** |
| BPI: "Pain on Average" (0, no pain; 10, worst pain) | Screening | 6.1 | 6.6 | 5.3 | 6.3 |
| | Baseline | 6.1 | 6.2 | 5.2 | 6.7 |
| | Day 6 | 5.3 | 4.5 | 4.9 | 4.9 |
| | Day 14 | 4.1*† | 3.8*† | 4.1 | 4.3*† |
| Acceptability of therapy (0, none; 5, excellent) | Screening | 2.5 | 2.4 | 2.6 | 2.5 |
| | Baseline | 2.7 | 3.0 | 3.1 | 2.3 |
| | Day 6 | 3.6 | 3.7 | 3.4 | 3.6 |
| | Day 14 | 3.8† | 3.7 | 4.0 | 3.8† |
| Pain relief from current Rx (0, none; 5, excellent) | Screening | 2.4 | 2.3 | 2.3 | 2.4 |
| | Baseline | 2.0 | 2.5 | 1.8 | 1.7 |
| | Day 6 | 3.0 | 3.2 | 2.6 | 3.1 |
| | Day 14 | 3.5*† | 3.6† | 3.4*† | 3.5*† |
| *Change from baseline where $p < 0.05$; †Change from screening where $p < 0.05$. | | | | | |

## DISCUSSION

This single-center, placebo-baseline-controlled, single-treatment, single-blind study was designed to evaluate the impact of using A-MQD on objective and subjective measures of sleep as well as pain in participants with osteoarthritis complaining of sleep disturbances. Objective single-blind placebo baseline sleep characteristics confirmed the subjective perception of sleep disturbance due to chronic pain. The sleep fragmentation, low sleep efficiency, and poor subjective sleep quality in these chronic osteoarthritis participants were consistent with observations in other sleep studies in chronic pain participants.[16-18] Importantly, these sleep disturbances were present to an even greater degree during screening when participants were observed on their previous stable regimens of pain and sleep aids.

After withdrawal of all pain and sleep medication to establish baseline characteristics, participants were treated with either 30 or 60 mg/d of study drug for a period of 14 to 20 days. The results were very encouraging and intriguing: on the basis of objective and subjective outcome measures, the study drug improved both sleep and pain. Although improvements were not always statistically significant, likely owing to the small sample size, the overall trends were positive.

Treatment effects on sleep architecture included increases in the amount stage 2 and stage 3/4 sleep relative to both placebo baseline and screening (prior therapy) levels. In contrast to previous PSG studies of acute dosing with opioids at bedtime, A-MQD increased *NREM sleep time* when taken in the morning. *REM latency* was also significantly reduced with respect to both placebo baseline and screening observations. While minor, nonsignificant REM suppression vs baseline was seen with A-MQD, the time spent in REM sleep was markedly increased relative to the values seen at screening when participants were still taking their prior pain medication.

In addition, objective measures of sleep initiation and continuity as assessed in the participant population as a whole were improved by study drug when compared with placebo-baseline levels. TST and SE were increased while LPS, NAW, and WASO were reduced. Importantly, LPS, SE, TST, and WASO improvements were even greater when compared with screening values obtained when participants were on their previous stable regimens of pain and sleep medications.

Subjective assessments of *sleep quality* indicated that

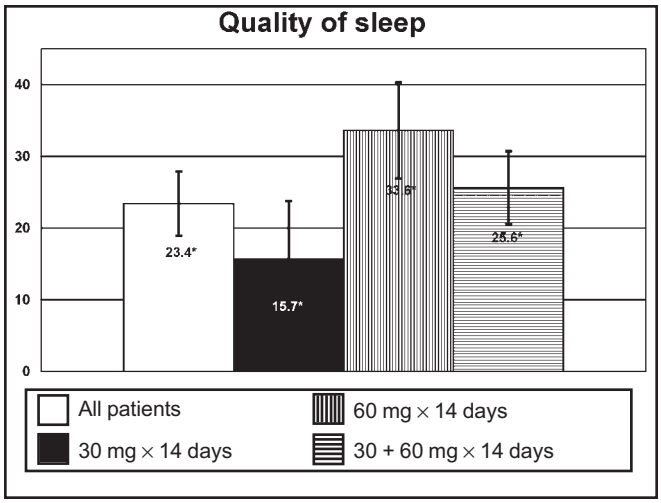



**Figure 5. Quality of sleep, mean change from baseline at day 14. Increase = Better sleep; Scale: 0 = Poor sleep; 100 = Best sleep* p < 0.05.**

there was a clear perception of improved sleep with A-MQD. Perceived *sleep quality* and the subjective *Number of Hours of Sleep* were significantly improved across the total participant population. Again, these improvements were even greater when compared with screening (prior therapy) levels. Although daytime sleepiness as measured by ESS was significantly impaired relative to placebo baseline for the total population at both the day 6 and day 15, the actual ESS scores were within the range traditionally considered normal (ESS < 7). In view of the well-known sedative effects of morphine, it is reasonable to observe some drowsiness in this relatively short study with its limited time to tolerate this effect. Study results may indicate that A-MQD's extended release formulation may produce milder effects on alertness than an immediate release treatment.

A-MQD was also clearly effective as a pain medication. Significant improvements were seen at both days 6 and 15 on the *BPI* and participant ratings of the *Acceptance of* and *Relief from Current Therapy*. Scores on each of these scales also indicated improvements relative to screening values, indicating that the study drug was better at managing pain symptoms than the previous therapies utilized by participants.

Furthermore, results from the neurocognitive battery seemed to indicate that A-MQD may have enhanced cognition in this participant group relative to prior therapy. While the underlying biological underpinnings of these findings are unknown, it is possible that either the reduction of pain or the resumption of sleep may have accounted for the enhancement of mnemonic and attentional functioning. These results will be presented at greater length in a subsequent publication.

As mentioned earlier, a limitation of this study is its design as a placebo-baseline-controlled, single-treatment, single-blind study. However, the choice of a baseline control design was deliberate because of two concerns. First, there were significant ethical concerns that a separate placebo control arm design would potentially convey negative consequences to participants resulting from the cessation of pain relief therapy. Second, concerns about loss of study sensitivity linked to the expected heterogeneity of the study population were expected. These expectations of participant heterogeneity were supported by the need to increase the dose of study medication for those participants complaining of inadequate pain relief at day 6. We hypothesize that participants in the 30-mg group had mild to moderate chronic osteoarthritic pain, while participants who received 60 mg for any period of time could be considered to have moderate to severe pain, which was more difficult to control by the use of medication. This difference in pain level could be expected to significantly impact the variability of improvements in sleep seen across treatment groups, especially if the dose level did not reach therapeutic levels for an individual participant.

The extension of time under treatment for participants in the 60 mg × 14 day group added a temporal difference into study group comparisons. This change was introduced to allow the acute effects associated with transition to a new dose level to stabilize and permit equal amounts of time at a pain relieving dose. Nonetheless, it may be argued that the drug effect after two weeks (observed for participants in the 30 mg × 14 day and 60 mg × 8 day groups) may not be comparable to the drug effect seen after three weeks of treatment (60 mg × 14 day group). Morphine therapies are associated with the evolution of some level of tolerance to side effects, so the protocol change was expected to make the groups more comparable.

The results of this study suggest that A-MQD may be an effective treatment for participants with osteoarthritis pain and accompanying sleep disturbances. The improvements seen in all participants within measures of pain and sleep relative to untreated participants (placebo baseline) and participants with previous pain therapy (screening) may indicate that the previous therapies 1) were insufficient for the level of pain being experienced and 2) may have exacerbated the secondary sleeping difficulties experienced by participants. These data confirm the activity of A-MQD for the treatment of chronic moderate to severe osteoarthritis pain and support prior observations that with A-MQD pain therapy participants may expect improvements in the sleep disturbances commonly experienced by this participant population. More research could provide additional, helpful insights to inform clinicians' choices regarding the relationship between management of chronic pain and its associated sleep disturbances as well as further delineate A-MQD's ability to improve sleep and daytime functional outcomes in chronic pain populations.

## ACKNOWLEDGMENTS

*The authors gratefully acknowledge the technical contributions of Cheryl Spinweber, PhD, and Al Agbulos, RPSGT, in reviewing the polysomnograms in this research study.*

*Murray Rosenthal, DO, California Clinical Trials, San Diego, California.*

*Polly Moore, PhD, California Clinical Trials, San Diego, California.*

*Eric Groves, MD, PhD, Ligand Pharmaceuticals Inc, San Diego, California.*

*Tad Iwan, BA, Ligand Pharmaceuticals Inc, San Diego, California.*

*Lisa Greenberg Schlosser, MS, Ligand Pharmaceuticals Inc, San Diego, California.*

*Zofia Dziewanowska, MD, PhD, Ligand Pharmaceuticals Inc, San Diego, California.*

*Andres Negro-Vilar, MD, PhD, Ligand Pharmaceuticals Inc, San Diego, California.*

## REFERENCES

1. Benca RM, Ancoli-Israel A, Moldofsky H: Special considerations in insomnia diagnosis and management: Depressed, elderly and chronic pain populations. *J Clin Psychiarty*. 2004; 65 (Suppl 8): 26-35.
2. Sutton DA, Moldofsky H, Badley EM: Insomnia and health problems in Canadians. *Sleep*. 2001; 24: 665-670.
3. McCracken LM, Iverson GL: Disrupted sleep patterns and daily functioning in patients with chronic pain. *Pain Res Manag*. 2002; 7: 75-79.
4. Nicassio PM, Wallston KA: Longitudinal relationships among pain, sleep problems and depression in rheumatoid arthritis. *J Abnorm Psychol*. 1992; 101: 514-520.
5. Drewes AM, Jannum P, Andreasen A, et al.: Self-reported sleep disturbances and daytime complaints in women with fibromyalgia and rheumatoid arthritis. *J Musculoskeletal Pain*. 1994; 2: 15-31.
6. Moffitt PF, Kalucy EC, Kalucy RS, et al.: Sleep difficulties, pain and other correlates. *J Intern Med*. 1991; 230: 245-249.
7. Moldofsky H, Scarisbrick P, England R, et al.: Musculosketal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. *Psychosom Med*. 1975; 37: 341-351.
8. Moldofsky H, Scarisbrick P: Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. *Psychosom Med*. 1976; 38: 35-44.
9. Drewes AM, Nielson KD, Arendt-Nielsen L, et al.: The effect of cutaneous and deep pain on the electroencephalogram during sleep: An experimental study. *Sleep*. 1997; 20: 632-640.
10. Kay DC, Einstein RB, Jasinski DR: Morphine effects on human REM state, waking state and NREM sleep. *Psychopharmacologica*. 1969; 14: 404-416.
11. Caldwell JR, Rapport RJ, Davis JC, et al.: Efficacy and safety of once daily morphine formulation in chronic, moderate to severe osteoarthritis pain. *J Pain Symptom Manage*. 2002; 23(4): 278-291.
12. Rauck RL, Bookbinder SA, Bunker TR, et al.: The ACTION study: A randomized, open-label, multicenter trial comparing SID ER morphine sulfate capsules (AVINZA®) to BID controlled-release oxycodone hydrochloride tablets (OxyContin®) for the RX of chronic, moderate to severe low back pain. *J Opioid Manage*. 2006; 2(3): 155-166.
13. Panjabi SS, Panjabi RS, Lawson KL, et al.: Cognitive function in chronic pain patients treated with once-a-day AVINZA® (morphine sulfate extended-release capsules). *In the 22nd Annual Meeting of the American Academy of Pain Medicine*, February 22-25, 2006. San Diego CA: American Academy of Pain Medicine, 2006: 83.
14. Panjabi SS, Panjabi RS, Lawson KL, et al.: Pain and emotional functioning assessments in patients treated with once-a-day AVINZA® in the management of chronic non-malignant pain. In the *22nd Annual Meeting of the American Academy of Pain Medicine*, February 22-25, 2006. San Diego CA: American Academy of Pain Medicine, 2006: 82-83.
15. Rechtschaffen A, Kales A: *A Manual of Standardized Terminology: Techniques and Scoring System for Sleep Stages of Human Subjects*. Los Angeles: UCLA Brain Information Service/Brain Research Institute, 1968.
16. Moldofsky H, Scarisbrick P, England P, et al.: Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. *Psychosom Med*. 1975; 37: 341-51.
17. Pilowsky I, Crettenden I, Townley M: Sleep disturbance in pain clinic patients. *Pain*. 1985; 23: 27-33.
18. Leigh TH, Hindmarch I, Bird HA, et al.: Comparison of sleep in osteoarthritic patients and age and sex matched controls. *Ann Rheum Dis*. 1988; 47: 40-42.

ORIGINAL ARTICLE

# Analgesic effects of lornoxicam after total abdominal hysterectomy

Ozgur Sapolya, MD
Beyhan Karamanhoglu, MD
Dilek Memis, MD

## ABSTRACT

*The authors investigated, in a randomized, placebo-controlled, double-blinded study, the efficacy and safety of lornoxicam on pain after abdominal hysterectomy and on tramadol consumption in patients. Fifty patients were randomized to receive either oral placebo or lornoxicam 8 mg one hour before surgery. Anesthesia was induced with propofol and maintained with sevoflurane in 50 percent $N_2O/O_2$ with a fresh gas flow of 2 L/min (50 percent $N_2O$ in $O_2$) and fentanyl (2 μg/kg). All patients received patient-controlled analgesia with tramadol with loading dose of 50 mg; incremental dose of 20 mg; lock out interval of 10 minute; and four-hour limit 300 mg. The incremental dose was increased to 30 mg if analgesia was inadequate after one hour. Patients were studied at one, two, four, eight, 12, and 24 hours for visual analogue (VAS) pain scores, heart rate, mean arterial pressure, periferic oxygen saturation, sedation, tramadol consumption, and length of hospitalization. VAS scores at one hour were significantly lower in the lornoxicam group ($p < 0.001$). The tramadol consumption at one, two, four, eight, and 12 hours was significantly lower in the lornoxicam group when compared with the placebo group ($p < 0.001$, $p = 0.008$, $p = 0.029$, $p = 0.034$, $p = 0.042$, respectively). Sedation scores were similar at all the measured times in the groups. Length of hospitalization was significantly shorter in lornoxicam group (4.8 ± 0.4 day) than placebo group (5.2 ± 0.5 day) ($p = 0.005$). There was difference in the incidence of nausea between the groups ($p = 0.047$). The number of patients and the doses of antiemetics given during the first 24 hours after surgery in lornoxicam group were less than those in placebo group ($p = 0.003$, $p = 0.034$, respectively).*

*In conclusion, a single oral dose of lornoxicam given preoperatively enhanced the analgesic effect of tramadol, decreasing tramadol consumption and side effects, and shortened the length of hospitalization.*

*Key words: analgesics opioid, tramadol, lornoxicam, postoperative pain, hysterectomy*

## INTRODUCTION

Postoperative pain is a factor that affects recovery from surgery and anaesthesia. The use of opioids by patient controlled analgesia (PCA) is popular, but is limited by side effects and by the fact that certain types of pain respond poorly to opioids.[1] Because of the multiplicity of mechanisms involved in postoperative pain, a multimodal analgesic regimen, using a combination of opioid and nonopioid analgesic drugs, is often used to enhance analgesic efficacy and to reduce opioid requirements and side effects.[2]

Lornoxicam is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs). It is rapidly eliminated, having a short plasma elimination half-life of three to five hours, which suggests its suitability for acute use during the postoperative period.[3,4] The clinical trials published so far, mostly comparative, clearly document lornoxicam's efficacy as a potent analgesic with excellent anti-inflammatory properties in a range of painful and/or inflammatory conditions, including postoperative pain. Lornoxicam has been shown to be at least as effective as comparable NSAIDs, and more effective than 10 mg morphine, when used at doses of 3 8 mg to control pain after oral surgery.[5,6]

The present study's aim was to determine the lornoxicam's effect on postoperative pain and on patient controlled tramadol consumption in patients after abdominal hysterectomy.

## METHODS

After obtaining the approval of the Institutional Ethics Committee (Trakya University, Edirne, Turkey) and written informed consent from the patients, 50 patients, ASA physical status I-II, undergoing elective total abdominal hysterectomy with salpingo-oophorectomy were studied. Patients were eligible for participation if they were at least 18 years old, weighed more than 40 kg, and could operate a patient controlled analgesia (PCA) device. Exclusion criteria were known allergy to opioids,

| Table 1. Demographic characteristics and perioperative data* | | |
|---|---|---|
| **Variable** | **Placebo (n = 25)** | **Lornoxicam (n = 25)** |
| Age (years) | 48.24 ± 7.95 | 47.72 ± 8.01 |
| Weight (kg) | 67.36 ± 13.3 | 68.04 ± 13.40 |
| Height (cm) | 158.0 ± 5 | 156 ± 7 |
| Body mass index (kg/m$^2$) | 28 ± 1.2 | 28.4 ± 2 |
| ASA physical status (I/II) | 15/10 | 16/9 |
| Duration of anesthesia (min) | 130.88 ± 31.51 | 129.12 ± 30.07 |
| *Values are shown as number (n) of patients or mean ± SD. No significant differences were found between the groups. | | |

asthma, contraindications to tramadol or any drug used, renal insufficiency, a history of a peptic ulcer, or a history of a bleeding diathesis.

The patients were randomly divided into two groups of 25 patients each. The study design was randomized and double-blinded: Patients were randomly allocated according to computer-generated randomization. For premedication, midazolam 0.07 mg/kg and atropine 0.01 mg/kg were administered IM 45 minutes before the surgical procedure. Patients in the control group received an oral placebo capsule, and those in the lornoxicam group received 8 mg lornoxicam (Xefo, 8 mg, Abdi Ibrahim, Istanbul, Turkey) (n = 20, Group I) one hour prior to surgery. The study drugs were prepared by the pharmacy, and an appropriate code number was assigned.

In the operating room, a crystalloid infusion was started through an IV cannula inserted in an antecubital vein, and the mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation ($SpO_2$) were monitored (Cato PM 8040; Dräger, Lübeck, Germany). Anesthesia was induced with propofol (2 mg/kg) and atracurium (0.5 mg/kg), and maintained with sevoflurane with a fresh gas flow of 2 L/min (50 percent $N_2O$ in $O_2$) and fentanyl (2 µg/kg). Surgery was performed via a Pfannenstiel incision. The lungs of the patients were mechanically ventilated (Cato; Dräger, Lübeck, Germany), and ventilation was adjusted to maintain end-expiratory $CO_2$ between 34 and 36 mmHg. At the end of surgery, neuromuscular block was antagonized with neostigmine 1.5 mg and atropine 0.5 mg.

| Table 2. Postoperative HR and MAP* | | | |
|---|---|---|---|
| **Hours after operation** | | **Placebo (n=25)** | **Lornoxicam (n = 25)** |
| 1 | HR | 78.80 ± 6.45 | 79.24 ± 9.79 |
| | MAP | 88.35 ± 11.22 | 88.52 ± 9.69 |
| 2 | HR | 79.20 ± 6.19 | 78.96 ± 8.93 |
| | MAP | 88.20 ± 10 | 88.96 ± 9.76 |
| 4 | HR | 79.44 ± 7.88 | 78.88 ± 7.10 |
| | MAP | 88.84 ± 10.50 | 89.52 ± 8.80 |
| 8 | HR | 81.04 ± 5.89 | 80.56 ± 4.86 |
| | MAP | 89.76 ± 9.81 | 88.04 ± 9.89 |
| 12 | HR | 80.16 ± 4.96 | 81.12 ± 5.66 |
| | MAP | 86.52 ± 8.25 | 89.52 ± 8.91 |
| 24 | HR | 80.0 ± 6.53 | 80.48 ± 7.60 |
| | MAP | 88.64 ± 8.50 | 87.04 ± 7.49 |
| *HR, heart rate (beats/min); MAP, mean arterial pressure (mmHg). HR and MAP are presented as mean ± SD. No statistical difference was found between groups. | | | |

| Table 3. Postoperative pain and sedation scores in lornoxicam and placebo groups* | | | | |
|---|---|---|---|---|
| Variable (h) | Placebo (n = 25) | | Lornoxicam (n = 25) | |
| | Sedation | VAS | Sedation | VAS |
| 1 | 2 (1-3) | 4 (1-8) | 2 (1-3) | 2 (0-5)† |
| 2 | 2 (1-3) | 3 (2-6) | 2 (1-3) | 2 (0-5) |
| 4 | 2 (2-2) | 3 (0-4) | 2 (2-3) | 2 (0-6) |
| 8 | 2 (2-2) | 2 (0-3) | 2 (2-3) | 1 (0-3) |
| 12 | 2 (2-3) | 0 (0-3) | 2 (2-3) | 0 (0-2) |
| 24 | 2 (2-2) | 0 (0-2) | 2 (2-2) | 0 (0-1) |

*Pain and sedation scores are median (min-max). †The VAS scores were significantly lower one hour postoperative in the lornoxicam group than in the placebo group ($p < 0.001$).

After tracheal extubation, patients were transferred to the postanaesthesia care unit (PACU). Postoperative pain was assessed based on the visual analogue score (VAS, where 0 cm, "no pain" and 10 cm, "worst pain imaginable"). Postoperative analgesia was provided with IV-PCA tramadol. The PCA technique and the VAS were explained to the patients during their preoperative visit. Patients were connected to the PCA device (Abbott Pain Management Provider, North Chicago, IL) upon their arrival in the PACU. All patients received tramadol PCA (3 mg/mL) with a loading dose of 50 mg, an incremental dose of 20 mg, a lockout interval of 10 minute, and a four-hour limit of 300 mg. The incremental dose was increased to 30 mg if the analgesia was inadequate after one hour. Sedation was assessed by the Ramsay sedation scale.[7] During the first hour in the PACU, and then at two, four, eight, 12, and 24 hours, the patients' pain scores were evaluated. HR, $SpO_2$, MAP, sedation, tramadol use, and total dose of tramadol were assessed by an anaesthesiology resident not otherwise involved in the study. The occurrence of any side effects, such as nausea and vomiting, constipation, respiratory depression, dizziness, somnolence, peripheral edema, diarrhea, headache, and pruritis, was recorded. Tramadol was stopped if a patient had an oxygen saturation, measured by pulse oximetry, less than 95 percent, or a serious adverse event related to opioid administration. On the patient's request, or if nausea and vomiting occurred, ondansetron 4 mg IV was given. All measurements were recorded by the same anaesthesia resident, who was blinded to the study drugs administered.

### Statistical analysis

A sample size of 25 patients by group was calculated to detect a significant difference of 15 percent or more in tramadol consumption with a power of 85 percent and a significance level of 5 percent. Descriptive statistics are expressed as mean ± SD unless otherwise stated. All variables were tested for normal distribution by Kolmogorov-Smirnov test. Student t test was used for comparison of the means of continuous variables and normally distributed data. Mann-Whitney U test was used otherwise. Two-way analysis of variance or Friedman test was used for variable differences in groups, and Bonferroni or Tukey HSD test was used for multiple comparisons. Categorical data were analyzed using $\chi^2$ test analysis or the Fisher exact, as appropriate. Significance was determined at $p < 0.05$.

## RESULTS

Fifty consecutive patients who fulfilled the inclusion criteria were included in the study. All the patients allocated completed the study; data from all 50 patients were therefore analyzed.

The groups were comparable with respect to age, body weight, height, ASA status, and duration of surgery (Table 1). MBP and HR did not differ between the groups at any of the measured times (Table 2).

The VAS scores were significantly lower one hour postoperative in the lornoxicam group than in the placebo group ($p < 0.001$) (Table 3). Sedation scores were similar at all the measured times in the lornoxicam and placebo groups (Table 3). No patient exhibited excessive sedation requiring alteration of the PCA settings or discontinuation.

Tramadol consumption at one, two, four, eight, and 12 hours was significantly lower in the lornoxicam group than in the placebo group ($p < 0.001$, $p = 0.008$, $p = 0.029$, $p = 0.034$, $p = 0.042$, respectively) (Table 4).

Length of hospitalization was significantly shorter in the lornoxicam group (4.8 ± 0.4 days) than in the placebo group (5.2 ± 0.5 days) ($p = 0.005$).

| Table 4. Total tramadol consumption (mg) in the lornoxicam and placebo groups* | | | |
|---|---|---|---|
| **Hours** | **Placebo (n = 25)** | **Lornoxicam (n = 25)** | **p** |
| 1 | 110.57 ± 27.54 | 80.54 ± 27.54 | < 0.001 |
| 2 | 168.01 ± 38.55 | 132.85 ± 50.51 | 0.008 |
| 4 | 222.62 ± 45.54 | 177.27 ± 68.15 | 0.029 |
| 8 | 310.54 ± 70.11 | 262.02 ± 86.35 | 0.034 |
| 12 | 350.14 ± 86.01 | 295.45 ± 98.40 | 0.042 |
| 24 | 392.89 ± 111.03 | 331.89 ± 111.03 | 0.082 |

*Tramadol doses are expressed as mean ± SD. Tramadol consumption at one, two, four, eight, and 12 hours was significantly lower in the lornoxicam group than in the placebo group.

The most common side effects seen during the study were nausea and vomiting (Table 5), and there was a difference in the incidence of nausea between the groups (p = 0.047). The number of patients and the doses in patients receiving antiemetics during the first 24 hours after surgery was less in the lornoxicam group than in the placebo group (p = 0.003, p = 0.034, respectively) (Table 6). No patient had oxygen saturation less than 95 percent or a serious adverse event related to opioid administration.

## DISCUSSION

The results of our preoperative oral single-dose study investigating lornoxicam's acute postoperative analgesic effects in patients after total abdominal hysterectomy show that: 1) Lornoxicam decreased postoperative tramadol consumption, 2) Lornoxicam was not associated with more side effects than the placebo, and 3) Lornoxicam shortened the length of hospitalization.

The main aim of combining different analgesic drugs is to obtain synergistic or additive analgesia, allowing a lower dose of each agent and improving the safety profile. This can be achieved by combining analgesics acting at different locations, e.g., centrally and peripherally acting analgesics. Tramadol can be used in PCA for moderate-to-severe postoperative pain. Its efficacy arises from two complementary mechanisms of action: stimulation of opioid receptors and inhibition of norepinephrine and 5-hydroxytryptamine reuptake in pain pathways.[8]

The NSAIDs act at peripheral nociceptors, preventing pain by inhibiting cyclo-oxygenase and thus reducing biosynthesis of pain-promoting prostoglandin derivatives in the periphery, produced in response to tissue injury. In addition, increasing evidence suggests that NSAIDs directly inhibit spinal nociceptor processing, an effect that correlates with various NSAIDs' ability to inhibit cyclo-oxygenase.[9,10]

The NSAIDs are commonly used analgesics for minor surgery and are useful adjunctive analgesics in patients undergoing major surgery, decreasing their pain and opioid requirements. They are well established, effective, and inexpensive. Trampitsch et al.[11] demonstrated that lornoxicam (8-mg bolus every eight hours for a total dose of 24 mg in the first 24 hours) administered preemptively improved the quality of postoperative analgesia and led to reduced consumption of opioid

| Table 5. Incidence of side effects* | | | |
|---|---|---|---|
| **Side effect** | **Placebo (n = 25)** | **Lornoxicam (n = 25)** | **p** |
| Nausea | 17 (68 percent) | 10 (40 percent) | 0.047 |
| Vomiting | 5 (20 percent) | 5 (20 percent) | 1.000 |
| Ortastatic hypotension | 0 (0 percent) | 1 (4 percent) | 0.820 |
| Flushing | 1 (4 percent) | 0 (0 percent) | 0.820 |

*Values are shown as number (n) of patients. The incidence of nausea was less in the lornoxicam group than in the placebo group.

| Table 6. Number of patients receiving antiemetics, and doses in patients receiving antiemetics during the first 24 hours after surgery* | | | |
|---|---|---|---|
| | **Placebo (n = 25)** | **Lornoxicam (n = 25)** | **p** |
| Number of patients receiving antiemetics | 16/25 | 7/25 | 0.034 |
| Number of doses in patients receiving antiemetics | 7.36 ± 6.08 | 3.84 ± 5.22 | 0.003 |
| *Values are shown as number (n) of patients. The number of patients and doses in patients receiving antiemetics during the first 24 hour after surgery was less in the lornoxicam group than in the placebo group. | | | |

analgesics postoperatively in patients undergoing gynecological operations. Ilias and Jansen[12] found that intravenous lornoxicam at a dose of 8 mg is superior to a placebo and is at least as effective as intravenous tramadol 50 mg in relieving moderate to intolerable posthysterectomy pain. Karaman et al.[13] found that lornoxicam 8 mg administered preemptively reduced postoperative pain and morphine consumption in patients undergoing gynecological operations in the early postoperative period. In our study, a single oral dose of lornoxicam given preoperatively enhanced tramadol's analgesic effect, decreasing tramadol consumption.

Assessment of acute pain utilizing the VAS in a scientific clinical investigation is inadequate. Sometimes this practice relies on subjective evaluation by a person who has little power to modify an inadequate prescription.[14] Fosnocht et al.[15] found that VAS is not a valid indicator of pain relief for individual patients. The concept of PCA may be regarded as a simple closed-loop system. The patient determines the dose required to maintain adequate analgesia. The optimum plasma concentration, as determined by the patient, is that which satisfies his subjective requirement for analgesia.[14]

Lornoxicam was well tolerated and was associated with a lower incidence of adverse events than tramadol alone. It may be an effective adjuvant to PCA tramadol for postoperative pain control. This combination reduces the total consumption of PCA tramadol and reduces side effects. Length of hospitalization was significantly shorter in the lornoxicam group than in the placebo group. Lornoxicam is well tolerated, elicited few side effects, and decreased patients' tramadol requirement; these effects may speed recovery and discharge.

In conclusion, a single oral dose of lornoxicam given preoperatively enhanced the tramadol's analgesic effect, decreasing both tramadol consumption and side effects. In addition, this strategy also may contribute to early discharge from the hospital after total abdominal hysterectomy. Further studies, however, are required in different pain models to investigate this drug's efficacy alone or in combination with other analgesics.

## ACKNOWLEDGMENTS

*Support was provided from institutional and/or departmental sources.*

*Ozgur Sapolya, MD, Assistant Director, Department of Anaesthesiology, Trakya University Medical Faculty, Edirne, Turkey.*

*Beyhan Karamanlhoglu, MD, Professor, Department of Anaesthesiology, Trakya University Medical Faculty, Edirne, Turkey.*

*Dilek Memis, MD, Associate Professor, Department of Anaesthesiology, Trakya University Medical Faculty, Edirne, Turkey.*

## REFERENCES

1. Dickenson A: Neurophysiology of opioid poorly responsive pain. *Cancer Surv.* 1994; 21: 5-16.
2. Fishman S, Borsook D: Opioids in pain management. In Benzon H, Raja S, Molloy RE, Strichartz G (eds.): *Essentials of Pain Medicine and Regional Anesthesia.* New York: Churchill Livingstone, 1999: 51-54.
3. Hitzenberger G, Radhofer-Welte S, Takacs F, et al.: Pharmacokinetics of lornoxicam in man. *Postgrad Med J.* 1990; 66 (Suppl 4): S22-S27.
4. Olkkola KT, Brunetto AV, Mattila MJ: Pharmacokinetics of oxicam nonsteroidal anti-inflammatory agents. *Clin Pharmacokinet.* 1994; 26: 107-120.
5. Norholt SE, Sindet-Pedersen S, Larsen U, et al.: Pain control after dental surgery: A double-blind, randomised trial of lornoxicam versus morphine. *Pain.* 1996; 67: 335-343.
6. Radhofer-Welte S, Rabasseda X: Lornoxicam, a new potent NSAID with an improved tolerability profile. *Drugs Today (Barc).* 2000, 36: 55-76.
7. Ramsay MA, Savege TM, Simpson BR, et al.: Controlled sedation with alphaxalone-alphadolone. *Br Med J.* 1974; 2: 656-659.
8. Schnitzer T: The new analgesic combination tramadol/acetaminophen. *Eur J Anaesthsiol.* 2003; 20 (Suppl 28): 13-18.
9. McCormack K: The spinal actions of nonsteroidal anti-inflammatory drugs and the dissociation between their anti-inflammatory and analgesic effects. *Drugs.* 1994; 47 (Suppl 5): 28-47.
10. McCormack K: Non-steroidal anti-inflammatory drugs and spinal nociceptive processing. *Pain.* 1994; 59: 9-43.
11. Trampitsch E, Pipam W, Moertl M, et al.: Preemptive randomized, double-blind study with lornoxicam in gynecological surgery. *Schmerz.* 2003; 17: 4-10.
12. Ilias W, Jansen M: Pain control after hysterectomy: An observer-blind, randomised trial of lornoxicam versus tramadol. *Br J Clin Pract.* 1996; 50: 197-202.
13. Karaman S, Gunusen I, Uyar M, et al.: The effect of preoperative lornoxicam and ketoprofen application on the morphine consumption of post-operative patient-controlled analgesia. *J Int Med Res.* 2006; 34: 168-175.
14. Mitchell RWD, Smith G: The control of acute postoperative pain. *Br J Anaesth.* 1989; 63: 147-158.
15. Fosnocht DE, Chapman CR, Swanson ER, et al.: Correlation of change in visual analog scale with pain relief in the ED. *Am J Emerg Med.* 2005; 23: 55-59.

# Journal of Opioid Management™

*A medical journal for proper and adequate use*

## REPRINT ORDER FORM

Note: While one photocopy is permissible, multiple reproduction of materials published in the *Journal of Opioid Management* is prohibited without written permission of the publisher.
For educational classroom use, quantity 200 or less, contact Copyright Clearance Center (222 Rosewood Dr., Danvers, MA 01923, 978-750-8400) directly. For all other uses, please order reprints using this form.

Author_____Issue_____

Title of article _____

Page numbers _____Quantity_____

Minimum order, 100—minimum price based on four pages. For orders over 500 copies, please write or call for quotation. Postage and/or freight included for shipment to US and Canada. Duties and taxes extra. For reprints over 20 pages, call for rates. All reprint prices in effect for 1-year from publication date. Past 1-year, call for rates. Delivery 3-6 weeks from order acceptance. All reprints run on Docutech. For reprints printed Offset on coated stock, call for custom quote.

| Pages | 1-4 | 5-8 | 9-12 | 13-16 | 17-20 |
|---|---|---|---|---|---|
| 100 Copies | 105.00 | 215.00 | 310.00 | 415.00 | 545.00 |
| 200 Copies | 200.00 | 400.00 | 600.00 | 800.00 | 1000.00 |
| 300 Copies | 285.00 | 570.00 | 855.00 | 1140.00 | 1425.00 |
| 400 Copies | 360.00 | 720.00 | 1080.00 | 1440.00 | 1800.00 |
| 500 Copies | 425.00 | 850.00 | 1275.00 | 1700.00 | 2125.00 |

**Billing Info:**

❑ All orders must be prepaid by check, credit card or purchase order.

❑ Check enclosed (remit in US dollars). Make checks payable to *Journal of Opioid Management.*

❑ Charge my ❑ Visa ❑ MasterCard ❑ AMEX ❑ Discover Account #

— — — — — — — — — — — — — — — —

Expiration date _____

Signature_____

Cardholder address_____

Tel ( ) _____Fax ( )_____

E-mail _____

Billing order/purchase number_____

**Ordering Info:**

Ordered by

Institution

Address

City State Zip

E-mail

**Ship To:**

Name

Institution

Address

City State Zip

E-mail

**Journal of Opioid Management**
**470 Boston Post Road, Weston, MA 02493 • 781-899-2702 • Fax: 781-899-4900 • www.opioidmanagement.com**

12565 12/27/04 Rev A

CASE STUDY

# Opioids applied topically to painful cutaneous malignant ulcers in a palliative care setting

Giovambattista Zeppetella, FRCP
Giampiero Porzio, MD
Federica Aielli, MD

## INTRODUCTION

The traditional view that opioids have only central effects has been challenged now as investigators have identified peripheral sites of opioid action. All classes of opioid receptors have been demonstrated on peripheral nerve terminals, and are similar to the population of receptors found in the central nervous system.[1] Opioid receptors are not obvious in normal tissue but become evident within minutes to hours after the start of inflammation and can be found within the dorsal root ganglia and peripheral sensory nerves, and on lymphocytes, macrophages, and mast cells.[2,3] The confirmation that peripheral opioid receptors exist has led to the possibility of specific targeting of peripheral receptors. The potential advantages of delivering opioids peripherally, for example, topical application, include maximizing opioid concentration at the site of pain and lower plasma levels with potentially fewer adverse effects and fewer drug interactions.

A number of studies have investigated the local analgesic effects of opioids in the clinical setting; most have focused at intra-articular opioid administration and have demonstrated that analgesia can be prolonged and effective, and successful doses are relatively low and usually free from systemic adverse effects.[4] Opioids have also been applied topically to malignant and nonmalignant ulcers in a palliative care setting. The most commonly applied opioid is morphine although there are also reports of diamorphine, fentanyl, oxycodone, hydromorphone, and methadone use. Most studies have been case reports in adults although some controlled studies in adults and small case series in children have also been published. The majority of patients described have presented with painful nonmalignant ulcers, in particular pressure sores. We describe four case studies of patients who present with pain from malignant ulcers in which topical morphine provided effective, safe, and well-tolerated analgesia.

## CASE STUDIES

### Case 1

GE was a 64-year-old woman with cervical carcinoma and pelvic metastases; her previous treatment included surgery, radiotherapy, and chemotherapy. On admission she presented with severe sacral pain (numerical rating score [NRS] 9) caused by a stage III, noninfected, malodorous ulcer. Her skin was erythematous and cytological examination did not reveal neoplastic infiltration. For regularly scheduled around-the-clock (ATC) analgesia she used transdermal fentanyl 100 μg/h, which controlled the background pain caused by the pelvic disease. The sacral ulcer was washed with ringer lactate and metronidazole solution (three times daily) after which morphine sulphate 10 mg in intrasite gel 8 g was applied directly to the ulcer; ATC analgesia was not modified. After 24 hours the patient reported a fall in pain intensity (NRS 4). Neither patients nor nursing staff reported local or systemic treatment related adverse effects and the patient was discharged after seven days, with almost complete control of pain (NRS 1), and ATC analgesia remained unchanged.

### Case 2

RA was a 76-year-old woman with breast cancer and liver, lung, and bone metastases. She had previously been treated with surgery, radiotherapy, and several lines of chemotherapy, and her on-going analgesic therapy included zoledronic acid 4 mg IV monthly and tramadol 100 mg three times daily, all used for the management of her background pain. On admission she presented with sternal pain resulting from a malignant ulcer. She rated her pain as NRS 6 and stated that the pain interrupted her sleep. Topical application of morphine sulphate 10 mg in intrasite gel 8 g after premedication with ringer lactate and metronidazole solution was started and carried out

three times daily; the dose of tramadol was not changed. After 24 hours the patient reported an NRS of 3 and her sleep improved. Nurses and patient reported no local or systemic adverse effects and the patient was discharged home after seven days with complete pain control (NRS 0). The patient continued on topical morphine application and the previous analgesic regimen remained unchanged.

### Case 3

VS was a 71-year-old woman with metastatic vulval cancer previously treated with radiotherapy and chemotherapy. On admission she complained of pain localized to the vulval and pubic regions, which she rated as NRS 9, and not controlled by a subcutaneous infusion of morphine 30 mg over 24 hours and oral preparations of gabapentin 300 mg three times daily and nimesulide 100 mg twice daily. Vulval examination revealed three noninfected malignant ulcers, two localized at the vulva and one at the pubis. Morphine sulphate 10 mg in intrasite gel 8 g was applied topically to the ulcers after premedication with ringer lactate and metronidazole solution three times daily; systemic medication was continued unchanged. Pain improved (NRS 5 after 24 hours) without local or systemic adverse effects. Patient was discharged after seven days with improved pain control (NRS 2); ATC analgesia remained unchanged.

### Case 4

TE was a 56-year-old man with lung cancer and skin metastases. He presented with a painful malignant lesion (NRS 8) on the right arm. ATC medication included modified release morphine 30 mg twice daily for background pain arising from her primary disease and cutaneous lesion, and normal release morphine 10 mg for breakthrough pain arising from the ulcer, which he required up to four times daily. An increase in both ATC and rescue medication produced little improvement in analgesia and was associated with nausea. ATC morphine was returned to the previous dose and morphine sulphate 10 mg in intrasite gel 8 g was applied topically to the ulcer and the dressing changed daily. In the next 48 hours the dose was increased to 15 mg and then to 20 mg after a further 24 hours, which produced a marked improvement in pain (NRS 2). His ATC systemic morphine remained unchanged and he rarely made use of rescue medication. The patient was discharged home to the care of his district nurses and he continued on the same dose of topically applied morphine for several months until his death.

## DISCUSSION

There has been an increasing interest in the use of topically applied opioids; however, this is not a new subject. In 1774, Heberden noted "patients with hemorrhoids should apply a mixture of a dram of the softened extract of opium for pain so excessive as to require immediate relief." He speculated that opium worked topically since there were very few central nervous effects. In 1885, Wood[5] wrote that morphine elicited analgesia when administered topically to painful site in peripheral tissues. With the increase in research activity in this area, particularly in animal models, it has been suggested that topically applied opioids not only provide relief from pain but also have anti-inflammatory effects and can promote wound healing.[6] The possible clinical application is important as the impact of malignant and nonmalignant ulcers in clinical care is significant. The effect on quality of life and the cost of hospital care of pressure ulcers, for example, is well recognized and has been described in both the US and UK settings.[7-9]

The literature describing the analgesic effect of topically applied opioids is growing (Table 1).[10-34] As with intraarticular opioids, the effective dose of topical opioids appears to be relatively low, and in most cases the starting dose appears to be effective with titration only necessary in a few studies. The four patients we describe reported successful analgesia despite a wide range of systemic ATC opioid dose, and analgesia was reported by some to occur almost immediately and by most within a few hours. The starting dose of morphine was the same for all patients regardless of the ulcer and the systemic ATC therapy; in one case, the dose required upward titration. The resulting analgesia ranged from partial to complete and the cases illustrate that the duration may be variable, but usually longer than seen with the corresponding opioid delivered systemically; some reports have described analgesia lasting for up to two days. In some studies the efficacy of topically applied opioids allowed a reduction in systemically administered opioids; furthermore, fewer doses of rescue medication rescue (as seen in case 4) further reduce the opioid burden and the consequent likelihood of adverse effects.

There is no universally accepted dosing schedule for topically applied opioids; in many cases, the opioid is applied according to the scheduling of the dressing change, the latter based on what has deemed to be appropriate for the wound. Some units give a trial dose of opioid, wait for pain to recur, and deliver future doses according to the length of pain relief seen with the trial dose. In the four cases described, two dosing schedules were described that varied according to the usual practice of our respective units and both proved to be effective. In case 4 where the patient required titration it may have been appropriate to reduce the dosing interval but, as pain was not controlled throughout the 24-hour period, rather than loss of control toward the end of the dosing schedule, an increase of dose rather than reduction of interval was considered and proved effective.

| Table 1. Selected studies reporting the use of topically applied opioids for local pain control | | | | | |
|---|---|---|---|---|---|
| **Author** | **Study type** | **Number** | **Opioid** | **Indication** | **Outcome** |
| Back and Finley[10] | Case reports | 3 | Diamorphine 10 mg in intrasite gel applied daily | Painful malignant and nonmalignant skin ulceration | All patients reported less pain with topical opioid |
| Duckett et al.[11] | Case series | 52 | Three doses 0.05, 0.375, 0.5 mg/mL morphine infused into bladder | Post-op bladder irritation in children | Higher doses helpful in the first 48 h post-operative |
| Krajnik and Zylicz[12] | Case report | 1 | 0.08 percent morphine in hydrogel (approx 3.2 mg of morphine applied in 4 g of gel) applied daily | Cutaneous non-Hodgkin's lymphoma | Effective local analgesia |
| Krajnik et al.[13] | Case reports | 6 | 0.1 percent morphine gel (five patients) or or 10 mg diamorphine in intrasite gel (one patient) applied twice or three times daily | Cutaneous lymphoma, malignant ulcer, oral mucositis, nonmalignant ulcer | All reported beneficial analgesia that was long-lasting |
| Twillman et al.[14] | Case reports | 9 | 0.1 percent morphine in intrasite gel (approx 1 mg morphine/1 mL intrasite gel) applied twice daily or as required | Pyoderma gangrenosum, sacral sore, malignant ulcer, diabetic ulcer, hydradenitis suppurativa, melanoma, swollen inflamed skin | All but one patient reported significant pain relief |
| Flock et al.[15] | Case report | 1 | 1 mg diamorpine/1 mL metronidazole gel (0.75 percent) applied for 48 h | Painful infected leg ulcer | Effective analgesia and ulcer healing |
| Paul[16] | Conference abstract | 4 | Fentanyl citrate 25 mg or 50 mg in KY jelly, metronidazole gel, or aquacell dressing applied daily | Painful malignant and nonmalignant ulcers | Effective analgesia, no adverse effects, less use of rescue analgesia |
| Long et al.[17] | Randomized controlled trial | 4 | Morphine infused sliver-sulfadiazine cream | Burns | Patients using topical morphine has lower pain scores |
| Ballas[18] | Case report | 2 | 5 mg oxycodone in 2 mL water (one patient) and 100 mg meperidine (pethidine) dissolved in water and applied with xylocaine (one patient) | Sickle cell leg ulcers | Effective almost immediate analgesia |
| Cerchietti et al.[19] | Randomized controlled trial | 26 | 15 mL 2 percent morphine mouthwash six times daily | Painful chemotherapy associated stomatitis | Pain intensity lower in morphine group |
| Cerchietti et al.[20] | Randomized controlled trial | 10 | 15 mL of either 1 percent or 2 percent morphine mouthwash every two to three h | Painful chemotherapy associated stomatitis | Both preparation effective, 2 percent produced more relief than 1 percent |
| Cerchietti et al.[20] | Randomized controlled trial | 22 | 15 mL of 2 percent morphine mouthwash every two to three h | Painful chemotherapy associated stomatitis | Pain reduction with few local adverse effects |

**Table 1. Selected studies reporting the use of topically applied opioids for local pain control (continued)**

| Author | Study type | Number | Opioid | Indication | Outcome |
|---|---|---|---|---|---|
| Cilakowska-Rysz et al.[21] | Conference abstract | 32 | Comparison of morphine sulphate hydrogel and morphine sulphate ointment | Malignant infiltration with intact skin, nonmalignant ulcers, post-shingles pain | Both preparations were equally efficacious |
| Flock[22] | Randomized controlled trial | 13 | Diamorphine 10 mg in intrasite gel versus intrasite gel (as placebo) applied daily | Grade II and III pressure ulcers | Seven patients completed, diamorphine significantly improved pain scores |
| Manzami-Maggi et al.[23] | Conference abstract | 8 | 0.3 percent morphine gel applied one to four times daily | Ulcerating pressures sores, arterial ulceration, ulcerating stomatitis | Moderate to good efficacy in three patients, no local toxicity |
| Zeppetella et al.[24] | Randomized controlled trial | 5 | Morphine 10 mg in intrasite gel applied daily | Painful malignant and nonmalignant skin ulceration | Lower pain scores with opioid compared to placebo; no local or systemic adverse effects |
| Abbas[25] | Case series | 17 | Diamorphine 5 to 10 mg in intrasite gel every 12 to 24 h | Pressure ulcers | Fall in VAS scores in 15 patients |
| Watterson et al.[26] | Case series | 2 | 10 mg morphine in 15 g intrasite gel | Epidermolysis bullosa | Reduction in pain scores |
| Ashfield[27] | Case study | 1 | 10 mg diamorphine in 8 g intrasite gel applied daily | Pressure ulcer | Effective analgesia |
| Gairard-Dory et al.[28] | Case series | 3 | 2 to 10 mL 0.1 percent morphine sulphate in carboxymethylcellulose given five to 60 min before eating | Chemotherapy induced oesophagitis | All patients reported effective analgesia |
| Gallagher et al.[29] | Case series | 4 | 100 mg methadone plus 10 g stomahesive powder applied daily | Malignant and nonmalignant ulcers | three patients in favor of morphine |
| Platzer et al.[30] | Case series | 6 | 0.1 percent morphine | Inflammatory skin pain | VAS scores fell in all cases |
| Porzio et al.[31] | Case series | 5 | 10 mg morphine in 8 g intrasite gel applied three times daily | Malignant and pressure ulcers | All patients reported reduced NRS scores |
| Varnassiere et al.[32] | Randomized controlled trial | 18 | Morphine 10 mg in intrasite gel applied daily | Chronic skin ulcers | No benefit if patient on systemic opioid |
| Zeppetella and Ribeiro[33] | Randomized controlled trial | 21 | Morphine 10 mg in intrasite gel applied daily | Malignant and nonmalignant ulcers | 16 patients completed, morphine treatment reduced numerical rating scores |
| Tran and Fancher[34] | Case study | 1 | 10 mg morphine sulphate in 8 g of a neutral water based gel applied | Mycosis Fungoides | Effective analgesia |
| Scott Groen | Personal communication | | 1 mL hydromorphone 1 mg/mL 2 mL propylene glycol, 7 mL 0.9 percent sodium chloride | Tache Pharmacy Winnipeg, Canada | |

There have been a few studies that have reported on the bioavailability of topically applied opioids. A study in volunteers who had morphine applied to de-epithelialized skin showed that 75 percent of the dose applied topically became bioavailable,[35] suggesting that a systemic opioid effect is possible. Other studies have reported that systemic absorption is not significant,[20,34,36] suggesting that the action could be local; this is supported by the our observations and the literature on the lack of reported systemic adverse effects and that topical administration appears to be efficacious across a wide range of systemically administered opioid doses. Topically applied opioids may, however, still have the potential to produce local adverse effects, either through the drug or the carrier. Few local adverse effects have been described in the literature and none were reported by either patients or nursing staff in the cases described, suggesting that this is a safe method of administering opioids. Although generally well tolerated, and frequently used in the literature, intrasite gel may not be appropriate for all ulcers. Glycol, metronidazole, and KY jelly have also been used as carriers, while others have sprayed the opioid directly on to the wound.

Among the limitations in this report is the potential to distinguish between an analgesic effect resulting from the cleansing agents and that arising from the topically applied opioid. There are small studies to suggest that topical opioid plus intrasite is more effective than intrasite alone;[24,33] however, this finding requires further confirmation. The issue of infection is also important and there are reports showing that local infection can be a cause of severe pain and this responds well to antibiotics;[37] in our cases the patients' ulcers were not infected.

Malignant and nonmalignant ulcers are a heterogeneous clinical problem; it is unlikely, therefore, that topical opioids would be the only solution. Preventative measures such as addressing mobility, nutrition, and skin health are desirable, as prevention is easier and less expensive than cure,[38] although there is a lack of evidence in the literature to support this.[39] Although patients with advanced disease may present with pressure ulcers, malignant cutaneous lesions can also occur. With malignant ulcers, healing is unlikely, so the goal of care shifts to wound management, palliation, and comfort; topically applied opioids in all four cases appear to have played a positive role in relief of pain and in practice are used alongside preventative physical measures.

The evidence to date is encouraging and suggests that topical opioid application could be a useful option in the management of painful skin ulcers. However, the studies to date have varied in study population, type of ulcer, opioid, carrier, and pain measurement; hence, there are many questions to be answered before this administration route can become routine medical practice. It is currently unknown, for example, which opioids are best suited to topical administration. Several have been used with success, morphine being the most common; the rationale for using diamorphine is debatable as it is generally considered to be a pro-drug, which in vivo is rapidly hydrolyzed by plasma cholinesterases and other blood and tissue esterases to active metabolites. The effective dose of opioid also requires clarification as in most studies an arbitrary dose of opioid was chosen. Perhaps, given the heterogeneity of malignant and nonmalignant ulcers, the dose may in fact vary between patients and dose titration in a way similar to the management of breakthrough pain,[40] which may be a safer and effective management strategy. The heterogeneity of malignant and nonmalignant ulcers may also influence the ideal opioid preparation; liquids, powder, or gel preparations may all be indicated and the choice is based on the wound characteristics, opioid stability, locally availability, and cost. The optimal frequency of administration is also unknown; strategies such as measuring the time to rescue medication following the application of opioid may be helpful in individualizing the frequency. It is possible that the frequency of dressing change and opioid administration may be different and alternative analgesic options will have to be considered. If these questions are to be addressed further, adequately powered placebo-controlled efficacy, titration, and safety studies are required.

*Giovambattista Zeppetella, FRCP, St Clare Hospice, Hastingwood, Essex, and Princess Alexandra NHS Trust, Harlow, Essex.*

*Giampiero Porzio, MD, Supportive Care Task Force, Medical Oncology Department, University of L'Aquila, L'Aquila, Italy.*

*Federica Aielli, MD, Supportive Care Task Force, Medical Oncology Department, University of L'Aquila, L'Aquila, Italy.*

## REFERENCES

1. Stein C: Peripheral mechanisms of opioid analgesia. *Anesth Analg.* 1993; 76: 182-191.
2. Antonijevic I, Mousa SA, Schafer M, et al.: Perineural defect and peripheral opioid analgesia in inflammation. *J Neurosci.* 1995; 15: 165-172.
3. Coggershall RE, Zhou S, Carlton SM: Opioid receptors in peripheral sensory axons. *Brain Res.* 1997; 764: 126-132.
4. Kalso E, Smith L, McQuay HJ, et al.: No pain, no gain: Clinical excellence and scientific rigour—Lessons learned from IA morphine. *Pain.* 2002; 98: 269-275.
5. Wood A. New method of treating neuralgia by direct application of opiates to the painful points. *Edinb Med Surg J.* 1885; 82: 265-281.
6. Poonawala T, Levay-Young BK, Hebbal RP, et al.: Opioids heal ischaemic wounds in rats. *Wound Repair Regen.* 2005; 13: 165-174.
7. National Pressure Ulcer Advisory Panel: *Pressure Ulcers in America: Prevalence Incidence, and Implications for the Future.* Reston, VA: National Pressure Ulcer Advisory Panel, 2001.
8. US Office of Disease Prevention and Promotion: *Healthy*

*People*. Washington, DC: US Dept of Health & Human Services, 2000.
9. Bennett G, Dealey C, Posnett J: Cost of pressure ulcers in the UK. *Age Ageing*. 2004; 33: 230-235.
10. Back IN, Finlay I: Analgesic effect of topical opioids on painful skin ulcers. *J Pain Symptom Manage*. 1995; 10: 493.
11. Duckett JW, Cangiano T, Cubina M, et al.: Intravesical morphine analgesia after bladder surgery. *J Urol*. 1997; 157: 1407-1409.
12. Krajnik M, Zylicz Z: Topical morphine for cutaneous cancer pain. *Palliat Med*. 1997; 11: 325.
13. Krajnik M, Zylicz Z, Finlay I, et al.: Potential uses of topical opioids in palliative care—Report of six cases. *Pain*. 1999; 80: 121-125.
14. Twillman RK, Long TD, Cathers TA, et al.: Treatment of painful skin ulcers with topical opioids. *J Pain Symptom Manage*. 1999; 17: 288-292.
15. Flock P, Gibbs L, Sykes N: Diamorphine-Metronidazole gel effective for treatment of painful infected leg ulcers. *J Pain Symptom Manage*. 2000; 20: 396-397.
16. Paul JR: Fentanyl topical gel for painful skin ulcers. *Palliat Med*. 2000; 14: 335.
17. Long TD, Cathers TA, Twillman R, et al.: Morphine-infused silver sulfadiazine (MISS) cream for burn analgesia: A pilot study. *J Burn Care Rehabil*. 2000; 22: 118-123.
18. Ballas SK: Treatment of painful sickle cell leg ulcers with topical opioids. *Blood*. 2002; 99: 1096.
19. Cerchietti LCA, Navigante AH, Bonomi MR, et al.: Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. *Cancer*. 2002; 15: 95: 2230-2236. Erratum in: *Cancer*. 2003; 15; 97: 1137.
20. Cerchietti LCA, Navigante AH, Korte MW, et al.: Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: A pilot study. *Pain*. 2003; 105: 265-273.
21. Cilakowska-Rysz A, Kazmierczak SF, Misiewicz B, et al.: Clinical efficacy of locally administered preparations containing morphine sulphate. 8th Congress of the European Association for Palliative Care. The Hague, April 2-5, 2003.
22. Flock P: Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer pain. *J Pain Symptom Manage*. 2003; 25: 547-554.
23. Manzambi-Maggi L, Bissig M, Neuenschwander H: Topic use of morphine. 8th Congress of the European Association for Palliative Care. The Hague, April 2-5, 2003.
24. Zeppetella G, Paul J, Ribeiro MD: Analgesic efficacy of morphine applied topically to painful ulcers. *J Pain Symptom Manage*. 2003; 25: 555-558.
25. Abbas SQ: Diamorphine-intrasite dressings for painful pressure ulcers. *J Pain Symptom Manage*. 2004; 28: 532-534.
26. Watterson G, Howard R, Goldman A: Peripheral opioids in inflammatory pain. *Arch Dis Child*. 2004; 89: 679-681.
27. Ashfield T: The use of topical opioids to relieve pressure ulcer pain. *Nurs Stand*. 2005; 19: 90-92.
28. Gairard-Dory AC, Schaller C, Mennecier B, et al.: Chemoradiotherapy-induced esophagitis pain relieved by topical morphine: Three cases. *J Pain Symptom Manage*. 2005; 30: 107-109.
29. Gallagher RE, Arndt DR, Hunt KL: Analgesic effects of topical methadone: A report of four cases. *Clin J Pain*. 2005; 21: 190-192.
30. Platzer M, Likar R, Stein C, et al.: Topische application von morphingel bei entzündlichen haut- and schleimhautläsionen. *Schmerz*. 2005; 19: 296-301.
31. Porzio G, Aielli F, Verna L, et al.: Topical morphine in the treatment of painful ulcers. *J Pain Symptom Manage*. 2005; 30: 304-305.
32. Vernassiere C, Cornet C, Trechot P, et al.: Study to determine the efficacy of topical morphine on painful chronic skin ulcers. *J Wound Care*. 2006: 14: 289-293.
33. Zeppetella G, Ribeiro MD: Morphine in intrasite gel applied topically to painful ulcers. *J Pain Symptom Manage*. 2005; 29: 118-119.
34. Tran QNH, Fancher T: Analgesia with topically applied morphine gel for painful ulcers: A case study and review of the literature. *J Support Oncol*. 2007; 5: 289-293.
35. Westerling D, Hoglund P, Lundin S, et al.: Transdermal administration of morphine to healthy subjects. *Br J Clin Pharm*. 1994; 37: 571-576.
36. Ribeiro MDC, Joel SP, Zeppetella G: The bioavailability of morphine applied topically to cutaneous ulcers. *J Pain Symptom Manage*. 2004; 27: 434-439
37. Bruera E, MacDonald N. Intractable pain in patients with advanced head and neck tumors: A possible role of local infection. *Cancer Treat Rep*. 1986; 70: 691-692.
38. McDonald A, Lesage P. Palliative management of pressure ulcers and malignant wounds in patients with advanced illness. *J Palliat Med*. 2006; 9: 285-295.
39. Reddy M, Gill SS, Rochon PA. Preventing pressure ulcers: A systematic review. *JAMA*. 2006; 296: 974-984.
40. Portenoy RK, Payne R, Coluzzi P, et al.: Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: A controlled dose titration study. *Pain*. 1999; 79: 303-312.

CASE STUDY

# Are we still scratching the surface? A case of intractable pruritus following systemic opioid analgesia

Dana Tarcatu, MD
Cristina Tamasdan, MD
Natalie Moryl, MD
Eugenie Obbens, MD, PhD

## ABSTRACT

*This article describes a case of severe opioid-induced pruritus following systemic morphine administration. Symptoms did not resolve after administration of antihistamines or rotation to fentanyl or hydromorphone, but oral oxycodone and small-dose intravenous naloxone did alleviate the patient's itching. The pathogenesis of opioid-induced pruritus and the rationale for opioid rotation are briefly discussed. Current and possible future therapeutic options are mentioned.*

*Key words: pruritus, systemic opioids, opioid rotation*

## INTRODUCTION

Generalized itch (pruritus) is an uncommon side effect of systemic opioid use, but it occurs frequently in conjunction with preoperative epidural or intrathecal opioid administration.[1] Occurrence and severity depend on the type of opioid used and individual tolerance.[2,3] The mechanism underlying the pruritogenic effect of systemic opioids is still not completely understood. The high incidence of pruritus seen with intraspinal administration of opioids suggests that spinal opioid receptors may be involved.[4] Recently, opioids have been shown to induce itching via specific binding to opioid receptors in the central and peripheral nervous system, mimicking the physiological effects of endorphins and enkephalins.[5] The relationship between itching and pain is bidirectional. Itching can be reduced by painful stimuli, and, vice versa, analgesia may reduce this inhibition and thus enhance the itch. This phenomenon is particularly relevant to spinally administered μ opioid receptor agonists, which induce segmental analgesia and segmental pruritus.[5,6] Because the perception of itching is modified by endogenous opioids via central receptors, it seems logical that opioid antagonists such as naloxone would demonstrate a high capacity to suppress pruritus induced by systemic opioid use.[7] In this case study we report the occurrence of severe itching after intravenous morphine administration in an opioid-tolerant patient. Pruritus was resolved by changing the opioid and route of administration and by adding a small dose of intravenous naloxone.

## CASE REPORT

A 15-year-old nonatopic male with desmoplastic small round cell tumor of the pelvis (postresection), who was undergoing chemotherapy (vincristine) and radiation therapy and had developed secondary acute myelogenous leukemia and neutropenic fever, was seen in consultation for mucositis pain. The reported "burning" pain involved the entire oral cavity, radiating down to the epigastric area. At that time, he was experiencing significant side effects from prior opioid use (nausea, vomiting, itching). Physical exam was remarkable for grade II mucositis. The patient was flushed in the face and scalp but had no urticaria lesions.

Upon admission, the patient was started on hydromorphone (Dilaudid) 0.4 mg every four hours; this dose was titrated rapidly up to 0.8 mg intravenously every four hours as needed. Because of resultant nausea, vomiting, and suboptimal analgesia, hydromorphone was changed to morphine sulfate 5 mg intravenously every three hours. With the first dose of morphine, the patient displayed onset of severe pruritus accompanied by urinary retention. Although his pain was better controlled after several subsequent doses, the itching was severe enough that it made him unwilling to continue taking morphine. Diphenhydramine 50 mg every six hours and hydroxyzine 50 mg every four hours were used as needed, without any noticeable improvement. Skin exam remained unremarkable, with some flushing without erythema, rash, dermatitis, or urticaria. Routine laboratory studies were also unremarkable; no eosinophilia was noted. Morphine was changed empirically to a continuous intravenous

infusion of fentanyl, administered as patient-controlled analgesia (PCA) at a basal rate of 50 μg/h. Titration of the dose up to 70 μg/h resulted in good pain control but made no difference with regard to the patient's itching. Over the next 12 hours, fentanyl was discontinued, and hydromorphone was restarted at 0.8 mg/h basal rate and 0.8 mg demand dose every 10 minutes. An average of 5 mg/h of additional hydromorphone was delivered via demand doses. The patient reported significant worsening of pruritus with every self-administered demand dose. After the pain management team was consulted, the patient was started on oxycodone oral elixir 45 mg every three hours as needed, and a continuous intravenous infusion of naloxone at 0.25 μg/kg/h was added. The hydromorphone PCA remained available to be used for demand doses of 1 mg every hour if the patient lost the capacity to swallow. During the next 24 hours, the patient used an average of 0.4 mg/h of hydromorphone as demand doses, with optimal pain control and no recurrence of itching. Until the patient's white blood cell count recovered and subsequent resolution of mucositis was seen, pain management continued, with oxycodone oral solution titrated up to 60 mg every three hours and hydromorphone intravenously as needed. Naloxone infusion was tapered and discontinued after seven days. After naloxone was discontinued, there was no further itching, and no other opioid-related side effects were observed.

## DISCUSSION

Opioid medications effectively treat pain, but they are associated with unwanted adverse effects, including nausea, vomiting, and pruritus. Pruritus can be severely distressing and as disabling as severe pain, and it may limit the acceptance of opioid therapy by both patients and caregivers.

Neurophysiologically, pruritogenic substances stimulate a subset of specialized skin C-fibers and initiate an itch sensation. These fibers are distinct from the polymodal C-type neurons, which transmit nociceptive (i.e., painful) stimuli to the central nervous system.[8] Many endogenous substances are regarded as "mediators of itch," such as amines (e.g., histamine), proteases, opioids, lipid peroxidation metabolites (e.g., leukotrienes, prostaglandins), neuropeptides (e.g., substance P), cytokines, growth factors (e.g., nerve growth factor), and many others. These agents may either directly sensitize the itch-mediating sensory nerve endings to various neuropeptides (such as substance P) or act on mast cells in the skin, leading to subsequent release of itch mediators, among which histamine functions as a key player.[9,10] Therefore, the bidirectional sensory neuron–mast cell interaction seems to be at the core of those processes that give rise to the onset of pruritus.

During the past 20 years, three opioid receptors—μ, δ, and κ—have been identified, and the genes coding for these receptors have been cloned.[11] The opioid receptors are transmembrane domain receptors linked to G proteins. The binding of opioids to these receptors initiates a cascade of events, culminating with protein phosphorylation and diverse physiological responses. Opioids are thought to produce their analgesic effect via agonist binding to Gi/Go-receptor-coupled complexes. These receptors inhibit the electrical firing of neurons and therefore block the perception of pain or the relay of pain signals from pain receptors. Opioids may also bind—at very small doses (pico- or nanomolar concentrations)—to Gs-coupled receptors. This connection activates an excitatory pathway that might explain the hyperalgesia occasionally reported with opioid administration, as well as some opioid-induced side effects such as pruritus, nausea, and vomiting.[12]

Recent animal studies have shown that histamine does not seem to be a player in mechanisms of opioid-induced itching and add further support to the idea that antihistamines are not effective in treating opioid-induced pruritus.[13,14] Most clinically used opioid analgesics are selective for the μ receptor, and this is the target receptor for morphine and other commonly used opioids, including oxycodone, hydromorphone, methadone, and fentanyl.[15] In addition, oxycodone, methadone, and buprenorphine may have clinically important activity at other opioid receptors.[16] In opioid-induced itching, μ opioid endogenic peptides (β endorphin, endomorphin-1, and endomorphin-2) are overly secreted, and the μ opioid receptors are proposed to be overexpressed as compared to κ opioid endogenic peptides (dynorphin A, dynorphin B, and dynorphin-associated peptides) and κ opioid receptors.[7]

Systemic administration of naloxone is a very potent and effective means of preventing or reversing itching invoked by agonists. Opioid receptor antagonists can be expected to effectively combat itch when it is invoked by μ opioid receptor analgesics or mediated by endogenous opioid peptides. The dose-response curve for opioid-induced itching appears to be bell shaped, similar to the progression of nausea and vomiting caused by the same medications.[17] It is also worth noting that opioid receptor antagonists produce parallel rightward shifts in the dose-response curves of morphine-induced scratching.[18] These observations indicate that the antipruritic effects of naltrexone and nalmefene are derived at opiate receptors through a competitive and reversible antagonist action. In contrast, in animal studies, κ agonists such as U-50488H produce downward shifts in the dose-response curve of morphine-induced scratching, and a selective antagonist can reverse their antipruritic actions.[19] The new synthetic κ receptor agonist TRK-820 was used to reduce itching and scratching in a mouse model, and its results seemed promising for possible translation into a

therapy for humans.[20] These observations indicate that κ agonists do not produce μ antagonism but rather inhibit μ-receptor-mediated itch through κ activation.

In our case, the use of intravenous morphine sulfate, a commonly used full μ receptor agonist, initiated the itching, which did not improve when morphine was changed to hydromorphone or fentanyl, μ1 and μ2 receptor agonists. When oral oxycodone was started in conjunction with intravenous naloxone, the itching improved significantly and resolved over the next 24 hours. Even after naloxone was discontinued, itching did not recur. Oxycodone is a semisynthetic opioid, derived from thebaine; it is classified as a pure opioid with a great affinity for μ receptors, greater than to κ receptors.[21] Despite a 10- to 40-fold lower affinity for the μ opioid receptor, oral oxycodone has nevertheless been found to produce pain relief that is generally comparable to that afforded by oral morphine. It has great bioavailability (60 percent), with roughly double the potency of and fewer adverse effects than morphine.[22] It has recently been proven, in both animal and human studies, that oxycodone analgesia is governed by the parent drug, with a negligible contribution from its circulating oxidative and reductive metabolites.[23]

## CONCLUSIONS

A patient's response to a medication depends on multiple considerations: pharmacokinetics, pharmacodynamics, and environmental and genetic factors. Opioid rotation helps some patients achieve better pain control with fewer associated adverse effects.[24] The pharmacological mechanisms underlying this phenomenon involve the diverse and combined effects of agonist binding to opioid receptors (μ, δ, κ); incomplete cross-tolerance; the diverse genetic background of patients, including allelic variations in the opioid receptors themselves; and differences in drug-clearance mechanisms.[25,26]

In the case described above, the resolution of the patient's pruritus seemed to be the result of two different, combined interventions. Oxycodone might have reestablished a balance between μ and κ opioid receptors, most likely through a predominantly κ1 agonistic effect, while naloxone provided an additional antipruritic effect through its action as a μ antagonist, with no reversal of analgesia at the small dose used. We are inclined to believe that even though the two interventions coincided, naloxone did not play a singular role, since itching did not recur after its discontinuation.

Data from prospective studies indicate that chronic itch is observed in 2 to 10 percent of patients receiving oral morphine for chronic cancer pain.[27] To date, the neurobiological mechanisms of the interaction between μ and κ opioid receptors in itch-selective neurons remain unclear. Recent studies in monkeys reinforce the idea that the μ opioid receptor—not histamine or the κ or δ receptor—mediates itching invoked by opioid analgesics. It is possible that activation of κ receptors in specific sensory neurons produces the antipruritic effect.[28] Current recommendations for the treatment of opioid-induced pruritus are empiric and anecdotal, as there are no prospective studies to support them. In general, treatment is based on the postulated mechanisms of action. Discontinuation of the offending drug, rotation to another opioid, and prevention/treatment with an opioid antagonist are all proposed management strategies. Therefore, it is pivotal to verify whether κ agonists have a broader application as antipruritics in humans. Future studies are required to establish different pruritus models and to investigate the types of κ agonists that are effective against itching invoked by pruritogenic agents other than opioids. These studies will make a substantial contribution to the in vivo pharmacology of pruritus and offer functional evidence of κ agonists' potential as a new generation of antipruritics.

*Dana Tarcatu, MD, Fellow, Pain and Palliative Care, Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, New York.*

*Cristina Tamasdan, MD, Fellow, Pain and Palliative Care, Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, New York.*

*Natalie Moryl, MD, Attending, Pain and Palliative Care, Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, New York.*

*Eugenie Obbens, MD, PhD, Acting Chief, Pain and Palliative Care, Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, New York.*

## REFERENCES

1. Ballantyne JC, Loach AB, Carr DB: The incidence of pruritus after epidural morphine. *Anaesthesia.* 1989; 44(10): 863.
2. Woodham M: Pruritus with sublingual buprenorphine. *Anaesthesia.* 1988; 43(9): 806-807.
3. Katcher J, Walsh D: Opioid-induced itching: Morphine sulfate and hydromorphone hydrochloride. *J Pain Symptom Manage.* 1999; 17(1): 70-72.
4. Ballantyne JC, Loach AB, Carr DB: Itching after epidural and spinal opiates. *Pain.* 1988; 33(2): 149-160.
5. Andrew D, Schmelz M, Ballantyne JC: Itch—mechanisms and mediators. In Dostrovsky JO, Carr DB, Koltzenburg M (eds.): *Proceedings of the 10th World Congress on Pain: Progress in Pain Research and Management.* Seattle: IASP Press, 2003, pp. 213-226.
6. Atanassoff PG, Brull SJ, Zhang J, et al.: Enhancement of experimental pruritus and mechanically evoked dysesthesiae with local anesthesia. *Somatosens Mot Res.* 1999; 16(4): 291-298.
7. Ko MC, Song MS, Edwards T, et al.: The role of central μ opioid receptors in opioid-induced itch in primates. *J Pharmacol Exp Ther.* 2004; 310(1): 169-176.
8. Schmidt R, Schmelz M, Forster C, et al.: Novel classes of responsive and unresponsive C nociceptors in human skin. *J Neurosci.* 1995; 15(1 Pt 1): 333-341.
9. Weidner C, Klede M, Rukwied R, et al.: Acute effects of substance

P and calcitonin gene-related peptide in human skin—a microdialysis study. *J Invest Dermatol*. 2000; 115(6): 1015-1020.
10. Heyer G, Dotzer M, Diepgen TL, et al.: Opiate and H1 antagonist effects on histamine induced pruritus and alloknesis. *Pain*. 1997; 73(2): 239-243.
11. Satoh M, Minami M: Molecular pharmacology of the opioid receptors. *Pharmacol Ther*. 1995; 68(3): 343-364.
12. Fine PG, Portenoy RK: *A Clinical Guide to Opioid Analgesia*. New York: McGraw-Hill, 2004.
13. Dunteman E, Karanicolas M: Transnasal butorphanol for the treatment of opioid-induced pruritus unresponsive to antihistamines. *J Pain Symptom Manage*. 1996; 12(4): 255-260.
14. Twycross R, Greaves MW, Handwerker H, et al.: Itch: Scratching more than the surface. *QJM*. 2003; 96(1): 7-26.
15. McQuay H: Opioids in pain management. *Lancet*. 1999; 353(9171): 2229-2232.
16. Poyhia R, Kalso EA: Antinociceptive effects and central nervous system depression caused by oxycodone and morphine in rats. *Pharmacol Toxicol*. 1992; 70(2): 125-130.
17. Wang SC: Emetic and antiemetic drugs. In Roots W, Hoffmann F (eds.): *Physiological Pharmacology*. New York: Academic Press, 1965, pp. 255-328.
18. Ko MC, Lee H, Song MS, et al.: Activation of kappa-opioid receptors inhibits pruritus evoked by subcutaneous or intrathecal administration of morphine in monkeys. *J Pharmacol Exp Ther*. 2003; 305(1): 173-179.
19. Kumagai H, Utsumi J: Endogenous opioid system in uraemic patients. *Br J Clin Pharmacol*. Abstracts of the Joint Meeting of the Seventh World Conference on Clinical Pharmacology and Therapeutics IUPHAR—Division of Clinical Pharmacology and the Fourth Congress of the European Association for Pharmacology and Therapeutics. 2000; 282.
20. Okano K, Togashi Y: Anti-pruritic effect of opioid kappa receptor agonist TRK-820. *Br J Clin Pharmacol*. Abstracts of the Joint Meeting of the Seventh World Conference on Clinical Pharmacology and Therapeutics IUPHAR—Division of Clinical Pharmacology and the Fourth Congress of the European Association for Pharmacology and Therapeutics. 2000; 283.
21. Lugo RA, Kern SE: The pharmacokinetics of oxycodone. *J Pain Palliat Care Pharmacother*. 2004; 18(4): 17-30.
22. Poyhia R, Vainio A, Kalso E: A review of oxycodone's clinical pharmacokinetics and pharmacodynamics. *J Pain Symptom Manage*. 1993; 8: 63-67.
23. Lalovic B, Kharasch E, Hoffer C, et al.: Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: Role of circulating active metabolites. *Clin Pharmacol Ther*. 2006; 79(5): 461-479.
24. Mercadante S: Opioid rotation for cancer pain: Rationale and clinical aspects. *Cancer*. 1999; 86(9): 1856-1866.
25. Gaveriaux-Ruff C, Kieffer BL: Opioid receptors: Gene structure and function. In Stein C (ed.): *Opioids in Pain Control: Basic and Clinical Aspects*. Cambridge, England: Cambridge University Press, 1999, pp. 1-20.
26. Knapp RJ, Porreca F, Burks TF, et al.: Mediation of analgesia by multiple opioid receptors. In Hill CS, Fields WS (eds.): *Advances in Pain Research and Therapy*. New York: Raven Press, 1989, pp. 247-289.
27. Kalso E, Vainio A: Morphine and oxycodone hydrochloride in the management of cancer pain. *Clin Pharmacol Ther*. 1990; 47(5): 639-646.
28. Ikoma A, Steinhoff M, Stander S, et al.: The neurobiology of itch. *Nat Rev Neurosci*. 2006; 7(7): 535-547.

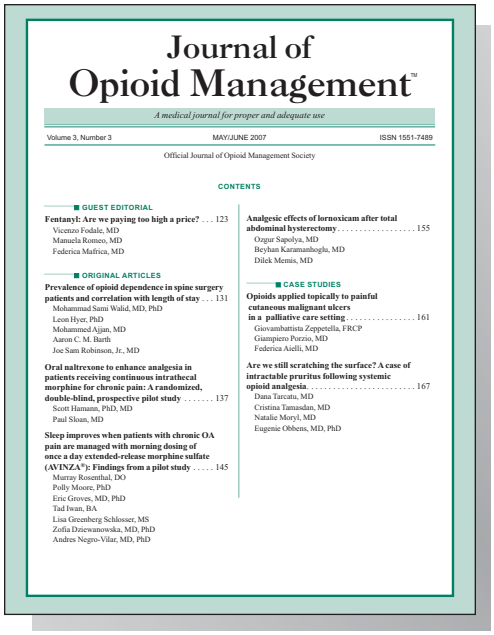
# INTRODUCING

# Journal of Opioid Management™

*A medical journal for proper and adequate use*

## Addresses all aspects of opioid use

- Federal spotlight on opioid abuse and addiction
- Pain management and opioids
- Pain control in end-of-life care using opioids
- Seven sins that physicians commit when prescribing opioids
- Legal issues and ongoing regulatory environment
- Adverse effects and cognitive function among primary care patients taking opioids for chronic pain
- Patient profiles and interaction with opioids
- Dosages and types of opioids, routes and intervals
- Management of opioid-tolerant chronic pain patients




Now indexed in **Index Medicus** and guided by the expertise of leaders in the field worldwide, ***Journal of Opioid Management*** is the only peer-reviewed periodical available today that covers all aspects of opioid use and safe management. Shouldn't the unchallenged journal of record for opioid management have a place in your professional library?

**NOTE!** The current FDA and DEA focus on curbing opioid abuse makes this journal a *must read* for all healthcare providers including primary care and palliative care physicians, oncologists, pharmacists, hospices and palliation centers. Because there are legal ramifications, each issue includes the perspectives of both defense and prosecuting attorneys as they examine all aspects of these important considerations.

# SUBSCRIBE TODAY

☑YES Please start my subscription to the ***Journal of Opioid Management*** — ISSN 1551-7489

***Individual:*** ***US subscribers*** ❑ 1 yr.–$298US ***Canadian subscribers*** ❑ 1 yr.–$323US ***Foreign subscribers*** ❑ 1 yr.–$363US

***Institution:*** ***US subscribers*** ❑ 1 yr.–$398US ***Canadian subscribers*** ❑ 1 yr.–$423US ***Foreign subscribers*** ❑ 1 yr.–$463US

***Library:*** ***US subscribers*** ❑ 1 yr.–$475US ***Canadian subscribers*** ❑ 1 yr.–$479US ***Foreign subscribers*** ❑ 1 yr.–$483US

Name _____

Title _____

Company _____

Street Address _____

City _____

State _____ Zip _____

E-mail: _____

❑Check enclosed

❑ MasterCard ❑ Visa ❑ Discover ❑ AMEX

Card No. _____

Exp. Date _____

Name on credit card _____

Address on credit card _____

X _____
Signature required

**Fed Tax ID # 20 882 8337**

**For faster service call our subscription department at 800-743-7206 x108, fax this form to 781-899-4900 or mail this form to:**
**Journal of Opioid Management, 470 Boston Post Road, Weston, MA 02493**

12882 06/26/07 Rev. A
JOMV3N3

Journal of
# Opioid Management™
*A medical journal for proper and adequate use*

**470 Boston Post Road, Weston, MA 02493 • 781-899-2702 • Fax: 781-899-4900**
**E-mail: jom@pnpco.com • Web site: www.opioidmanagement.com**

## *Call for manuscripts*

**Editorial Policy**

The mission of the ***Journal of Opioid Management*** is to educate and promote, through scientifically rigorous research, the adequate and safe use of opioids in the treatment of pain as well as the legal and regulatory issues surrounding abuse, addiction, and prescription practices (both over- and under-prescribing). Original articles, case studies, literature reviews, editorials, and letters to the editor concerning all aspects of opioid management will be considered for publication. All submissions, excluding editorials and letters to the editor, are subject to peer review by the editorial board prior to acceptance.

**Manuscript Submission**

To submit a manuscript, please go to *http://jom.allentrack2.net.* Click on "New users should register for a new account." After you register you will be able to click on a link to submit a manuscript, this will forward you to a page with instructions.

**Manuscript Format**

Please be sure to turn **OFF** the ***track changes*** feature on all documents before submission. The cover page should indicate the article's title, the full name, highest pertinent academic degrees, institutional affiliations, and current address of each author, contact information for the author handling all correspondence, telephone number, fax number, and, if the manuscript was orally presented at a meeting, the name of the organization, place, and date it was read. The first use of an uncommon abbreviation should be preceded by the full name. Brief definitions of key terms may be appended to the manuscript and can be presented in parentheses after the term within the article. With the exception of forum articles, book reviews, or letters to the editor, manuscripts should include the following five sections: Abstract, Introduction, Methods, Results, and Discussion. Subheads should be inserted at suitable levels. Style should conform to "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (available online at *http://www.icmje.org).*

**Figures & Tables**

The ***Journal*** welcomes illustrations, charts, and photographs to accompany articles. Figures should be titled and numbered consecutively according to the citation in the text. Information presented in figures and tables should be explained in the text. If data have been published previously, an appropriate reference should be included.

Short, descriptive legends should be provided on a separate page. Legends for figures previously published should include a complete reference to the original publication, with the copyright designation. Copies of the publisher's and author's permission to use the figure must be provided. Photographs should include legends and should be numbered consecutively according to the citation in the text and labeled on the back. Tables, photos, and figures must be submitted in the following formats: TIFF, JPEG, or EPS.

**Manuscript review**

Manuscripts are received with the understanding that they are submitted solely to ***Journal of Opioid Management*** and that, apart from abstracts, none of the material contained in the manuscript has been published previously or is under consideration for publication elsewhere. Authors should secure all necessary clearances and approvals prior to submission.

***Journal of Opioid Management*** is a refereed journal. All manuscripts are generally subject to review by at least two members of the editorial advisory board who are noted experts in the appropriate subject area. The ***Journal*** reserves the right to make editorial revisions prior to publication.

All manuscripts are acknowledged immediately, and every effort will be made to advise contributors of the status of their submissions within 60 days.

**References**

References are organized in AMA format; that is, they are to be cited numerically in the text and in consecutive order, including the first three authors followed by et al., and listed at the end of the article in the following format:

***Journal articles—***

1. Mudd P, Smith JG, Allen AZ, et al.: High ideals and hard cases: The evolution of opioid therapy for cancer pain. *Hastings Cent Rep*. 1982; 12(2):11-14.

***Books—***

1. Bayles SP (ed.): *Nutritional Supplements and Interactions with Analgesics*. Boston: GK Hall & Co., 1978.

***Book chapters—***

1. Martin RJ, Post SG: Introducing alternative prescribing strategies. In Smith J, Howard RP, and Donaldson P (eds.): *The Oncology Management Handbook*. Madison, WI: Clearwater Press, 1998, pp. 310-334.

***Web sites—***

Health Care Financing Administration: HCFA Statistics at a glance. Available at: www.hcfa/gov/stats/stahili.htm. Accessed December 27, 2002.

**Ethics**

Style should conform to "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" prepared by the International Committee of Medical Journal Editors and published in *Ann Intern Med* 1997; 126: 36-47, and available on the web at *http:www.acponline.org/journals/annals/01jan97/unifreqr.htm.*

The ***Journal*** expects authors to disclose any commercial or financial associations that might pose a conflict of interest in connection with the submitted article. All funding sources supporting the work should be acknowledged on the title page.

Manuscripts and all correspondence regarding them should be addressed to the Managing Editor, ***Journal of Opioid Management***, 470 Boston Post Road, Weston, MA 02493.

12530 11/16/06 Rev. C

# AVINZA® Ⓒ II

**(morphine sulfate extended-release capsules)**
**30 mg, 60 mg, 90 mg, 120 mg**

**BRIEF SUMMARY**
The following is a brief summary. Before prescribing, please consult full prescribing information.

**Rx Only**

**WARNING:**
**AVINZA capsules are a modified-release formulation of morphine sulfate indicated for once daily administration for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. AVINZA CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLESAUCE. THE CAPSULE BEADS ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE. 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.**

**INDICATIONS AND USAGE:** AVINZA capsules are a modified-release formulation of morphine sulfate intended for once daily administration indicated for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time.
AVINZA is **NOT** intended for use as a prn analgesic.
The safety and efficacy of using AVINZA in the postoperative setting has not been evaluated. AVINZA is not indicated for postoperative use. If the patient has been receiving the drug prior to surgery, resumption of the pre-surgical dose may be appropriate once the patient is able to take the drug by mouth. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (see American Pain Society guidelines)
**CLINICAL PHARMACOLOGY: Food Effects:** When a 60 mg dose of AVINZA was administered immediately following a high fat meal, peak morphine concentrations and AUC values were similar to those observed when the dose of AVINZA was administered in a fasting state, although achievement of initial concentrations was delayed by approximately 1 hour under fed conditions. Therefore, AVINZA can be administered without regard to food. When the contents of AVINZA were administered by sprinkling on applesauce, the rate and extent of morphine absorption were found to be bioequivalent to the same dose when administered as an intact capsule.
**Special Populations: Geriatric:** Elderly patients (aged 65 years or older) may have increased sensitivity to morphine. AVINZA pharmacokinetics have not been studied specifically in elderly patients.
**Nursing Mothers:** Low levels of morphine sulfate have been detected in maternal milk. The milk:plasma morphine AUC ratio is about 2.5:1. The amount of morphine delivered to the infant depends on the plasma concentration of the mother, the amount of milk ingested by the infant, and the extent of first pass metabolism.
**Pediatric:** The pharmacokinetics of AVINZA have not been studied in pediatric patients below the age of 18. The range of dose strengths available may not be appropriate for treatment of very young pediatric patients. Sprinkling on applesauce is **NOT** a suitable alternative for these patients.
**Gender:** A gender analysis of pharmacokinetic data from healthy subjects taking AVINZA indicated that morphine concentrations were similar in males and females.
**Race:** There may be some pharmacokinetic differences associated with race. In one published study, Chinese subjects given intravenous morphine had a higher clearance when compared to Caucasian subjects (1852 +/- 116 ml/min compared to 1495 +/- 80 ml/min).
**Hepatic Failure:** Morphine pharmacokinetics have been reported to be significantly altered in patients with cirrhosis. Clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine plasma AUC ratios also decreased in these subjects, indicating diminished metabolic activity.
**Renal Insufficiency:** Morphine pharmacokinetics are altered in patients with renal failure. Clearance is decreased and the metabolites, M3G and M6G, may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function.
**Drug-Drug Interactions:** Known drug-drug interactions involving morphine are pharmacodynamic, not pharmacokinetic. (see **PRECAUTIONS, Drug Interactions**)
**CONTRAINDICATIONS:** AVINZA is contraindicated in patients with known hypersensitivity to morphine, morphine salts, or any components of the product. AVINZA, like all opioids, is contraindicated in patients with respiratory depression in the absence of resuscitative equipment and in patients with acute or severe bronchial asthma.
AVINZA, like all opioids, is contraindicated in any patient who has or is suspected of having paralytic ileus.
**WARNINGS:** AVINZA must be swallowed whole (not chewed, crushed, or dissolved) or AVINZA may be opened and the entire bead contents sprinkled on a small amount of applesauce immediately prior to ingestion. **THE CAPSULES MUST NOT BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.** (see **BOX WARNING, CLINICAL PHARMACOLOGY**)
**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.**
**THE DAILY DOSE OF AVINZA MUST BE LIMITED TO A MAXIMUM OF 1600 MG/DAY. AVINZA DOSES OF OVER 1600 MG/DAY CONTAIN A QUANTITY OF FUMARIC ACID THAT HAS NOT BEEN DEMONSTRATED TO BE SAFE, AND WHICH MAY RESULT IN SERIOUS RENAL TOXICITY.**
**Misuse, Abuse and Diversion of Opioids:** Morphine is an opioid agonist and a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty. Morphine can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing AVINZA in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Abuse of AVINZA by crushing, chewing, snorting, or injecting the dissolved product will result in the immediate release of the entire daily dose of the opioid and pose a significant risk to the abuser that could result in overdose and death. Intravenous abuse of a water extract of AVINZA may lead to serious pulmonary complications due to the extraction of talc along with morphine sulfate. (see **DRUG ABUSE AND ADDICTION**)
Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.
**Interactions with Alcohol and Drugs of Abuse:** Morphine may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. *In vitro* studies performed by the FDA demonstrated that when AVINZA 30 mg was mixed with 900 ml of buffer solutions containing ethanol (20% and 40%), the dose of morphine that was released was alcohol concentration-dependent, leading to a more rapid release of morphine. While the relevance of *in vitro* lab tests regarding AVINZA to the clinical setting remains to be determined, this acceleration of release may correlate with *in vivo* rapid release of the total morphine dose, which could result in the absorption of a potentially fatal dose of morphine.
**Impaired Respiration:** Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation.
Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale and in patients having a substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnea.
**Head Injury and Increased Intracranial Pressure:** The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Morphine produces effects which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries. Morphine should only be administered under such circumstances when considered essential and then with extreme care.
**Hypotensive Effect:** AVINZA, like all morphine products, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume or concurrent administration of drugs such as phenothiazines or general anesthetics. (see also **PRECAUTIONS, Drug Interactions**)
AVINZA may produce orthostatic hypotension and syncope in ambulatory patients.
AVINZA is an opioid analgesic which should be administered with caution to patients in circulatory shock, as vasodilation produced by the drug may further reduce cardiac output and blood pressure.
**Gastrointestinal Obstruction:** AVINZA should not be administered to patients with gastrointestinal obstruction, especially paralytic ileus because AVINZA, like all morphine preparations, diminishes propulsive peristaltic waves in the gastrointestinal tract and may prolong the obstruction.
**PRECAUTIONS: General:** AVINZA is intended for use in patients requiring continuous around-the-clock treatment with an opioid analgesic. It is not appropriate as a prn treatment for pain. As with any opioid, it is critical to adjust the dose of AVINZA for each individual patient, taking into account the patient's prior experience with analgesics. (see **DOSAGE AND ADMINISTRATION**)
**Use in Pancreatic/Biliary Tract Disease:** AVINZA should be used with caution in patients with biliary tract disease, including acute pancreatitis, as morphine may cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions.
**Special Risk Groups:** AVINZA should be administered cautiously and in reduced dosages in patients with severe renal or hepatic insufficiency, Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients. (see **Geriatric Use** and **CLINICAL PHARMACOLOGY, Special Populations**)
Caution should be exercised in the administration of morphine to patients with CNS depression, toxic psychosis, acute alcoholism and delirium tremens, and seizure disorders.
**Driving and Operating Machinery:** Patients should be cautioned that AVINZA could impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.
Patients should also be cautioned about the potential combined effects of AVINZA with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol. (see **PRECAUTIONS, Drug Interactions**)
**Tolerance and Physical Dependence:** Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.
The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.
In general, opioids should not be abruptly discontinued. (see **DOSAGE AND ADMINISTRATION, Cessation of Therapy**)
**Drug Interactions: CNS Depressants:** The concurrent use of other central nervous system (CNS) depressants including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, or other tranquilizers or alcohol increases the risk of respiratory depression, hypotension, profound sedation, or coma. Use with caution and in reduced dosages in patients taking these agents.
**Muscle Relaxants:** Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
**Mixed Agonist/Antagonist Opioid Analgesics:** Mixed agonist/-antagonist analgesics (i.e., pentazocine, nalbuphine and butorphanol) should NOT be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.
**Monoamine Oxidase Inhibitors (MAOIs):** MAOIs markedly potentiate the action of morphine. AVINZA should not be used in patients taking MAOIs or within 14 days of stopping such treatment.
**Cimetidine:** Concomitant administration of morphine and cimetidine has been reported to precipitate apnea, confusion and muscle twitching in an isolated report. Patients should be monitored for increased respiratory and CNS depression when receiving cimetidine concomitantly with AVINZA.
**Food:** AVINZA can be administered without regard to food. (see **CLINICAL PHARMACOLOGY, Food Effects**)
**Carcinogenicity/Mutagenicity/Impairment of Fertility:** Studies in animals to evaluate the carcinogenic potential of morphine sulfate have not been conducted. No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, the results of *in vitro* studies showed that morphine is non-mutagenic in the *Drosophila melanogaster* lethal mutation assay and produced no evidence of chromosomal aberrations when incubated with murine splenocytes. Contrary to these results, morphine was found to increase DNA fragmentation when incubated *in vitro* with a human lymphoma cell line. *In vivo*, morphine has been reported to produce an increase in the frequency of micronuclei in bone marrow cells and immature red blood cells in the mouse micronucleus test and to induce chromosomal aberrations in murine lymphocytes and spermatids. Some of the *in vivo* clastogenic effects reported with morphine in mice may be directly related to increases in glucocorticoid levels produced by morphine in this species.
**Pregnancy: Teratogenic Effects (Pregnancy Category C):** No formal studies to assess the teratogenic effects of morphine in animals have been performed. Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic of those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. Morphine was not a significant teratogen in the rat at exposure levels significantly beyond that normally encountered in clinical practice. In one study however, decreased litter size and viability were observed in the offspring of male rats administered morphine at doses approximately 3-fold the maximum recommended human daily dose (MRHDD) for 10 days prior to mating. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.
In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with this drug anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.
**Nonteratogenic Effects:** Published literature has reported that exposure to morphine during pregnancy is associated with reduction in growth and a host of behavioral abnormalities in the offspring of animals. Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, lengths or widths at birth and during the neonatal period, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed. Behavioral abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine persisting into adulthood.
Controlled studies of chronic *in utero* morphine exposure in pregnant women have not been conducted. Infants born to mothers who have taken opioids chronically may exhibit withdrawal symptoms, reversible reduction in brain volume, small size, decreased ventilatory response to CO2 and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.
**Labor and Delivery:** Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. AVINZA is not recommended for use in women during and immediately prior to labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid-induced respiratory depression in the neonate.
**Neonatal Withdrawal Syndrome:** Chronic maternal use of opioids during pregnancy may cause newborns to suffer from neonatal withdrawal syndrome (NWS) following birth. Manifestations of this syndrome include irritability, hyperactivity, abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, weight loss, and failure to gain weight. The time and amount of the mother's last dose, and the rate of elimination of the drug from the newborn may affect the onset, duration, and severity of the disorder. When severe symptoms occur, pharmacologic intervention may be required.
**Nursing Mothers:** Low levels of morphine sulfate have been detected in human milk. Breast-feeding infants might experience withdrawal symptoms upon cessation of AVINZA administration to the mother. Because of the potential for nursing infants to experience adverse reactions, a decision should be made whether to discontinue nursing or discontinue AVINZA, taking into account the benefit of the drug to the mother.
**Pediatric Use:** Safety and effectiveness of AVINZA in pediatric patients below the age of 18 have not been established. The range of dose strengths available may not be appropriate for treatment of very young pediatric patients. Sprinkling on applesauce is **NOT** a suitable alternative for these patients.
**Geriatric Use:** Of the total number of subjects in clinical studies of AVINZA, there were 168 patients age 65 and over, including 64 patients over the age of 74, 100 of whom were treated with AVINZA. Subgroup analyses comparing efficacy were not possible given the small number of subjects in each treatment group. No overall differences in safety were observed between these subjects and younger subjects. In general, caution should be exercised in the selection of the starting dose of AVINZA for an elderly patient, usually starting at the low end of the dosing range. As with all opioids, the starting dose should be reduced in debilitated and non-tolerant patients. (see **CLINICAL PHARMACOLOGY, Special Populations, Geriatric** and **PRECAUTIONS, Special Risk Groups**)
**ADVERSE REACTIONS:** In controlled and open label clinical studies, 560 patients with chronic malignant or non-malignant pain were treated with AVINZA. The most common serious adverse events reported with administration of AVINZA were vomiting, nausea, death, dehydration, dyspnea, and sepsis. (Deaths occurred in patients treated for pain due to underlying malignancy.) Serious adverse events caused by morphine include respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.
**Adverse Events:** The common adverse events seen on initiation of therapy with morphine are dose-dependent and are typical opioid-related side effects. The most frequent of these include constipation, nausea and somnolence. The frequency of these events depends upon several factors including the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. These events should be anticipated and managed as part of opioid analgesia therapy.
The most common adverse events (seen in greater than 10%) reported by patients treated with AVINZA during the clinical trials at least once during therapy were constipation, nausea, somnolence, vomiting, and headache. Adverse events occurring in 5-10% of study patients were peripheral edema, diarrhea, abdominal pain, infection, urinary tract infection, accidental injury, flu syndrome, back pain, rash, sweating, fever, insomnia, depression, paresthesia, anorexia, dry mouth, asthenia and dyspnea. Other less common side effects expected from opioid analgesics, including morphine, or seen in fewer than 5% of patients taking AVINZA in the clinical trials were:
*Body as a Whole:* malaise, withdrawal syndrome.
*Cardiovascular System:* bradycardia, hypertension, hypotension, palpitations, syncope, tachycardia.
*Digestive System:* biliary pain, dyspepsia, dysphagia, gastroenteritis, abnormal liver function tests, rectal disorder, thirst.
*Hemic and Lymphatic System:* anemia, thrombocytopenia.
*Metabolic and Nutritional Disorders:* edema, weight loss.
*Musculoskeletal:* skeletal muscle rigidity.
*Nervous System:* abnormal dreams, abnormal gait, agitation, amnesia, anxiety, ataxia, confusion, convulsions, coma, delirium, euphoria, hallucinations, lethargy, nervousness, abnormal thinking, tremor, vasodilation, vertigo.
*Respiratory System:* hiccup, hypoventilation, voice alteration.
*Skin and Appendages:* dry skin, urticaria.
*Special Senses:* amblyopia, eye pain, taste perversion.
*Urogenital System:* abnormal ejaculation, dysuria, impotence, decreased libido, oliguria, urinary retention.
**DRUG ABUSE AND ADDICTION: AVINZA is a mu-agonist opioid and is a Schedule II controlled substance. Morphine, like other opioids used in analgesia, can be abused and is subject to criminal diversion.**
Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.
"Drug seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.
Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence. The converse is also true. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.
Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.
**AVINZA is intended for oral use only. Abuse of the crushed capsule poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the capsule excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.**
**AVINZA OVERDOSAGE: Symptoms:** Acute overdosage with morphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, and death.
**Treatment:** Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdose of an extended release formulation such as AVINZA has been ingested. Elimination or evacuation of gastric contents may be necessary in order to eliminate unabsorbed drug. Before attempting treatment by gastric emptying or activated charcoal, care should be taken to secure the airway. Pure opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. Since the duration of reversal is expected to be less than the duration of action of AVINZA, the patient must be carefully monitored until spontaneous respiration is reliably re-established. AVINZA, as with other controlled delivery preparations in overdose situations, may continue to release morphine for 36 to 48 hours or longer following ingestion, and management of an overdose should be monitored accordingly. If the response to opioid antagonists is sub-optimal or only brief in nature, additional antagonist should be administered as directed by the manufacturer of the product.
Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Such agents should be administered cautiously to persons who are known, or suspected to be physically dependent on AVINZA. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome.
**Opioid-Tolerant Individuals:** In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of an opioid antagonist should be reserved for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and titrated with smaller than usual doses.
Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.
**DOSAGE AND ADMINISTRATION: AVINZA MUST BE SWALLOWED WHOLE (NOT CHEWED, CRUSHED, OR DISSOLVED) OR AVINZA MAY BE OPENED AND THE ENTIRE BEAD CONTENTS SPRINKLED ON A SMALL AMOUNT OF APPLESAUCE IMMEDIATELY PRIOR TO INGESTION. THE BEADS MUST NOT BE CHEWED, CRUSHED, OR DISSOLVED DUE TO RISK OF ACUTE OVERDOSE. INGESTING CHEWED OR CRUSHED AVINZA BEADS WILL LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.**
**Patients must not consume alcoholic beverages while on AVINZA therapy. Additionally, patients must not use prescription or non-prescription medicine 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.**
**The daily dose of AVINZA must be limited to a maximum of 1600 mg/day. AVINZA doses of over 1600 mg/day contain a quantity of fumaric acid that has not been demonstrated to be safe, and which may result in serious renal toxicity.** (see **WARNINGS**)
**The 60, 90, and 120 mg capsules are for use only in opioid tolerant patients.**
All doses are intended to be administered once daily. As with any opioid drug product, it is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of AVINZA, attention should be given to the following:
1. the total daily dose, potency and specific characteristics of the opioid the patient has been taking previously; 2. the reliability of the relative potency estimate used to calculate the equivalent morphine dose needed; 3. the patient's degree of opioid tolerance; 4. the general condition and medical status of the patient; 5. concurrent medications; 6. the type and severity of the patient's pain.
**Cessation of Therapy:** When the patient no longer requires therapy with AVINZA capsules, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.
**SAFETY AND HANDLING:** AVINZA consists of hard gelatin capsules containing polymer-coated morphine sulfate beads that pose no known risk of handling to healthcare workers. All opioids are liable to diversion and misuse both by the general public and healthcare workers and should be handled accordingly.

CAUTION: DEA Order Form Required. Rx Only.

King Pharmaceuticals


AVI4553 03/2007

King's Professional Information Services: 1-800-776-3637
Rev. 2/07

SODAS® is a registered trademark of Elan Corporation, plc.
U.S. Patent No.: 6,066,339

For patients with chronic, moderate to severe pain

# More time with friends

## True, 24-hour pain control with QD dosing helps patients get back to active living[1]

- Sustained 24-hour pain control day after day, week after week[1,2]
- 49% mean reduction in daily pain scores at end of titration[1]
- Consistent improvement in physical and social functioning[3]
- Improved quality and duration of sleep[1,2]
- 30 days = 30 doses

### Important Safety Information

**AVINZA® capsules are a modified-release formulation of morphine sulfate indicated for once-daily administration for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. AVINZA® CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLESAUCE. THE CAPSULE BEADS ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE. PATIENTS MUST NOT CONSUME ALCOHOLIC BEVERAGES WHILE ON AVINZA® THERAPY. ADDITIONALLY, PATIENTS MUST NOT USE PRESCRIPTION OR NONPRESCRIPTION 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.**

The most common serious adverse events reported with administration of AVINZA® were vomiting, nausea, death, dehydration, dyspnea, and sepsis. (Deaths occurred in patients treated for pain due to underlying malignancy.) Serious adverse events caused by morphine include respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

AVINZA® is contraindicated in patients with known hypersensitivity to morphine, morphine salts, or any components of the product. AVINZA®, like all opioids, is contraindicated in patients with respiratory depression in the absence of resuscitative equipment and in patients with acute or severe bronchial asthma.

AVINZA®, like all opioids, is contraindicated in any patient who has or is suspected of having paralytic ileus.

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale and in patients having a substantially decreased respiratory reserve (eg, severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnea.

AVINZA® is **NOT** intended for use as a prn analgesic. The safety and efficacy of using AVINZA® in the postoperative setting has not been evaluated. AVINZA® is not indicated for postoperative use. If the patient has been receiving the drug prior to surgery, resumption of the pre-surgical dose may be appropriate once the patient is able to take he drug by mouth.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Association guidelines.) Morphine sulfate is a Schedule II controlled substance that can be abused in a manner similar to other legal or illegal opioids.

AVINZA® should be administered cautiously and in reduced dosages in patients with severe renal or hepatic insufficiency, Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients.

**Patients must not consume alcoholic beverages while on AVINZA® therapy. Additionally, patients must not use prescription or nonprescription medicine 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.**

**The daily dose of AVINZA® must be limited to a maximum of 1600 mg/day. AVINZA® doses of over 1600 mg/day contain a quantity of fumaric acid that has not been demonstrated to be safe, and which may result in serious renal toxicity** (see **WARNINGS**).

**The 60-, 90-, and 120-mg capsules are for use only in opioid-tolerant patients.**

**For additional Important Safety Information, please see brief summary of full Prescribing Information on adjacent page. For questions regarding AVINZA®, please call the AVINZA® Information Service at 1-888-8-AVINZA or visit us on the web at www.avinza.com.**

**References: 1.** Rauck RL, Bookbinder SA, Bunker TR, et al. The ACTION study: a randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulfate capsules (AVINZA®) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin®) for the treatment of chronic, moderate to severe low back pain. *J Opioid Manag.* 2006;2:155-166. **2.** Caldwell JR, Rapoport RJ , Davis JC, et al, for the Avinza™ TRG004-04 Study Group. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage.* 2002;23:278-291. **3.** Rauck RL, Bookbinder SA, Bunker TR, et al. A randomized, open-label, multicenter trial comparing once-a-day AVINZA® (morphine sulfate extended-release capsules) versus twice-a-day OxyContin® (oxycodone hydrochloride controlled-release tablets) for the treatment of chronic, moderate to severe low back pain: improved physical functioning in the ACTION trial. *J Opioid Manag.* 2007;3:35-43.

King Pharmaceuticals www.kingpharm.com **Please visit us at www.avinza.com.**

24 hour AVINZA® (morphine sulfate extended-release capsules)

ALL DAY. EVERY DAY.