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A medical journal for proper and adequate use

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Journal of Opioid Management™

A medical journal for proper and adequate use

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GUEST EDITORIAL

King of Pain: What Elvis's death tells us about media coverage of celebrities and the pain/addiction interface

Steven D. Passik, PhD
Kenneth L. Kirsh, PhD

Media coverage of celebrities' problems with prescription medications creates an extra level of fear and reticence around classes of medications such as opioids. While patients should approach these medications seriously and with caution, the message sent by the media seems to be that addiction and abuse are unavoidable conclusions with this modality. In this editorial, we highlight the much publicized death of Elvis Presley as an example and discuss the ramifications media slant can have for both professionals and the lay public with regards to pain management.

Elvis Presley died of a drug overdose while sitting on the toilet. This indignity is nothing compared to the gradual and inevitable tarnishing of his image, portrayed as he was in later life and death as a fat, slovenly drug addict. Elvis was the "King of Rock and Roll," but he was also the King of Pain. Born on January 8, 1935, in Tupelo, Mississippi, Elvis Aaron Presley would have turned 72 this year; in death he can enlighten us about how the media portrays the interface of pain and addiction in celebrities who have had difficulties in this spectrum. We as pain practitioners need to think about how we can counter these portrayals.

Whatever else he was, Elvis was a chronic pain patient.[1,2] He suffered for years from debilitating stomach pain resulting from Crohn's disease. He was prescribed chronic steroids for this inflammatory disease, and this was the only treatment that offered him some relief. Elvis gained a significant amount of weight from the steroids. He broke bones because of them. He got jumpy and couldn't sleep. In order to continue to give his fans what they wanted in spite of these side effects, he took pain and anxiety medications. Elvis died just trying to be Elvis.

Brookoff[1] has argued that much of America's perception of Elvis is based not on his suffering but his drug addiction; in analyzing the actual medical facts of the case and then comparing them to the typical perception, Brookoff says, we obtain a commentary as much on how our society feels about people who take controlled substances and are overweight as on the realities of Elvis's situation. So we will focus, then, for the rest of this piece on the problematic media portrayals of celebrities' pain and addiction and the dilemmas they create for those of us working in pain management. Finally, we will propose a solution.

It is clear that a great deal of fear exists regarding the use of opioids among patients, their caregivers, and their families.[3-5] While clearly not the sole source of opiophobia in society, Elvis's and other celebrities' highly publicized experiences with pain medications are bound to exacerbate an already wary view of pain treatment. Our pain patients (with both malignant and nonmalignant pain) are constantly asking if they are going to be turned into addicts. They think, "It happened to [insert celebrity name], and it could happen to me." Thus, a frequent question becomes, "Are we all liable to become enslaved by these powerful medications and end up in rehab?" It is at this moment that we are challenged to teach patients about addiction risk.[6] The benefit for us is that we can use this discussion as a jumping point for explaining to patients why we do the things we do to manage risks with opioids, such as opioid agreements and urine toxicology screens, and to explain to them that the celebrities they read about are likely not treated with such traditional limits.[7]

We must teach our patients that Elvis is the exception, not the rule. Elvis had a history of drug and alcohol abuse. His mother may have died of complications of alcoholism. His early life was complicated by his father's bootlegging and jail time. He lost his twin at birth and lived with chronic feelings of emptiness.[8] Combine those risk factors with his wealth, celebrity lifestyle, and status, which clearly opened the door for special treatment and relatively free availability of drugs, and we have a recipe for disaster.

In short, the trappings of fame can encourage an early downfall in individuals prone to substance abuse or misuse when they experience pain. As an introduction of risk management strategies, we can explain how it might sometimes be the case that when famous people have

pain, faulty assumptions get made that because they are successful, they can 1) take pain medications without risk; 2) continue to travel around the world while taking medications, unmonitored by physicians, psychologists, or other professionals; and 3) receive renewals on their prescriptions whenever they need or want them, with prescriptions often being written by multiple doctors.

We need to explain to our patients that while some people can benefit from such a loose approach, most people can not. Therefore, this is not the way in which most of us practice pain management. We can also explain that all pain management should be a carefully monitored team approach, with prescriptions coming from a single physician.[9,10]

Celebrities with pain who take pain medications in a more responsible fashion—and do well—don't make the news. Their pain management remains a private matter between them and their physicians. The now extinct "Many Faces of Pain" program of several years back was an effort to have some of this group of celebrities lecture on their pain and how their lives were enhanced by effective, safe opioid therapy. The program had a tremendous impact on the general public (as the first author personally witnessed when working with Lynda Carter in such a program in Lexington, Kentucky).[11] It would be good to see programs like it again.

The general public, of which our patients are a subset, gets fed a steady diet of rhetoric about the "dangers" of these "powerful" medications. Patients must be taught that the risk of addiction lies not in the medications but in a complex interaction between medications and people.[12] This interaction defies simplistic solutions such as avoiding pain medicines altogether. We need to educate professionals and patients so that they can have open discussions about the risks and benefits of these medications and so doctors can tailor therapy to every individual patient. To make this happen, we need to provide professionals with enough time and reimbursement to implement complex treatments for their complex patients, so they don't have to try to squeeze this group into less structured treatment settings. In an upcoming paper, Acosta and Haller[13] show that even patients who are actively abusing drugs can benefit from opioids under highly structured conditions with psychotherapeutic, motivational, and monitoring strategies as part of the package. The pain community must not be glib about these results; it is not just that they benefited (i.e., had good pain relief, curbed their use of nonprescription opioids, and even displayed a trend toward diminished use of other illicit drugs and alcohol) but that their risks were identified and managed in a highly labor-intensive fashion, complete with motivational therapies, behavioral management, and compliance monitoring.

Our patients must be encouraged to discuss their personal and family drug use histories with physicians openly so that their care can be planned. We have to build their trust so that they do not fear that the potentially beneficial medications they need will be withheld because of their honest admissions. We must also be prepared to make the necessary referrals or provide psychological help and monitoring if needed.

Elvis, if he were alive, might say to doctors, "Don't be cruel; prescribe these medications for pain patients." But it is not only cruel to withhold them; it can be cruel to prescribe them and not take steps to assess addiction risk in each patient or implement safeguards when necessary. Elvis died trying to be Elvis. No other pain patient should die for simply trying to live his or her life.

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NEW RESEARCH FINDINGS FROM THE AAPM ANNUAL MEETING

The twenty-third annual meeting of the American Academy of Pain Medicine took place February 7–10, 2007, in New Orleans, Louisiana. The meeting covered highly pertinent topics such as opioid prescribing, opioid addiction, neuromodulation, and the recognition and management of complications arising from interventional procedures. Among the presentations was one on a community survey conducted by Eriator and colleagues exploring public perception of and response to warning signs of inappropriate use of prescription drugs. Their data showed that despite current government statistics pointing to prescription opioids as the most abused substance in the United States, contributing to more accidental overdose deaths than cocaine and heroin combined, only 9 percent of those surveyed considered prescription drug abuse to be a major issue.

Another important study, reported by Wasan and colleagues, evaluated the merit of screening tests as predictors of aberrant drug-related behavior in chronic pain patients. The researchers found that various psychiatric factors, including mood disorders, psychological problems, and psychosocial stressors, are associated with a greater likelihood of drug-positive urine screens and significantly higher scores on the Aberrant Drug Behavior Index. This is an important finding for opioid prescribers, as such screening could aid in early recognition and monitoring of high-risk patients.

One of the most interesting discussions took place in a premeeting conference, "The Truth about Pain Management: The Interface of Pain and Addiction," conducted by Drs. Howard Heit, Edward Covington, and Douglas Gourlay. Dr. Heit offered a concise overview of current theories on addiction and their relevance to pain practice. Dr. Gourlay followed this presentation with a discussion of the concept of "universal precautions" in pain medicine, which require a strategy centered on careful assessment, ongoing evaluation, the establishment of clear lines of communication and firm boundaries between the patient and the prescriber, and meticulous documentation.

A second panel discussion, presided over by Dr. Covington, questioned whether doctors may have gone from being overly reluctant to prescribe opioids to patients with chronic noncancer pain to being excessively aggressive with opioid treatments. Mounting evidence suggests that opioids are not universally effective and may be associated with poor long-term outcomes. While there is a great deal of debate surrounding this particular topic, it is generally agreed that the best approach is to individualize pain patients' therapy as much as possible and employ a combination of treatments, including rehabilitative approaches, cognitive-behavioral therapy, and nonopioid analgesics such as NSAIDs or tricyclic antidepressants, rather than rely solely on standardized opioid regimens. While most pain specialists are quite knowledgeable on these points, primary care physicians are increasingly responsible for treating and monitoring pain patients on opioid therapy. Because these doctors are less likely to have well-developed and tested policies and procedures in place for caring for complicated pain patients, they are the most likely to encounter problems with regulatory agencies. Recommendations for improving this situation include greater involvement on the part of specialists and improved pain education at both the medical school and continuing education levels. (Source: *Medscape Neurology & Neurosurgery*, March 8, 2007; *www.medscape.com/viewarticle/553069*)

PAIN LINKED TO SOME MAJOR PSYCHIATRIC DISORDER DIAGNOSES

A study presented at the annual meeting of the American Association for Geriatric Psychiatry claims there is a significant association between pain and the major categories of psychiatric disorders in hospitalized geriatric patients. Led by Theodore Osuala, MD, a research team from the University of Maryland Medical Center in Lanham, Maryland, reviewed pain evaluations at admission and in discharge summaries of 504 patients age 60 or older at the center's acute geriatrics psychiatry inpatient unit. The data analyzed included psychiatric diagnosis, presence or absence of pain, and pain syndrome diagnosis. Self-reported pain symptoms were seen in 25 percent of the patients in the group. The incidence of pain differed significantly according to diagnosis: pain was reported in 34 percent of patients with depression, 20 percent of those with mania, 20 percent of those with psychotic disorders, and 14 percent of those with dementia. The average pain score was 5.9 on a 10-point scale. Of all subjects with documented pain, 58 percent were treated with pain medication while in the hospital.

The results of this study confirm previous work showing a relationship between pain and depression in the general psychiatric population. The findings may also indicate that pain is undertreated in geriatric psychiatry patients and underappreciated in patients with other psychotic

disorders/dementias. (Source: Lexa W. Lee, Medscape Medical News, March 5, 2007)

PSYCHIATRIC FACTORS LINKED TO INCREASED RISK FOR MISUSE OF OPIOID MEDICATIONS

The results of a study presented at the American Academy of Pain Medicine's annual meeting suggest that psychiatric factors, including a history of mood disorders or psychological problems, are associated with an increased risk for misuse of prescription opioids among outpatients receiving opioid therapy for chronic noncancer pain. The lead researcher, Dr. Ajay Wasan, of Brigham and Women's Hospital in Boston, Massachusetts, says that it is known that noncancer patients are more likely to abuse opioids than cancer patients, but to date there is little reliable data on which patients with chronic noncancer pain are most likely to be noncompliant with therapy.

In the current multicenter study, researchers related psychiatric history and current psychological adjustment to aberrant drug-related behavior. Patients completed the Prescription Drug Use Questionnaire, the Brief Pain Inventory, the Screener and Opioid Assessment for Pain Patients (SOAPP), and the Current Medications Misuse Questionnaire (COMM), a newer study tool. Patients were followed for five months, at which time a urine toxicology screen was performed. The Prescription Opioid Therapy Questionnaire, a tool that rates opioid-misuse behaviors, was completed by treating physicians. Using the combined results from the tests and urine screens, patients were classified as positive or negative on the Aberrant Drug Behavior Index (ADBI).

Of 228 patients, 103 were rated "low psych" and 125 "high psych." The high psych patients had been taking opioids for longer periods and scored significantly higher on the SOAPP and COMM ($p < 0.001$). Their urine screens were more frequently abnormal ($p < 0.01$), and their ADBI scores were significantly higher ($p < 0.001$). The researchers concluded that psychiatric factors, such as a history of mood disorders, psychological problems, and psychosocial stressors, may place patients at risk for misuse of prescription opioids. (Source: Lexa W. Lee, Medscape Medical News, March 1, 2007)

PHYSICIANS DEBATE LINK BETWEEN MORPHINE AND DOUBLE EFFECT

Two papers published in the March 10, 2007, *Palliative Medicine* state that medical practitioners are poorly informed about morphine's role in hastening the death of terminal patients and are passing their misconceptions on to the public. The papers are supported by top palliative care specialists in the United Kingdom, who have authorized a letter condemning the credence given to outdated perceptions by the media and the medical community.

Professor Bassam Estfan and colleagues, of the Taussig Cancer Center, have demonstrated that when properly administered in pain patients, morphine does not cause respiratory depression, the mechanism by which a high dose becomes lethal. In their study of 30 patients admitted for inpatient palliative care for severe cancer pain, they did not note any significant changes in breathing after controlling the pain with morphine.

The findings are especially relevant to the ongoing case of Kelly Taylor, a terminally ill woman suffering from constant, debilitating pain who went to court over her right to receive a dose of morphine high enough to induce unconsciousness. Doctors are unwilling to prescribe an amount of morphine adequate to control her pain, insisting that such a dose would likely induce death, amounting to physician-assisted euthanasia—a phenomenon known as "double effect." But many palliative care specialists believe the correlation between double effect and morphine is erroneous, and several insist that unconsciousness could not be sustained with morphine at any dose. "Unlike many drugs, morphine has a very wide safety margin," says Dr. Rob George of University College London, a consultant in palliative medicine. "Evidence over the last 20 years has repeatedly shown that, used correctly, morphine is well tolerated, does not cloud the mind, does not shorten life, and its sedating effects wear off quickly. This is obviously good for patients in pain, but not for those who want to be put into a coma." Dr. George insists that there is no evidence that morphine, when given knowledgeably, is fatal. (Source: Physorg.com, March 2, 2007; Medical News Today, March 10, 2007)

POTENTIAL NEW PAIN DRUG DEVELOPED AT UNIVERSITY OF LEICESTER AND FERRARA

Professor David Lambert, of the University of Leicester, and Dr. Girolamo Calo, in Ferrara, Italy, have collaborated on a new pain medication—UFP-101—that may be as effective as morphine while avoiding many of morphine's unwanted side effects.

"Morphine produces its clinical effects by interaction with opioid receptors," Lambert explained. "In addition to acting as a pain killer, this drug produces a number of unwanted side effects of importance from a clinical (e.g., depression of breathing, constipation, and tolerance) and social (addiction) viewpoints. Clearly there is a place for new morphine-like drugs without these side effects." Lambert has been studying opioids and opioid receptors since 1991, with emphasis on understanding receptor function and exploring new substances that can effectively target these receptors. An inaugural public lecture on the development and proposed role of UFP-101 was scheduled for March 20, 2007. (Source: Physorg.com, University of Leicester, March 16, 2007)

CALENDAR

The Canadian Pain Society
Pain Relief: A Basic Human Right
May 23–26, 2007
Westin Ottawa Hotel
Ottawa, Ontario, Canada

For registration information, contact:
Georgina Smith, Manager, Registrations
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Web site: *www.canadianpainsociety.ca/congres/Ottawa2007/index.htm*

The European Association for Palliative Care
EAPC 10th Congress
June 7–9, 2007
University Congress Centre ELTE
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Alliance of State Pain Initiatives
18th Annual Meeting—Alliance of State Pain Initiatives
June 21–23, 2007
Radisson Hotel Boston
Boston, Massachusetts

For registration information, contact:
Ronna Popkin
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E-mail: *rapopkin@wisc.edu*
Web site: *www.aspi.wisc.edu*

Department of Pain Medicine and Palliative Care, Beth Israel Medical Center
The International Association for Pain and Chemical Dependency

The 7th International Conference on Pain & Chemical Dependency
June 21–24, 2007
Sheraton New York Hotel & Towers
New York, New York

For registration information, contact:
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University of South Carolina School of Medicine-Palmetto Health Richland Continuing Medical Education Organization
University of South Carolina-Beaufort
Pain Management for Primary Care Physicians
July 23–26, 2007
The Sea Pines Resort
Sea Pines, South Carolina

For registration information, contact:
Continuing Medical Education
Tel.: 800-335-2582
Fax: 843-842-1870
E-mail: *chuck@seapines.com*
Web site: *www.seapinescme.com*

American Society of Pain Educators
ASPE Pain Educators Forum: Pain Week 2007
September 6–9, 2007
Red Rock Casino, Resort, and Spa
Las Vegas, Nevada

For registration information, contact:
Tel.: 877-733-9797
Fax: 973-453-8246
E-mail: *dw@paineducators.org*
Web site: *www.paineducators.org/PainWeek.asp?id=78*

ORIGINAL ARTICLE

A comparison of oral midazolam, oral tramadol, and intranasal sufentanil premedication in pediatric patients

Fatma Bayrak, MD
Isil Gunday, MD
Dilek Memis, MD
Alparslan Turan, MD

ABSTRACT

Background: *This study was designed to evaluate the efficacy and safety of oral midazolam, tramadol drops, and intranasal sufentanil for premedication of pediatric patients.*

Methods: *Sixty children, three to 10 years of age, who were designated as American Society of Anesthesiologists physical status I and who were undergoing adenotonsillectomy as inpatients were randomized to receive a dosage of 0.5 mg/kg (total of 4 mL) midazolam in cherry juice (n = 20, Group M), 3 mg/kg tramadol drops (n = 20, Group T), or 2 μg/kg intranasal sufentanil (n = 20, Group S). Clinical responses (sedation, anxiolysis, cooperation) and adverse effects (respiratory, hemodynamic, etc.) were recorded. Safety was assessed by continuous oxygen saturation monitoring and observation. Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate) were recorded before drug administration (baseline) and then every 10 minutes until the induction of anesthesia.*

Results: *Mean blood pressure decreased significantly after five minutes of intranasal sufentanil administration relative to Groups M ($p < 0.01$) and T ($p < 0.05$), whereas heart rate remained unchanged. Oxygen saturation and respiratory rate decreased significantly after 20 and 30 minutes of intranasal sufentanil administration relative to Groups M and T ($p < 0.05$). Anxiety scores showed rates of 45 percent in Group M, 5 percent in Group T, and 40 percent in Group S. Anxiety scores in Groups M and S were better than those of Group T ($p < 0.01$). Cooperation scores for face-mask acceptance showed rates of 85 percent in Group M, 45 percent in Group T, and 85 percent in Group S ($p < 0.01$).*

Conclusion: *Intranasal sufentanil and oral midazolam are more appropriate premedication options than tramadol drops in children.*

Key words: children, oral midazolam, oral tramadol, intranasal sufentanil

INTRODUCTION

Surgery and anesthesia induce considerable emotional stress in both parents and children.[1] The aftereffects of this stress, including prolonged night terrors, negativism, a variety of phobias, hysterical reactions, and anxiety reactions, may endure long after the hospital experience has ended. Preanesthetic medication may reduce the risks of adverse psychological and physiological sequelae of induction of anesthesia in distressed children. Premedication may be administered orally, intramuscularly, intravenously, rectally, nasally, or sublingually, and should provide effective anxiolysis and conscious sedation in order to improve the conditions surrounding parental separation and induction of general anesthesia.

Midazolam is the most commonly ordered premedication in pediatric anesthesia practice. More than 85 percent of anesthesiologists responding to a national survey of premedication practices conducted by Kain et al.[2] indicated that they prescribed midazolam when they chose to premedicate. The benefits of effective premedication include a reduction in both patient and parental separation anxiety, partial anterograde amnesia, facilitation of a smooth anesthetic induction, and a reduction in reported undesirable postoperative behavioral changes.[3,4] There are numerous published reports documenting the safety and efficacy of oral midazolam premedication in children between one and 12 years of age.[5,6]

Tramadol hydrochloride is a racemic mixture of two enantiomers. It has analgesic activity suitable for mild to moderate pain, with part of its analgesic activity modulated via μ receptors. It has a low affinity for opioid receptors, but it also exerts its effect through direct modulation of central monoaminergic pathways. In children older than one year, tramadol is well tolerated and is an effective postoperative analgesic, with adverse effects similar to those of other opioids.[7]

Sufentanil is the most potent opioid available today,

and is perhaps closer to the future of opioids than any of the other drugs available to clinicians. It is more than twice as lipid soluble as fentanyl; however, its properties, including its high degree of plasma protein binding (98 percent) and lower volume of distribution, are the probable explanation for sufentanil's shorter elimination half-life and duration of effect compared with fentanyl. Sufentanil also has a high affinity for the μ receptor—higher than that of any other opioid.[8] Intranasal sufentanil has been used in pediatric populations to ease separation from parents, decrease coughing, decrease inhalation anesthetic requirements, and provide faster and smoother recoveries.[9] Nasal midazolam in doses of 0.2 or 0.3 mg/kg has been used to provide sedation within five to 10 minutes and to ease separation.

Intranasal sufentanil, oral midazolam, and oral tramadol are all effective for preinduction of pediatric patients, but there are no data on which to base a choice between them. The purpose of this study was to evaluate the efficacy and safety of three different pediatric premedication regimens.

METHODS

After obtaining institutional review board approval and informed parental consent, we studied children aged three to 10 years with American Society of Anesthesiologists (ASA) physical status I who were undergoing minor surgery for adenotonsillectomy with general anesthesia. Exclusion criteria included 1) known adverse reaction to benzodiazepines; 2) use of sedative/hypnotic, narcotic, anticonvulsant, stimulant, or other medications reported to affect the minimum alveolar anesthetic concentration of inhaled anesthetics within the previous month; and 3) the presence of neurologic, renal, or hepatic disease. All patients were allowed food ad libitum eight hours before surgery and a maximum of 10 mL/kg clear liquid four hours before the anticipated time of general anesthesia induction. Patients were randomly assigned to one of the following groups according to computer-generated random numbers: 0.5 mg/kg midazolam in cherry juice (4 mL total) (n = 20, Group M), 3 mg/kg tramadol drops (n = 20, Group T), or 2 μg/kg intranasal sufentanil (n = 20, Group S). Noninvasive mean blood pressure (MBP), heart rate (HR), respiratory rate (RR), and oxyhemoglobin saturation (SpO_2) were measured before drug administration and 40 minutes before separation from parents. Safety was assessed by measuring RR and SpO_2 throughout the study. An SpO_2 of < 90 percent was considered clinically significant. An RR of < 16 breaths/min (three to seven years old) or < 12 breaths/min (seven to 10 years old) was defined as hypoventilation

Clinical responses (sedation, anxiolysis, cooperation) and adverse effects (respiratory, hemodynamic, etc.) were assessed by an observer blinded to dose. Safety was assessed by continuous SpO_2 monitoring and observation. Vital signs (BP, pulse, RR) were recorded before drug administration (baseline) and then every 10 minutes until the induction of anesthesia. There was no attempt to control for surgical procedure or additional drugs administered during the induction of anesthesia, as the primary end points for the study were patients' pharmacodynamic responses prior to induction. The authors felt this type of study would be the most generalizable because it closely reflects standard anesthetic practices. A blinded observer evaluated preoperative emotional state, response to premedication, induction, and side effects.

Anxiolysis was assessed on a 4-point scale (poor = afraid, combative, crying, restrained; fair = fearful, moderate apprehension; good = slightly fearful, easily calmed by strangers, noncombative; excellent = no fear or apprehension displayed; not applicable = patient asleep).[10] An anxiety score was also recorded at the time of attempted separation from parents. An anxiety score of 3 or 4 was considered satisfactory. The timing of attempted child-parent separation, which occurred from five to 40 minutes after premedication, was determined by operating-room availability and patient response.

Cooperation was also assessed using a 4-point scale (poor = strongly refuses intervention; fair = considerable effort required to achieve compliance with intervention; good = accepts intervention reluctantly; excellent = accepts intervention readily; not applicable = patient asleep). A cooperation score of 3 or 4 was considered satisfactory. Cooperation was assessed at the time of facemask application (67 percent N_2O in oxygen [6 L/min fresh gas flow]) and 30 seconds later, when sevoflurane (2 percent) was added.[11]

Anesthetic technique was standardized. After standard monitors were applied, including an automated BP cuff, electrocardiograph, and pulse oximeter, general anesthesia was induced in all patients using sevoflurane and 67 percent N_2O in oxygen. The concentration of sevoflurane was gradually increased by 0.5 percent every four to five breaths. When the patient was asleep, a forearm peripheral vein was cannulated, and intravenous administration of lactated Ringer's solution containing 2 percent dextrose was started. Ventilation was first assisted and then controlled to obtain end-tidal CO_2 tensions between 30 and 35 mmHg. End-tidal sevoflurane concentration was maintained at 2 percent in 67 percent N_2O in oxygen throughout anesthesia and surgery. When hemodynamic variables were stable, 0.1 mg/kg vecuronium was administered intravenously in all patients. The complications of mask induction and endotracheal intubation were noted, including laryngospasm, arterial oxygen saturation less than 90 percent, and vomiting. At the completion of surgery, residual muscle relaxant was antagonized with 0.02 mg/kg atropine and 0.05 mg/kg

Table 1. Patients' demographic, surgical, and anesthetic data (mean ± SD)			
	Group M (n = 20)	**Group T (n = 20)**	**Group S (n = 20)**
Age (years)	6.20 ± 1.70	6.75 ± 1.60	6.25 ± 1.50
Male/female	12/8	12/8	7/13
Weight (kg)	22.95 ± 5.89	20.80 ± 7.24	21.90 ± 4.50
Duration of surgery (min)	62 ± 12	58 ± 15	60 ± 14
Duration of anesthesia (min)	78 ± 10	75 ± 12	74 ± 16

neostigmine administered intravenously, and sevoflurane and N_2O were discontinued. The patient's trachea was extubated after confirming spontaneous respiration, spontaneous eye opening, or purposeful muscular movements in the upper extremities.

Statistical analysis was performed using one-way analysis of variance to compare demographic variables and hemodynamic data among groups. When a significant difference was identified, it was followed by an unpaired Student's t-test with Bonferroni correction to adjust for multiple comparisons. Intergroup differences in categoric demographic data, the level of sedation, incidence of adverse effects, and parental satisfaction were also compared using the χ^2 test or Fisher's exact test as appropriate. Changes in hemodynamics and SpO_2 over time were analyzed by two-way analysis of variance with repeated measures, followed by the Wilcoxon signed-rank test. A p value less than 0.05 was considered statistically significant.

RESULTS

There were no significant differences among the three groups in terms of age, gender distribution, weight, duration of surgery, or anesthesia (Table 1). Significant difference was seen with respect to MBP and SpO_2 before premedication among different groups (Table 2). MBP decreased significantly five minutes after intranasal sufentanil administration relative to Groups M ($p < 0.01$) and T ($p < 0.05$), whereas HR remained unchanged. SpO_2 and RR decreased significantly 20 and 30 minutes after intranasal sufentanil administration relative to Groups M and T ($p < 0.05$). There were no clinically important mean changes in MBP, RR, or SpO_2 measurements between the treatment groups.

Upon separation from parent(s), significantly greater proportions of children in the midazolam and tramadol groups were classified as being "asleep" and "calm but awake" than in the sufentanil group. Although three children in the sufentanil group were restless, agitated, crying, or upset at the time of separation, none required restraint when an anesthetic mask was applied for inhalational induction. An anxiety score was also recorded at the time of attempted separation from parents. Satisfactory anxiety scores were achieved with rates of 45 percent in Group M, 5 percent in Group T, and 40 percent in Group S. Anxiety scores in Groups M and S were better than those in Group T ($p < 0.01$). Cooperation scores for face-mask acceptance showed rates of 85 percent in Group M, 45 percent in Group T, and 85 percent in Group S ($p < 0.01$).

Five patients experienced nausea before mask induction (one patient in Group M, three patients in Group T, and one patient in Group S). No clinically important desaturation or laryngospasms were observed in any children during or after the administration of medication.

DISCUSSION

The present results show that oral midazolam and intranasal sufentanil are superior to oral tramadol. Although midazolam can be used as a preanesthetic medication via oral, nasal, rectal, intramuscular, or intravenous routes, oral administration is the most common for children. It is reported that 80 percent of children premedicated with oral midazolam at a dose of between 0.5 and 1.0 mg/kg are sedated satisfactorily for minor surgery.[6,11] Pediatric pharmacokinetic studies show that the time to maximum plasma concentration after oral administration of 0.25 to 1.0 mg/kg midazolam is 50 minutes (15 to 60 minutes), although clinical studies show a peak sedative effect occurring at 30 minutes after oral administration of midazolam 0.5 mg/kg.[11-13] In the present study, children entered the operating room 40 minutes after midazolam medication, as we predicted that the peak plasma level of midazolam would occur at that time.

During the past two decades, anesthesiologists have been provided with a number of new, potent opioid analgesics and sedatives/hypnotics, as well as an increased understanding of the pharmacokinetic and pharmacodynamic principles that govern the medications' action and disposition. These developments have suggested that nasal mucous membranes may be useful as an alternate route of analgesic and anesthetic drug delivery.[14] The easiest mucosal technology is the

Table 2. Preoperative changes in MBP, HR, SpO_2, and RR (mean ± SD)

	MBP			HR			SpO_2			RR		
	Group			Group			Group			Group		
Time	**M**	**T**	**S**	**M**	**T**	**S**	**M**	**T**	**S**	**M**	**T**	**S**
Basal	77.9 ± 6.1	77.5 ± 7.9	73.8 ± 10.2	103.4 ± 9.7	99.3 ± 9.3	98.3 ± 10.1	98.6 ± 0.6	98.8 ± 0.4	98.5 ± 0.6	20.8 ± 3.1	18.2 ± 3.5	18.8 ± 1.8
5 min	80.1 ± 6.8	77.2 ± 9.6*	70.1 ± 7.5**	97.4 ± 22.2	99.6 ± 8.6	102.8 ± 8.8	98.5 ± 0.6	98.6 ± 0.7	98.3 ± 0.5	20.2 ± 3.2	18.5 ± 3.0	18.7 ± 1.8
10 min	78.7 ± 8.5	76.7 ± 10.2	71.8 ± 10.1	100.4 ± 7.3	101.4 ± 8.8	99.9 ± 12.3	98.7 ± 0.5	98.6 ± 0.7	98.3 ± 0.8	19.8 ± 3.5	18.6 ± 3.3	17.8 ± 2.1
20 min	75.9 ± 8.5	77.6 ± 9.6	72.8 ± 10.1	98.8 ± 7.3	100.1 ± 9.8	99.8 ± 12.5	98.4 ± 0.6	98.4 ± 0.5	97.7 ± 1.2***	19.7 ± 3.4	18.1 ± 2.7	17.4 ± 2.1***
30 min	75.3 ± 7.2	78.6 ± 8.5	73.1 ± 11.3	99.1 ± 7.3	101.9 ± 12.0	96.1 ± 12.5	98.1 ± 1.0	98.8 ± 0.5	97.9 ± 0.9***	19.9 ± 3.2	18.7 ± 3.3	17.3 ± 2.2***
40 min	78.7 ± 3.5	78.3 ± 7.5	77.3 ± 7.2	98.05 ± 7.8	100.9 ± 8.0	97.1 ± 10.0	98.8 ± 0.4	98.8 ± 0.6	98.8 ± 0.4	19.2 ± 3.1	18.5 ± 2.8	18.1 ± 2.1

n = 20 in each group; MBP (mmHg) = mean blood pressure; HR (beats/min) = heart rate; SpO_2 (percent) = peripheral oxygen saturation; RR(breaths/min) = respiratory rate; * $p < 0.05$, Group M compared to Group T; ** $p < 0.001$, Group M compared to Group S; *** $p < 0.05$, Group S compared to Groups M and T.

transnasal mucosal approach, and this route has been the subject of recent investigation. In one study, sufentanil (1.5, 3.0, or 4.5 μg/kg) was administered to 80 children ranging in age from six months to seven years. Easy separation from parents was achieved in 86 percent of the children 10 minutes after premedication administration. Unfortunately, 61 percent of the children cried after drug administration, and side effects included reduced ventilatory compliance (chest-wall rigidity) with higher doses (3.0 and 4.5 μg/kg). Nevertheless, nasal transmucosal drug delivery may have value, especially for frightened or uncooperative children.[9] Nasal sufentanil has been used in pediatric populations to ease separation from parents, decrease coughing, decrease requirements for inhalation anesthetic, and provide faster and smoother recoveries.[9,15] In our study, we found that intranasal sufentanil has similiar premedication qualities as compared with midazolam but is a better premedication than tramadol.

Tramadol, a synthetic 4-phenyl-piperidine analog of codeine, is a centrally acting atypical opioid.[16] Although tramadol's mode of action is not completely understood, at least two complementary mechanisms are believed to contribute to its effect. Tramadol's opioid activity results from low-affinity binding of the parent compound to μ opioid receptors and higher-affinity binding of the M1 (0-desmethylated) metabolite.[17] Tramadol is also a weak inhibitor of norepinephrine and serotonin reuptake.[18] In one study, Payne and Roelofse[19] administered tramadol drops 3 mg/kg plus oral midazolam 0.5 mg/kg 30 minutes prior to anesthesia. They found that no respiratory depression was seen, and preanesthetic behavior patterns were largely the same between the study group and the control: 85 percent of patients in the tramadol group were drowsy but awake, versus 90 percent in the placebo group, and similarly satisfactory induction behavior was seen in 95 percent of the tramadol group versus 90 percent of the placebo group. The researchers concluded that tramadol 3 mg/kg has no clinical respiratory depressant effect and that behavior and recovery times are unaffected. After oral administration, tramadol demonstrates 68 percent bioavailability, with peak serum concentrations reached within two hours.[16] In our present study, children entered the operating room 40 minutes after administration of tramadol, as we thought that it was predicted that the peak plasma level of tramadol occurred at that time, and that intranasal sufentanil and midazolam are better premedications than tramadol.

This study demonstrated a wide safety profile for oral midazolam, oral tramadol, and nasal sufentanil administration; no patient developed clinically important desaturation before the induction of anesthesia. There were slightly significant BP, RR, and SpO_2 decreases in Group S, but these changes were not clinically important. In this study, five patients experienced nausea before mask induction; these events may have been related to the drug or to the patient's response to having to ingest something he or she did not want; it is difficult in many instances to separate a true pharmacodynamic effect from the psychological response of a child. There were no adverse respiratory events before induction. It must be understood, however, that this study involved a highly selected population of patients, the vast majority of whom were ASA class I. This study excluded patients with serious underlying medical conditions, and the responses of and potential for adverse respiratory events in higher-risk patients are likely to be different.

In summary, the data demonstrate that commercially prepared oral midazolam and intranasal sufentanil are rapidly taken up, with the majority of patients demonstrating a satisfactory degree of sedation and anxiolysis within five minutes of consumption relative to tramadol drops. Satisfactory sedation and anxiolysis seem to last for up to 40 to 45 minutes. The present results show that oral midazolam and intranasal sufentanil are superior premedications in pediatric patients as compared to oral tramadol.

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ORIGINAL ARTICLE

Urine drug test interpretation: What do physicians know?

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ABSTRACT

Objective: *To determine the level of urine drug test (UDT) interpretive knowledge of physicians who use these instruments to monitor adherence in their patients on chronic opioid therapy.*

Methods: *A seven-question instrument consisting of six five-option, single-best-answer multiple choice questions and one yes/no question was completed by 114 physicians (77 who employ UDT and 37 who do not) attending one of three regional opioid education conferences. We calculated frequencies and performed χ^2 analyses to examine bivariate associations between UDT utilization and interpretive knowledge.*

Results: *The instrument was completed by 80 percent of eligible respondents. None of the physicians who employ UDT answered all seven questions correctly, and only 30 percent answered more than half correctly. Physicians who employ UDT performed no better on any of the questions than physicians who do not employ UDT.*

Conclusions: *Physicians who employ UDT to monitor patients receiving chronic opioid therapy are not proficient in test interpretation. This study highlights the need for improved physician education; it is imperative for physicians to work closely with certified laboratory professionals when ordering and interpreting these tests.*

Key words: urine drug test, chronic opioid therapy, interpretation, physician knowledge

INTRODUCTION

The United States has one of the highest levels of prescription opioid use in the world, and the rate is increasing, accompanied by a parallel increase in abuse of such medications.[1,2] Abuse of opioids is often associated with concomitant abuse of other drugs, both illicit and unauthorized licit.[3-5] Physicians, apprehensive about clinical, medicolegal, and regulatory risks, are increasingly using urine drug tests (UDTs) as an objective means of behavioral monitoring in patients on chronic opioid therapy. Little information exists, however, concerning physicians' knowledge of accurate interpretation of these tests. Our objective in this preliminary study was to determine the level of physician proficiency in UDT interpretation, particularly with regard to frequently prescribed opioids and common drugs of abuse.

METHODS

Neither we nor others were able to identify any published, validated psychometric tools purporting to evaluate physicians' UDT interpretive knowledge in the context of the medical clinic.[6] A seven-question survey comprising six five-option, single-best-answer multiple choice questions and one yes/no question about UDT interpretation was developed by two of the authors, one (GMR) a board-certified pain management specialist and the other (RB) a board-certified clinical chemist and toxicologist. The survey was designed to be used in a preliminary and exploratory study of several aspects of physicians' knowledge about UDT. No formal psychometric validation was conducted on the instrument. The survey content was generated on the basis of the most common and/or critical interpretive errors seen in our tertiary care medical center and community-based primary care clinics. Four questions concerned administration of prescription opioids, one question concerned administration of heroin, one question concerned passive inhalation of marijuana, and one question concerned ingestion of poppy seeds. The questionnaire was vetted by seven experts in the field of clinical and forensic toxicology (including three directors of Substance Abuse and Mental Health Services Administration–certified drug testing laboratories and the chief toxicologist for the state of North Carolina), which led to refinement of the survey questions. The questionnaire can be found in the Appendix. The study was approved by the University of Florida College of Medicine's institutional review board.

Table 2. Knowledge level by UDT ordering status, n (percent)[a]				
Total # correct on knowledge questions	**Order UDT**		**χ^{2} [b]**	**p**
	Yes (n = 77)	**No (n = 37)**		
0	2 (3)	1 (3)	6.12	0.41
1	12 (16)	4 (11)		
2	17 (22)	12 (32)		
3	22 (29)	8 (22)		
4	18 (23)	5 (14)		
5	5 (6)	5 (14)		
6	1 (1)	2 (5)		
7	0	0		
Percent correct on specific questions	**Order UDT**		**OR[c]**	**95 percent CI**
	Yes (n = 77)	**No (n = 37)**		
1	29	38	0.66	0.28 to 1.50
2	61	54	1.33	0.60 to 2.94
3	7	5	0.64	0.19 to 2.17
4	22	22	1.02	0.39 to 2.66
5	79	76	1.22	0.48 to 3.11
6	17	32	0.42	0.17 to 1.05
7	52	43	1.41	0.64 to 3.12

[a] Total percent may total > 100 due to rounding

[b] χ^{2} test of difference in proportion of UDT ordering status by total number of correct answers for knowledge questions

[c] Odds ratio (OR) modeling UDT testing as "yes" = 1 and "no" = 2

The questionnaires were distributed to all attendees (n = 151) at each of three opioid education conferences sponsored by the Opioid Management Society (Philadelphia, September 16 and 17, 2006; Miami, October 28 and 29, 2006; and Houston, November 11 and 12, 2006). The questionnaires were accompanied by a cover sheet explaining the purpose and voluntary nature of the study. A brief verbal description of the study's aims was given by one of the investigators (GRW or GMR) at the time of questionnaire distribution. The questionnaires were distributed, completed, and collected early in the conference, immediately prior to a presentation on clinical UDTs. Participants had 15 minutes to complete the questionnaire.

Data analysis

Frequencies were calculated for each variable. We then applied χ^{2} tests to examine bivariate associations between UDT utilization and UDT interpretive knowledge. The p values, odds ratios, and 95 percent confidence intervals for observed associations are reported.

RESULTS

One hundred and fifty-one questionnaires were distributed, and 121 completed questionnaires were returned. Seven questionnaires were discarded because the respondents were either physicians not involved in

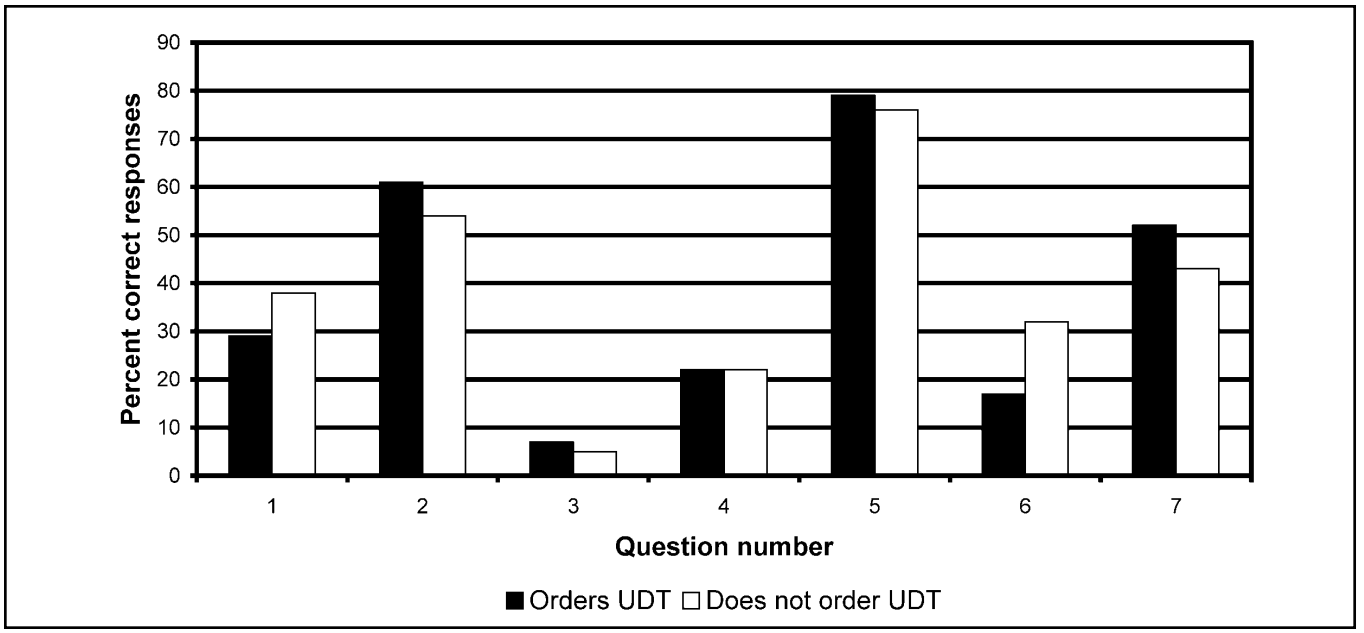

Figure 1.

clinical medicine or nonphysicians who were not responsible for ordering/interpreting UDTs. One hundred and fourteen completed physician questionnaires were returned, for an overall response rate of 80 percent. Seventy-seven respondents (68 percent) indicated that they employ UDT. Seventy-six percent indicated that they prescribe opioids for chronic nonmalignant pain, 19 percent indicated that they were board certified in pain management, and 6 percent indicated that they were board certified in addiction medicine or addiction psychiatry. Table 1 includes the overall number and percentage of questions answered correctly, stratified by physician UDT practice. These data are presented graphically in Figures 1 and 2.

None of the 77 physicians who indicated that they employ UDT answered all seven questions correctly; one (1 percent) answered six questions correctly, five (6 percent) answered five questions correctly, 18 (23 percent) answered four questions correctly, 22 (29 percent) answered three questions correctly, 17 (22 percent) answered two questions correctly, 12 (16 percent) answered one question correctly, and two (3 percent) answered no questions correctly. The percentages of respondents making two or fewer errors did not statistically differ between those who employ UDT and those who do not ($\chi^2 = 3.63$; $p = 0.82$).

Question 1: Codeine administration

Codeine is metabolized in part to morphine by means of the cytochrome P450 2D6 isoenzyme. Consequently, both codeine and morphine are ordinarily detectable in the urine of patients administered codeine-containing products. Twenty-nine percent of physicians who employ UDT answered this question correctly. Most incorrect respondents failed to recognize that morphine is a metabolite of codeine and/or incorrectly identified dihydrocodeine as a codeine metabolite. Although 38 percent of physicians who do not employ UDT answered this question correctly, the difference in correct response rates between those who employ UDT and those who do not employ UDT was not statistically significant.

Question 2: Morphine administration

Sixty-one percent of respondents who employ UDT recognized that morphine is the only opioid detectable in the urine of patients administered only morphine. Twenty-six percent of respondents believed that morphine, codeine, and dihydrocodeine would be detectable; 10 percent believed that morphine and codeine would be detectable; and 1 percent believed that only dihydrocodeine would be detectable. There were no statistically significant differences in correct response rates between physicians who employ UDT and those who do not.

Question 3: Heroin use

Heroin is metabolized to morphine, 6-monoacetylmorphine, and other metabolites. The parent compound has a half-life of several minutes and therefore is not usually detectable on UDT. The intermediate metabolite, 6-monoacetylmorphine, is generally detectable for several hours after heroin administration.[6] Nine percent of physicians who employ UDT and 14 percent of those who do

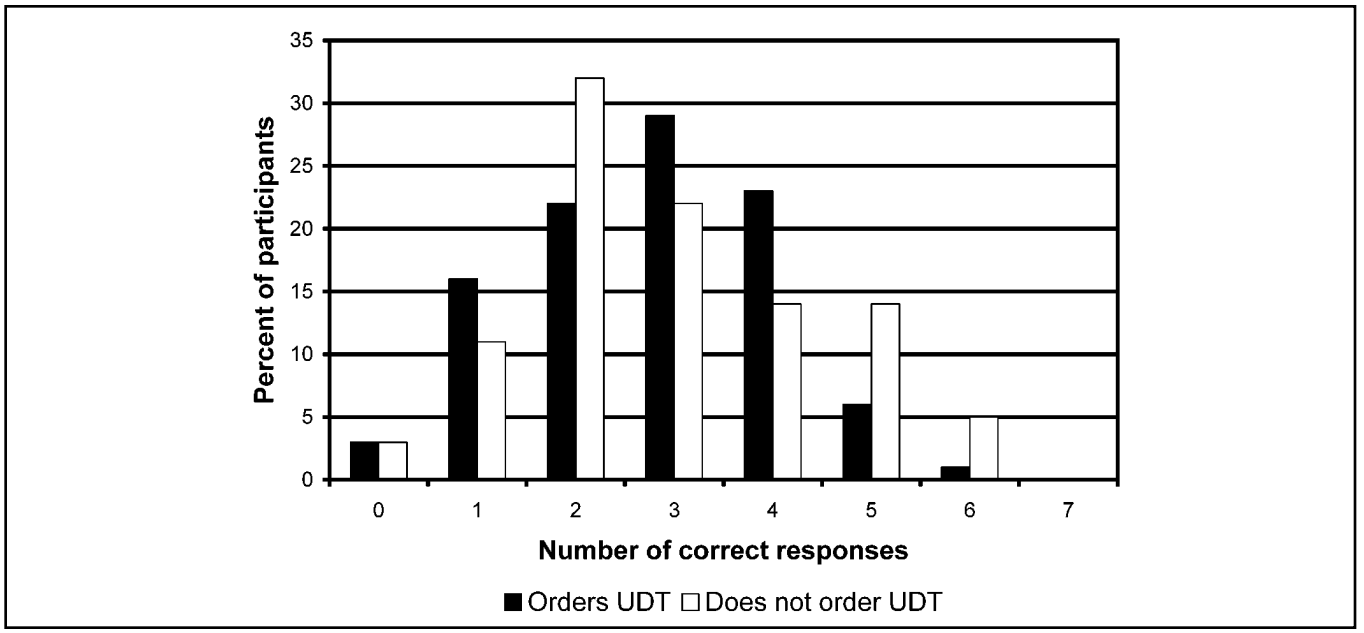

Figure 2.

not recognized that morphine is the only opioid likely to be detected in the urine of people taking only heroin. Most incorrect respondents indicated that heroin and/or hydromorphone would be detected. Although physicians who employ UDT were 36 percent less likely to answer this question correctly than those who do not employ UDT, this difference did not reach statistical significance.

Question 4: Poppy seed consumption

Codeine and morphine are components of poppy seeds, moderate consumption of which can result in positive UDT for both opioids.[7] Twenty-two percent of physicians who employ UDT recognized this pharmacologic fact. There were no statistically significant differences in correct response rates between physicians who employ UDT and those who do not.

Question 5: Secondhand exposure to marijuana smoke

Casual, passive exposure to marijuana smoke does not cause positive urine screens for Δ^9-tetrahydrocannibinol (THC) at the federally mandated cutoff of 50 ng/mL.[7] Seventy-nine percent of physicians who employ UDT answered this question correctly, compared to 76 percent of physicians who do not employ UDT, a difference that was not statistically significant.

Question 6: Explanations for negative screens

Negative urine drug screens in patients taking opioids may be due to several factors, including lack of drug use in the one to three days preceding the UDT, inability of many screening assays to detect synthetic and semisynthetic opioids in therapeutic doses, and rapid metabolism of the drug (due to, for example, cytochrome P450 enzyme induction).[7-9] Seventeen percent of physicians who employ UDT answered this question correctly. Most incorrect responses were due to the failure to recognize rapid opioid metabolism as a cause of negative screens, although a substantial number of physicians failed to recognize a lack of assay sensitivity/specificity and absence of recent use as possible causes of negative screens. Paradoxically, 32 percent of physicians who do not employ UDT answered this question correctly, a difference that was statistically significant ($\chi^2 = 11.23$; $p = 0.04$).

Question 7: Possible false negative hydromorphone screening assays

When administered in therapeutic doses, hydromorphone, a semisynthetic opioid, is not detectable by many opiate screening assays. If patients administered hydromorphone screen negative for opiates on immunoassay, the drug should be detectable by specific confirmatory tests such as gas chromatography/mass spectroscopy. Fifty-two percent of physicians who employ UDT answered this question correctly. Fourteen percent of physicians indicated that they would readminister the same screening assay at the next office visit, 10 percent of physicians would notify law enforcement, 10 percent would taper and discontinue opioid therapy, and 3 percent would refer the patient to an addiction specialist. The difference in correct response rates between physicians who employ UDT and those who do not was not statistically significant.

DISCUSSION

Limited available data indicate that physicians are not truly proficient in UDT interpretation. In a study of primary care physicians engaged in the practice of adolescent medicine, nearly all of whom had used UDT in their practice, Levy et al.[5] found that the majority lacked essential knowledge regarding proper specimen collection and validation, interpretation of positive and negative results, and the need for confirmatory testing. For example, only 12 percent of the physicians surveyed knew that oxycodone is not detectable by most screening immunoassays, only 40 percent of physicians knew that poppy seeds could produce a positive screen for opioids, and less than 50 percent of physicians knew the temporal limits of detection of THC in the urine of regular marijuana users. Durback et al.,[10] in a study of emergency medicine physicians, found that only 5 percent were able to correctly identify those substances detectable by the UDT method used in their hospital, and nearly three-quarters of the participants incorrectly believed that all benzodiazepines could be detected.

The present study, involving physicians who attended an opioid education conference and who prescribe opioid therapy for chronic pain, confirms and extends previous work demonstrating a uniformly inadequate physician knowledge base with regard to UDT interpretation. Of the 77 physicians who employ UDT, none were able to answer all seven test questions correctly, and only 30 percent were able to answer more than half correctly. Physicians who employ UDT, as well as physicians who are board certified in pain management, performed no better on any of the seven questions than physicians who do not employ UDT.

Misinterpretation of UDT potentially has important and negative consequences for patients. Misinterpretation of (false) negative test results may lead the clinician to a false sense of confidence that substance abuse does not exist. Misinterpretation of (false) positive tests has potential negative consequences for the patient, including false accusations of abuse, unjustified loss of opioid privileges, deterioration of the physician-patient relationship, painful and possibly dangerous opioid withdrawal, compromised ability to receive appropriate therapy from future physicians, and involvement of law enforcement. UDT misinterpretation may also have ramifications for the physician. While we were unable to identify any published cases, we assert that false accusations of substance misuse based on inaccurate UDT interpretation do have potential medicolegal consequences.

There are several limitations to this study. One is the issue of response bias. It is likely that those physicians who chose not to complete the questionnaire were less likely to employ UDT and/or less confident about their knowledge of UDT interpretation. It is likely, therefore, that while the response rate (80 percent) was relatively high, the low level of knowledge demonstrated in this article would have been lower still had the physician response rate been more robust. Another limitation involves the structure and content of the test questions. With regard to the former, it is possible that the test questions were suboptimally constructed and hence difficult to answer. While the stem items were highly focused and we avoided the use of negative-stem questions, we did incorporate four "all of the above" options, a practice which some education experts believe to be flawed.[11] This type of question, however, is common in medical continuing education, and physicians are highly experienced in answering such questions. With regard to the content, questions were developed based on what the authors determined to be essential core content for interpretation of UDT for patients on chronic opioid therapy in the context of clinical medicine. The questionnaire was vetted by a panel of experts in toxicology and laboratory medicine, but the reliability and validity of the instrument have not been established among clinicians. None of the respondents commented that the questions were ambiguous or unfair. Finally, it might be argued that physicians attending an opioid education conference are not representative of all physicians who employ UDT, as the former group might have attended in order to remedy self-perceived knowledge deficits. This, however, seems unlikely to have biased our results. Limited data from other physician groups who employ UDT—those engaged in the practices of adolescent or emergency medicine—indicate that UDT knowledge is poor in unselected physician groups.[9,10] Furthermore, a majority of physicians report receiving insufficient chronic pain education in their graduate and postgraduate medical training.[12,13]

UDT education can be addressed in several ways. Physicians can consult a number of published sources, including a superb monograph published by the California Academy of Family Physicians[14] and *The Medical Review Officer's Manual*.[15] Medical Review Officer certification courses offer two-day comprehensive training in all aspects of UDT, albeit in the context of federally mandated workplace testing, which differs in important respects from clinical testing.

CONCLUSION

This study demonstrates that physicians' knowledge of UDT interpretation is inadequate; physicians who employ UDT are no more proficient in their interpretation than their peers who never employ UDT. Interpretation of UDT results can be highly complex, and the results have potentially serious consequences for both patient and physician. Physicians who employ UDT should have a solid, basic knowledge of interpretation

and should work closely with certified clinical chemistry/toxicology professionals when ordering and interpreting these tests.

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APPENDIX. URINE DRUG TESTING (UDT) QUESTIONNAIRE: KNOWLEDGE QUESTIONS*

1. In a patient prescribed Tylenol #3 (codeine and acetaminophen), one would reasonably expect which of the following to be detected in the urine:
   a. codeine
   b. dihydrocodeine
   c. morphine
   d. all of the above
   e. a and c only

2. In a patient prescribed MS Contin (morphine), one would reasonably expect which of the following to be detected in the urine:
   a. codeine
   b. dihydrocodeine
   c. morphine
   d. all of the above
   e. a and c only

3. In a patient using heroin, one would be likely to detect which of the following in the urine:
   a. heroin
   b. hydromorphone
   c. morphine
   d. all of the above
   e. a and c only

4. A patient on OxyContin (oxycodone) therapy is administered a random urine drug test. He notifies you that he ate a large lemon poppy seed muffin for breakfast. What substances might reasonably be detected in the urine?
   a. oxycodone
   b. codeine
   c. morphine
   d. all of the above
   e. a and c only

5. A patient on chronic opioid therapy tests positive for cannabis on a random urine drug screen. She explains that her husband sometimes smokes pot in their bedroom. Is this a plausible explanation for the test findings?
   a. yes
   b. no

6. Which of the following are plausible explanations for a negative urine opiate drug screen in a patient on chronic opioid therapy:
   a. Patient ran out of opioid early and has not used any in a few days.
   b. Patient is a "fast metabolizer."
   c. Drug screen does not detect that particular opioid.
   d. a, b, and c
   e. a and c only

7. A patient on chronic Dilaudid (hydromorphone) therapy tests negative for opioids on a urine drug screen. The patient claims to be using the medicine as prescribed. The most appropriate next step would be to:
   a. subject this urine to a different type of test
   b. readminister a urine drug screen at the next visit
   c. taper and discontinue opioid therapy
   d. refer the patient to a detoxification/rehabilitation program
   e. notify law enforcement

* Correct responses are bolded.

For chronic, moderate to severe pain

AVINZA® in ACTION

QD dosing for continuous 24-hour efficacy*

Significant improvement in physical and social functioning and sleep[1,2]*

King Pharmaceuticals®, Inc. and AVINZA®—now united for the management of pain

*Compared with baseline.

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

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 the 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 Prescribing Information on adjacent page.

References: 1. 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;3:25-43. **2.** Caldwell JR, Rapoport RJ, Davis JC, et al. 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 Manag*. 2002;23:278-291.

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AVINZA®

(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.

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ORIGINAL ARTICLE

Psychological factors as predictors of opioid abuse and illicit drug use in chronic pain patients

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ABSTRACT

Background: *Psychopathology (depression, anxiety, somatization disorder) and substance abuse (opioid misuse and illicit drug use) are common in patients with chronic pain and present problems for public health and clinical management. Despite a body of literature describing various methods for identifying psychopathology, opioid misuse, and illicit drug use in chronic pain patients, the relationship between psychopathologies, substance abuse, and chronic pain has not been well characterized.*

Methods: *This report describes a total of 500 consecutive pain patients prescribed and receiving stable doses of opioids. The patients were evaluated for psychopathology, opioid abuse, and illicit drug use during the course of regular pain management treatment. The relationships between psychopathology and drug abuse and/or illicit drug use in chronic pain patients were examined, and psychological evaluation for depression, anxiety, and somatization disorder was performed.*

Results: *Depression, anxiety, and somatization disorder were documented in 59, 64, and 30 percent of chronic pain patients, respectively. Drug abuse was significantly higher in patients with depression as compared to patients without depression (12 percent with depression versus 5 percent without). Current illicit drug use was higher in women with depression (22 percent) than women without depression (14 percent) and in men with or without depression (12 percent). Current illicit drug use was also higher in men with somatization disorder (22 percent) than men without (9 percent).*

Conclusion: *This study demonstrated that the presence of psychological features of depression and somatization disorder may be markers of substance abuse diathesis in chronic pain patients.*

Key words: psychopathology, substance abuse, opioid abuse, illicit drug use, MCMI, P3, DSM-IV-TR, endophenotype

INTRODUCTION

Pain is defined as both a physiological sensation and a psychological condition or state.[1] Thus, the neural event of pain is in many ways inextricable from the psychological or phenomenal experience of pain.[2] Chronic pain in particular manifests a psychological constellation of cognitive, emotional, and behavioral characteristics.[3] There is extensive literature associating chronic pain and psychological disorders.[2-28] Numerous studies have shown that a significant proportion of pain patients present with depression, anxiety, and somatization disorder, either alone or in combination.[4-28] In studies that have evaluated chronic pain patients, the comorbidity of major depression ranged from 15 percent to 56 percent, significantly higher than the occurrence of major depression within the general (i.e., non–chronic pain) population, which ranged from 5 percent to 10 percent. Similarly, the occurrence of somatization disorder ranged from 20 percent to 31 percent in chronic pain patients, compared to 1 percent to 4 percent in the general population. Thus, it becomes evident that 1) psychological factors are reciprocally interactive in the initiation and expression of the pathology of chronic pain; 2) unrecognized and untreated psychopathology may increase pain intensity, disability, and exacerbation of environmental influences; 3) this reflects the truly biopsychosocial dimensionality of chronic pain, and, therefore, 4) such dimensions must be considered in any meaningful paradigm for chronic pain management.[5-8]

A considerable amount of research has been devoted to profiling the psychological and behavioral characteristics of chronic pain patients in an attempt to accurately

identify strategies and tactics of effective co-management of psychological and physical symptoms and the combined effects of disability (e.g., anxiety has been shown to decrease patients' pain threshold and tolerance, and both anxiety and depression have been associated with magnification of medical symptoms).[10,11,23] Yet a persistent problem is the overuse/abuse of both prescription drugs and illicit agents in this patient population. Surveys have shown that persons with a history of at least one major depressive episode within the past year were significantly more likely to have used illicit drugs during that time period compared to those persons without a major depressive episode (28.8 percent versus 13.8 percent), and substance dependence or abuse was more prevalent among persons with a major depressive episode than among nondepressed persons (22.0 percent versus 8.6 percent). Similarly, serious psychological distress was highly correlated with substance dependence or abuse: 21.3 percent (4.6 million) of adults with serious psychological distress were shown to be dependent on or to have abused alcohol or illicit drugs in 2004, as compared to only 7.9 percent of adults without serious psychological distress. Similarly, the risk and prevalence of substance abuse has been associated with pre- and comorbidity of psychological disorders in patient populations receiving controlled substances.[29-35] Regier et al.[34] demonstrated that patients with a lifetime mental disorder present with more than twice the risk of having an alcohol disorder and over four times the risk of having (another) substance abuse disorder. Webster and Webster[29] have shown that depression is a risk factor for opioid abuse (as ascertained by the Opioid Risk Tool), although Ives et al.[36] failed to reveal a direct correlation between depression and opioid misuse.

The potential magnitude of this problem becomes evident when one considers that, according to the 2004 National Survey on Drug Use and Health, there were 35.1 million (14.7 percent) persons aged 12 or older who had had at least one major depressive episode in their lifetime. Of these, 19.3 million persons (8.1 percent of the population) had had a major depressive episode in the past 12 months, including 2.2 million youths (aged 12 to 17) and 17.1 million adults (aged 18 or older). This survey also estimated the prevalence of serious psychological distress, defined as a high level of distress due to any type of mental problem. In 2004, there were 21.4 million adults with serious psychological distress, representing 9.9 percent of all adults.[37]

Despite the noted increase in the prevalence of pain, psychological, and substance abuse disorders and the growing body of evidence to support the comorbidity (and putative relationship) of these disorders, there is sparse literature addressing the viability of psychological factors as predictors of opioid abuse and/or illicit drug use in chronic pain patients. Controlled substance abuse among chronic pain patients is common. The prevalence of prescription drug overuse and abuse has been reported to be between 9 and 41 percent for patients receiving opioids for chronic pain. This is particularly significant, given that as many as 90 percent of patients in pain management settings receive opioids for chronic pain.[38-47]

Recently, we have evaluated multiple variables that may be useful in identifying controlled substance abuse and illicit drug use in chronic pain patients.[38] Our work has revealed that pain resulting from motor vehicle accidents, involvement of multiple painful sites, and a past history of illicit drug use were all significant risk factors. In addition to these variables, Ives et al.[36] identified past cocaine abuse, drug or DUI conviction, and past alcohol abuse as predictors of misuse.

In light of the fact that drug use represents a significant epidemiological problem, compounds the impact of chronic pain and psychological conditions, and considerably complicates (if not impedes) effective care, tactics for the detection and reduction/prevention of continued drug misuse/abuse assume an important place in the initiation of therapeutic intervention. Multiple investigators have described screening instruments to detect opioid abuse or misuse in chronic pain patients.[38,45,48-57] However, most of the screening instruments currently in use have not included or accounted for psychological variables.

Our earlier work evaluated depression as a variable.[38] However, our study was limited in that it did not consider the broader effects of pain and comorbid psychopathologies as part of a spectrum disorder (or disorder continuum), and therefore did not examine patterns or the role of anxiety and somatization disorder as covariables in drug misuse/abuse in chronic pain patients. The hypothesis that chronic pain and these disorders may be covariant is strengthened by the findings of Dersh et al.,[11] according to which chronic pain patients were 10.2 times more likely than persons in the general population to have a major Axis I psychiatric disorder. The Dersh et al.[11] evaluation of Axis I disorders included drug abuse and alcohol abuse/dependence, as well as major depression, dysthymia, any anxiety disorder, and panic disorder. Their study showed that drug abuse and dependence were present in 10.7 percent of the patients. There was a correlation between the occurrence of pain and several types of pathologies classified in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), most notably major depressive disorder, drug abuse/dependence, and personality disorders, although anxiety disorders were less frequent than major depressive disorders.

Therefore, given that pain is by definition both a physiological and psychological event, and considering the reported relationship between particular Axis I psychological disorders (e.g., depression, anxiety, somatization)

and substance abuse, we pose the question of whether determination of psychological presentation (i.e., the presence of co- and/or premorbid psychological disorder[s]) may have some value toward predicting (or alerting to) the predisposition/sensitivity to substance abuse in chronic pain patients. Thus, this study investigated the pattern of depression, anxiety, and somatization disorder in chronic pain patients who were either misusing opioids or using illicit drugs in an attempt to correlate these findings and better clarify the value of psychological condition as a predictor of substance abuse among chronic pain patients in interventional pain management settings.

METHODS

This article reports the results of routine psychological testing for 500 consecutive patients taking prescribed opioids for pain management through a private practice in an interventional pain management setting. All patients provided valid and informed consent for obtaining information on drug use, random drug testing, and confidential publication of results. Appropriate precautions were taken to protect the privacy and confidentiality of patients participating in this evaluation. All patients also signed agreements that included permission to contact pharmacies and physicians and to perform random drug screening. All patients in this study were receiving stable doses of hydrocodone, oxycodone, methadone, or morphine in pharmacologic support of interventional pain management techniques. In this way, opioid use constituted supplemental pain management and was not the mainstay of the treatment protocol. Inclusion criteria for data evaluation required that patients were willing to participate, were in stable condition, and were in a pain management program encompassing interventional techniques and opioid drug administration. Exclusion criteria were defined as an inability to understand the consent, refusal to sign the consent, refusal to follow the terms of the agreement, refusal to submit to random drug testing, and unstable pain control.

Upon inclusion, initial evaluation consisted of monitoring controlled substance intake—with special focus upon externally provided drugs—and documentation of past history of illicit drug use. History of illicit drug use was determined from patients' reports of such use/activity.

Data collected included information from records, pharmacies, referring physicians, and all physicians involved in patient treatment. Data were collected using a preprinted format including demographic information and drug history and were compared with all acquired information.

Rapid urine drug screening (Instant Technologies, iCup®, Norfolk, VA) was performed on all the patients participating in the study. The rapid drug screen is a one-step, lateral-flow immunoassay for the simultaneous detection of up to nine drugs via urinalysis. Each analysis occupies a separate channel intended for use in the qualitative detection of various drugs.

Psychological evaluation focused on signs and symptoms that were representative of the DSM-IV-TR characterizations of depression, anxiety, and somatization disorder. Psychological status was evaluated by obtaining a psychological history using a DSM-IV-TR criteria-based questionnaire, followed by a physician-conducted interview and/or administration of the Millon Clinical Multiaxial Inventory (MCMI-II or MCMI-III) and/or administration of the Pain Patient Profile (P-3®).[58-60] Evaluation using the DSM-IV-TR criteria-based questionnaire involved multiple questions with content validity for determinations of clinically relevant features of depression, anxiety, and somatization disorder.[4,58]

The MCMI is a 175-question psychological tool that does not require administration by a psychologist, is commonly utilized to evaluate psychological involvement in various medical syndromes, and is easily administered in outpatient interventional pain practices.[59] The MCMI evaluates personality disorders and various clinical syndromes including depression, generalized anxiety, and somatoform disorder.

The P-3 is a 34-item instrument for briefly assessing psychological characteristics known to affect the pain perception and treatment response of pain patients.[60] It is somewhat specifically used to evaluate comorbidity of depression, anxiety, and somatization in pain patients.

A prospective evaluation of the effectiveness of the DSM-IV-TR questionnaire, pain management questionnaire, and clinical interview showed these techniques to reliably assess depression and anxiety in an interventional pain management setting.[4] Therefore, diagnostic impressions of psychological conditions were based on the results of these tests throughout the (opioid) treatment period.

Substance abuse was operationally defined as occurring 1) when patients received controlled substances from any place or source other than the prescribing physician, with the exception of the short-term use of controlled substances for acute injury/insult and/or emergency, and/or 2) when patients escalated the use of controlled substances beyond the dose(s) and schedule prescribed. Drug trafficking was defined according to the legal determination as described by statute and in courts of law. Past history of illicit drug use was based on patient report/history and/or information afforded by the patient's medical record.

All patients underwent rapid urine drug testing. Patients were considered positive for current illicit drug use if one of the monitored illicit drugs (including cocaine, marijuana [THC], amphetamines, or methamphetamine) was detected by urinalysis, with the qualifying conditions that 1) positive results for the presence of

Table 1. Demographic characteristics				
		Male n = 205 (41 percent)	**Female n = 295 (59 percent)**	**Total N = 500**
Age (years)	< 45	65 (32 percent)	123 (42 percent*)	188 (38 percent)
	45 to 64	121 (59 percent)	133 (45 percent)	254 (51 percent)
	≥ 65	19 (9 percent)	39 (13 percent)	58 (11 percent)
	Range	25 to 77	21 to 78	21 to 78
	Mean ± SE	49.5* ± 11.1	48.0 ± 13.2	48.6 ± 12.4
Duration of pain (years)	< 5	44 (22 percent)	78 (26 percent)	122 (24 percent)
	5 to 9	60 (29 percent)	81 (28 percent)	141 (28 percent)
	≥ 10	101 (49 percent)	136 (46 percent)	237 (47 percent)
	Range	1 to 44	1 to 44	1 to 44
	Mean ± SE	11.6* ± 9.2	10.1 ± 7.5	10.7 ± 8.2
Mode of onset	Gradual onset	58 (28 percent)	129 (44 percent*)	187 (37 percent)
	Motor vehicle accident	38 (19 percent)	62 (21 percent)	100 (20 percent)
	Other incident	48 (23 percent)	65 (22 percent)	113 (23 percent)
	Work-related injury	61 (30 percent*)	39 (13 percent)	100 (20 percent)
Number of regions involved	one region	95 (46 percent)	85 (29 percent)	180 (36 percent)
	two regions	82 (40 percent)	158 (54 percent*)	240 (48 percent)
	three regions	28 (14 percent)	52 (18 percent)	80 (16 percent)
History of previous spine surgery		96 (47 percent*)	80 (27 percent)	176 (35 percent)
Insurance status	Third-party	76 (37 percent)	116 (39 percent)	192 (38 percent)
	Medicare with/without third-party support	80 (39 percent*)	74 (25 percent)	154 (31 percent)
	Medicare and Medicaid	28 (14 percent)	57 (19 percent)	85 (17 percent)
	Medicaid	21 (10 percent)	48 (16 percent)	69 (14 percent)
Past history of illicit drug use		33 (16 percent)	47 (16 percent)	80 (16 percent)

* Indicates a significant difference between male and female patients.

Table 2. Psychological characteristics						
	Depression		Anxiety		Somatization disorder	
	Positive	Negative	Positive	Negative	Positive	Negative
Male (n = 205)	111 (54 percent)	94 (46 percent)	119 (58 percent)	86 (42 percent)	55 (27 percent)	150 (73 percent)
Female (n = 295)	185 (63 percent)	110 (37 percent)	200 (69 percent*)	95 (32 percent)	96 (32 percent)	199 (68 percent)
Total (N = 500)	296 (59 percent)	204 (41 percent)	319 (64 percent)	181 (36 percent)	151 (30 percent)	349 (70 percent)
* Indicates a significant difference between male and female patients.						

cocaine (and its metabolites) was considered definite by rapid urine drug screen, and 2) positive identification(s) of methamphetamine, amphetamine, and/or marijuana were checked for false positives with a follow-up laboratory evaluation and exclusion of drugs causing false-positive results. For example, tentatively positive THC results were confirmed with secondary laboratory testing if a patient was on pantoprazole (Protonix®) or denied using marijuana. All results confirmed by secondary laboratory evaluation were considered final.

Data were tabulated using Microsoft Access® 2003, and SPSS (version 9.0) was used to generate frequency tables. The χ^2 statistic was used to determine significant differences between groups. Fisher's exact test was used post hoc (wherever the expected value was less than five). Student's t-test was used to determine significant sex-based differences. All results were considered statistically significant at $p < 0.05$.

RESULTS

Patient flow

Data were evaluated for the prevalence of opioid abuse and illicit drug use in 500 patients. Initially, 566 patients were eligible, but 66 patients refused to participate in the study. All patients were evaluated for opioid abuse and underwent urinalysis for cocaine, amphetamines, methamphetamine, and marijuana (THC).

Demographic characteristics

Table 1 illustrates the demographic characteristics of age, duration of pain, mode of onset of pain, number of body regions involved, history of previous spine surgery, insurance status, and past history of illicit drug use among male and female patients.

The proportion of female patients was higher in the age group of those younger than 45 years (42 percent versus 32 percent), whereas the proportion of male patients was higher in the 45-to-64 age group (59 percent versus 45 percent). Mean age was slightly higher for males (49.5 years versus 48.0 years).

The duration of pain was evaluated in three groupings: less than five years, five to nine years, and 10 years or longer. Overall, 75 percent of the patients had had pain for more than five years, and 47 percent had had pain for more than 10 years. Mean duration of pain was longer in males (11.6 years versus 10.1 years).

Thirty-seven percent of patients reported pain to be of gradual onset without injury. A significantly higher proportion of female patients presented with gradual-onset pain (44 percent versus 28 percent). The study also showed a significantly greater proportion of males than females with work-related injuries (30 percent versus 13 percent).

The number of body regions involved was different between males and females. Among males, 46 percent had involvement of one body region; a greater proportion of females than males presented with involvement of two or more body regions (72 percent versus 54 percent).

A history of previous spine surgery was present in 35 percent of the patients. Surgery was more common among males (47 percent versus 27 percent).

Insurance status showed significant differences. A greater proportion of males than females were covered by Medicare with or without third-party insurance (39 percent versus 25 percent). Overall, 38 percent of patients were covered by third-party insurance, 31 percent were covered by Medicare with or without third-party supplemental insurance, 17 percent were covered by Medicare and Medicaid, and 14 percent were covered by Medicaid only. A total of 48 percent of patients were covered by Medicare, and 31 percent had Medicaid coverage.

Psychological characteristics

Psychological characteristics are illustrated in Table 2. Overall, depression, anxiety, and somatization disorder

Table 3. Prevalence of drug abuse and illicit drug use			
	Male (n = 205)	**Female (n = 295)**	**Total (N = 500)**
Drug abuse			
Doctor shopping	9 (4.4 percent)	16 (5.4 percent)	25 (5 percent)
95 percent CI	(2 percent, 7 percent)	(3 percent, 8 percent)	(3 percent, 7 percent)
Trafficking	12 (6 percent)	9 (3 percent)	21 (4 percent)
95 percent CI	(3 percent, 9 percent)	(1 percent, 5 percent)	(2 percent, 6 percent)
Total opioid abuse	20 (10 percent)	26 (9 percent)	46 (9 percent)
95 percent CI	(6 percent, 14 percent)	(6 percent, 12 percent)	(7 percent, 12 percent)
Illicit drug use			
Marijuana	15 (7 percent)	39 (13 percent*)	54 (11 percent)
95 percent CI	(4 percent, 11 percent)	(9 percent, 17 percent)	(8 percent, 14 percent)
Cocaine	10 (5 percent)	14 (5 percent)	24 (4.8 percent)
95 percent CI	(2 percent, 8 percent)	(2 percent, 7 percent)	(3 percent, 7 percent)
Methamphetamine/amphetamines	2 (1 percent)	9 (3 percent)	11 (2 percent)
95 percent CI	(0 percent, 2 percent)	(1 percent, 5 percent)	(1 percent, 4 percent)
Total illicit drug use	25 (12 percent)	55 (19 percent)	80 (16 percent)
95 percent CI	(8 percent, 17 percent)	(14 percent, 23 percent)	(13 percent, 19 percent)
* Indicates a significant difference between male and female patients.			

were documented in 59, 64, and 30 percent, respectively. A greater proportion of female than male patients were diagnosed with anxiety (69 percent versus 58 percent). There were no significant differences noted between male and female patients with depression or somatization disorder.

Opioid abuse/misuse and illicit drug use

A past history of illicit drug use was identified by self-report in 16 percent of patients. Table 3 illustrates drug abuse and illicit drug use characteristics. A total of 9 percent of patients were either "doctor shopping" or trafficking in opioids. While there were no significant differences noted between males and females, there was an insignificant trend among male patients for trafficking and among female patients for doctor shopping.

Table 3 also illustrates illicit drug use. Overall, the prevalence of illicit drug use was 16 percent—19 percent among females and 12 percent among males. Marijuana use was significantly higher in females than in males (13 percent versus 7 percent).

Drug abuse and illicit drug use characteristics by psychological status

Table 4 illustrates drug abuse and illicit drug use characteristics based on psychological diagnosis. There were no differences in current illicit drug use noted with regard to depression, anxiety, or somatization disorder. However, drug abuse was significantly higher in patients with depression than in those without (12 percent).

Table 5 shows drug abuse and illicit drug use characteristics based on psychological diagnosis and gender. Current illicit drug use was more frequent in women with depression than without (22 percent versus 14 percent) and more prevalent in depressed women than men (22 percent versus 12 percent). Prescription drug abuse was

Table 4. Drug abuse and illicit drug use characteristics based on psychological diagnosis						
	Depression		Anxiety		Somatization disorder	
	Yes (n = 296)	No (n = 204)	Yes (n = 319)	No (n = 181)	Yes (n = 151)	No (n = 349)
Current illicit drug use	53 (18 percent)	27 (13 percent)	18 (15 percent)	10 (12 percent)	13 (24 percent)	15 (10 percent)
Drug abuse	35 (12 percent*)	11 (5 percent)	35 (11 percent)	11 (6 percent)	16 (11 percent)	30 (9 percent)
* Indicates significant difference.						

also higher in women with depression (11 percent versus 4 percent). Current illicit drug use was highest in males with somatization disorder (22 percent versus 9 percent without).

DISCUSSION

This study showed a high prevalence of depression (59 percent), anxiety (64 percent), and somatization disorder (30 percent) in patients with chronic pain. Female pain patients presented with comorbid anxiety more often than male pain patients. Depression was shown to be a predictor of comorbid substance abuse, with 12 percent of depressed chronic pain patients showing substance abuse, versus 5 percent of pain patients without depression. Current illicit drug use was shown to be significantly higher in patients with depression than without and among females as compared to males. In this latter regard, subset analysis factoring for gender revealed that 22 percent of women with depression were using illicit drugs. Female patients with depression also showed a significantly higher prevalence of drug abuse (11 percent versus 4 percent). In contrast, male patients with somatization disorder showed a significantly higher prevalence of current illicit drug use compared to male patients without somatization disorder. These results are consistent with those of other studies that have shown an increased prevalence of depression, anxiety, somatization, and substance abuse/dependence disorders in chronic pain patients as compared to the general population.[4-28,36,61,62] Furthermore, given the correlation between chronic pain, patterns of emotional reactivity (to internal and external environmental stimuli evidenced in the presented psychopathologies), and substance abuse, the findings of the current study strengthen our previous work, which demonstrated that other biopsychosocial factors (such as pain subsequent to motor vehicle accidents, involvement of multiple anatomic regions, and past history of illicit drug use) are predictive for substance abuse in chronic pain patients.[38] Although our study did not demonstrate a clear association between current illicit drug use or drug abuse and anxiety or somatization disorder in women, this could be because the clinical testing instruments used were not sufficiently sensitive to detect such relationships. On the other hand, in regard to illicit drug use and abuse in the population of pain patients studied here, anxiety and somatization behaviors may have been nested within the features of depression.

To date, there is a relative paucity of valid measures that specifically address the predictive correlation between psychopathological variables and the potential for substance abuse in chronic pain patients. Of those in existence, most notable is a preliminary validation of the Opioid Risk Tool, in which Webster and Webster[29] identified five factors—family history of substance abuse, personal history of substance abuse, age of 45 years or younger, history of preadolescent sexual abuse, and the presence of particular psychological disorders (i.e., attention deficit disorder, obsessive-compulsive disorder, unipolar depression or bipolar disorder, or schizophrenia)—as potential risks for opioid abuse. Most other studies have not focused upon the role of psychological comorbidity in substance abuse in chronic pain patients; instead, they have tended to examine reactivity to and influence of environmental and circumstantial factors as possible risk predictors.

Chabal et al.[45] developed a prescription abuse checklist consisting of five criteria—overwhelming focus on opioid issues persisting beyond the third clinic treatment session; a persistent pattern of early refills; multiple telephone calls or office visits requesting more opioids; reports of consistent problems associated with the opioid prescription (including but not limited to lost, spilled, and/or stolen medications); and opiates obtained from multiple providers, emergency rooms, or illegal sources—that might be indicative of a high(er) substance abuse risk. Compton et al.[49] identified three items that were particularly viable in identifying misuse of opioids; these included belief of addiction by the patient, increasing analgesic dose or frequency, and route of administration preference. Passik et al.[50] developed a questionnaire that was employed among a small group of cancer and HIV patients to evaluate medication use, present and past

Table 5. Drug abuse and illicit drug use based on psychological diagnosis and gender							
		Depression		Anxiety		Somatization disorder	
		Yes	No	Yes	No	Yes	No
Current illicit drug use	Male (n = 205)	12 percent (13/111)	12 percent (12/94)	14 percent (17/119)	9 percent (8/86)	22 percent* (12/55)	9 percent (13/150)
	Female (n = 295)	22 percent** (40/185)	14 percent (15/110)	20 percent (41/200)	15 percent (14/95)	18 percent (17/96)	19 percent (38/199)
Drug abuse	Male (n = 205)	15 percent (14/111)	6 percent (6/94)	11 percent (13/119)	8 percent (7/86)	14 percent (8/55)	8 percent (12/150)
	Female (n = 295)	11 percent* (21/185)	4 percent (5/110)	11 percent (22/200)	4 percent (4/95)	8 percent (8/96)	9 percent (18/199)

* Indicates significant differences between women with or without depression and men with or without somatization disorder.
** Indicates significant differences between men and women and women with and without depression.

drug use, patients' beliefs about addiction risk, and aberrant drug-taking attitudes and behaviors.

Atluri and Sudarshan[54] developed a screening tool for detecting the risk of inappropriate prescription opioid use in chronic pain patients that identified six clinical criteria: patient focus on procuring opioids, opioid overuse, other substance use, nonfunctional exaggeration of pain, and unclear and/or improbable pain etiology. Manchikanti et al.[52] evaluated the instrument developed by Atluri and Sudarshan[54] and specifically identified three primary factors that appeared to reliably predict potential substance abuse: excessive opiate needs, deception or lying to obtain controlled substances, and doctor shopping. Holmes et al.[56] developed and introduced the Pain Medicine Questionnaire (PMQ) to assess the risk for opioid medication misuse in chronic pain patients. The PMQ is a 26-item questionnaire that evaluates various dimensions of chronic pain and attempts to isolate pain-related variables and factors that may suggest abuse liability. Savage[57] suggested that opioid addiction and/or its potential might be reflected or revealed through behaviors such as an unwillingness to taper opioids or try alternate pain treatments, decreased levels of function despite seemingly appropriate analgesia, and frequent requests for medication refills before renewal is due.

Clearly, the relationship between psychological state/condition (e.g., the presence or absence of psychopathology, as either directly indicated [as by Webster and Webster[29]] or implied through patterns of reactivity, behaviors, etc.), chronic pain, and the potential for substance abuse is strong, and we concur with the opinion raised in several studies that this reflects a biological basis for the comorbidity of certain psychopathologies (including substance abuse disorders) and chronic pain.[29,58-60,62] This thesis is fortified by the demonstrated co-involvement of several neuropharmacologic systems (e.g., serotonin, norepinephrine, dopamine, glutamate, gonadal steroids) and anatomical structures (namely the thalamocortico-limbic pathway) common to these disorders.[64,65]

It may be that the neural and/or glial chemistry, micro- and macrostructural anatomy of brain regions that are involved in mediating intero- and exteroceptive sensory (i.e., noxious) input, and the associative and emotive aspects of reinforcement and/or reward are disrupted or dysfunctional.[66] Underlying these neural (and possibly glial) phenotypic variations might be genetic variations that could potentially induce pleiotropic effects upon several substrates of neural and/or glial function (e.g., alterations in transmitter, receptor, and/or effector-signaling molecule synthesis or expression; expression of variant membrane constituents, including differentially sensitive ionic channels; etc.) to alter the pattern(s) of activity at brain loci that are involved in establishing "common neural bases" that predispose one to (or directly subserve) chronic pain, depression, somatization, and substance abuse.[67] Recent studies have shown that these loci include (but are not limited to) the parabrachial nucleus, amygdala, nucleus accumbens, and cingulate and frontal cortices as target zones of ascending sensory and internal associative/regulatory pathways.[68] The affective components operative in chronic pain (i.e., pain as protracted disease process and illness, affective pain) are akin to those of mood disorder and somatic sensitization.[69] Particular individuals are predisposed to the development of neural sensitization within these pathways as a consequence of overreactivity to insult and trauma, inflammation, or aberrant response to environmental input. The overexpression of neural substrates that subserve algesia or distress, together with a suppression or underexpression of pain-modulating, reinforcement, and reward substrates, might induce pathologic patterns of sensory hyperreactivity, altered cognitive processing and emotional responses, and loss of impulse control. In this way, persistent pain, psychopathology, and substance

abuse may be correlated and reflect related mechanistic processes.[70-73] As Koob and Le Moal[74] note, persistent pain involves "sensitization . . . that is defined by enhanced responsiveness to incoming signals . . . in the peripheral and central nervous system . . . . [A]ddiction also can be considered a type of chronic pain syndrome characterized by emotional pain, dysphoria . . . and interpersonal difficulties . . . . Drugs can be . . . self-medication for such pain."

Chromosomal quantitative trait loci (QTL) that affect neural phenotypes relevant to types of pain and certain psychopathologies including substance abuse have recently been identified.[75-77] These QTLs can either operate singly or multiply to affect particular phenotypes. Most surely, the phenotypes for pain, psychopathology, and substance abuse are multifactorial; therefore, it is likely that such QTLs establish a probabilistic basis for the (co)occurrence of these phenotypes along a continuum, while the actual expression of phenotypes as clinically relevant disorders is epigenetically influenced by the central nervous microenvironment and/or effects incurred by ongoing interactions between internal and external environments throughout the lifespan.[78,79] Variant patterns of these conditions appear to validate this possibility.

Tsuang et al.[80] showed that genetic influence in the abuse of marijuana, stimulants, and sedatives is shared across drugs. Thus, an abuser of one drug is more likely than nonabusers to go on to abuse a different category of drug. However, it has been shown that the genetic influence for heroin/opioid abuse is specific to heroin/opioids and is not shared with other drugs.[81,82] Thus, the high probability of genetic influence on opioid abuse fortifies the repeated finding that familial and personal history of opioid drug abuse is heavily weighed in risk analyses of opioid misuse.[29] Taken together, such findings suggest that genotypic variants might predispose either 1) a "generalized" pattern of diathesis, in which neural substrates of environmental sensitivity, responsivity, reinforcement, and reward are altered to affect interpretive/ associative aspects of bodily sensations (including discomfort and pain), appetitive drives, and emotionality; or 2) more "specific" diatheses, in which particular neural phenotypes are affected which directly correlate to certain forms of pain and/or psychopathology and substance dependency.[83,84] Albeit speculative, it is tempting to postulate that genetic alteration in the expression of opioid, glutamate, and/or GABAergic receptors (or receptor-linked mechanisms) and/or cation-channel expression might underlie sensitivity to pain, development of particular types of pain (e.g., neuropathic syndromes), the constellation of somatic and cognitive features found in forms of depression and somatization disorder, and decreased viability of opioid-dependent neuromodulation, therefore impacting predisposition to escalative misuse of opioids.

If we consider that these comorbidities may represent environmentally dependent, differential expression of neural and behavioral phenotypes that are established by a relatively confined set of genomic influences, then we may view chronic pain as a spectrum disorder that may co-manifest (other) neuro- and psychopathological effects/conditions.[85,86] Working from the concept that chronic pain and psychological disorders may be correlated along a neuropathological continuum, it becomes important to recognize that 1) these disorders represent underlying genomic diatheses, and the expression of phenotypic substrates is differentially dependent upon particular interactions with internal and external environmental factors; 2) it is possible—and likely—that such genetic-environmental covariance sustains that comorbidity; 3) this covariance is equally likely on several dimensions of cause and effect; and 4) these effects may be manifested in the co-terminal expression of chronic pain and mood, somatization, and substance abuse disorders. Thus, it may be that (clinically relevant) depressive and somatization signs and symptoms are viable psychological endophenotypes that have predictive value for the substance abuse potential of chronic pain patients, particularly if viewed alongside other identified biopsychosocial risk factors.

To be sure, these conclusions are highly speculative, and multiple issues may be raised regarding methodology and the relevance and relativity of definitions of opioid abuse, illicit drug use, doctor shopping, and drug trafficking. We posit that the sampling methodology we used was appropriate for the type of evaluation, and that the methods of psychological evaluation were also appropriate to context, setting, and applicability to interventional pain management. In this latter regard, it has been shown that the psychological diagnostic impressions achieved by utilizing DSM-IV-TR criteria were superior to self-report questionnaires or loosely structured interviews.[4,11] In the present study, we have included patients who have been characterized with depressive features by evaluation of past psychological history, DSM-based questionnaire, and use of the MCMI; thus, the number of patients presenting with such operationally defined depression may be higher than in our previous work. However, we believe that this multifocal assessment approach has higher sensitivity and therefore more reliably captured depression within this patient population.

The major purpose of this study was to evaluate and address the predictive value of multiple risk factors for drug abuse and illicit drug use in chronic pain patients. Therefore, the present study is an extension of our previous work, which identified physical factors predisposing subjects to substance abuse.[38] By now evaluating and

identifying psychological factors, we move toward a biopsychosocial approach to assessment, upon which a more comprehensive scope and trajectory of care might be conceived and implemented.

Clearly, our knowledge of pain, psychological conditions, and substance abuse influence the epistemic basis of both medical practice and the ethics that guide such care.[87,88] An understanding of the neurobiology of these disorders allows us to view them as pathological processes ascribed to a disease model. But this remains a double-edged sword, for while we adopt an integrative-approach disease model of assessment, we often continue to adhere to an older, more Cartesian, dualistic (body versus mind) approach to care, which can foster clinical disregard of psychological disorders—including substance abuse—as being "only in the mind." However, nesting neurobiology within a biopsychosocial framework allows for insight into the mechanisms and effects of genetic, phenotypic, and environmental interactions in the expression of disease and manifestation of illness, and it equally compels the use of a biopsychosocial approach to treatment of these disorders.[89-91] In sum, the better we understand how genetics and neurobiology affect individual patients, the better we will be able to adapt clinical practice to meet the complex individual medical needs of each person in pain.

CONCLUSION

This study demonstrated that 1) the presence of psychological features of depression and somatization may be endophenotypes of substance abuse diathesis in chronic pain patients, and 2) these psychological features are reasonable predictors of substance abuse in chronic pain patients. These conclusions are based upon both the quantitative analyses of specific data and reflection upon the most contemporary understanding of the neurogenetics of these pathologies, hypothesized herein to be components of a neuropathological spectrum disorder. This provides a basis for both theoretical and predictive contextual knowledge, and we advocate that such knowledge should inform and sustain the ethical practice of pain medicine.[92,93] A deepened understanding of pain, psychopathology, and addiction allows for an enhanced ability to treat, heal, and care as necessary. Ongoing work by our group is dedicated to continued research to advance this approach.

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ORIGINAL ARTICLE

Prevalence and characteristics of breakthrough pain in patients receiving opioids for chronic back pain in pain specialty clinics

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ABSTRACT

Objective: *We sought to assess the prevalence and characteristics of breakthrough pain (BTP) in patients with chronic back pain.*

Design: *Researchers utilized a telephone survey using a pain assessment algorithm. This report represents a subset of patients from a larger survey of 228 patients with chronic pain unrelated to cancer.*

Participants: *This study employed 117 subjects taking opioids for a primary diagnosis of back pain and receiving care at geographically dispersed pain treatment centers. Subjects had pain lasting at least six months and had "controlled" baseline pain.*

Results: *Eighty-seven subjects (74 percent) experienced 93 types of BTP. The median number of BTP episodes per day was two; median time to maximum intensity was 10 minutes, and median duration was 55 minutes. Onset could not be predicted for 46 percent of pains. Eighty-three percent of subjects used shorter-acting opioids for BTP. Other medications used for pain included NSAIDs, antidepressants, anticonvulsants, skeletal muscle relaxants, intrathecal local anesthetics, and transdermal local anesthetics.*

Conclusions: *These patients with opioid-treated chronic back pain commonly experienced BTP, which often had a rapid onset and a relatively short duration and was difficult to predict. Opioids were the mainstay of pharmacologic therapy, but nonopioid analgesics and adjuvant analgesics were commonly used.*

Key words: back pain, chronic pain, breakthrough pain, prevalence, survey methodology

INTRODUCTION

Chronic low back pain is a common clinical problem that poses a significant burden to the healthcare system in the United States. A systematic review of the literature on the prevalence of low back pain reveals a point prevalence ranging from 12 to 33 percent, a one-year prevalence ranging from 22 to 65 percent, and a lifetime prevalence ranging from 11 to 84 percent.[1] A recent study of the general population in the United Kingdom found that 6.2 percent of women and 3.9 percent of men had chronic back pain that was intense and disabling.[2] Chronic pain is known to have a detrimental effect on both general and psychological health, as well as social well-being.[3,4] A recent study in patients with persistent low back pain showed that 50 to 75 percent of patients reported problems with activities of daily living, and more than 20 percent of patients required help with such activities as a result of their pain.[3] Chronic low back pain also exerts an important economic toll; the annual cost associated with lower back pain (including both direct and indirect costs) has been estimated to range between $50 billion and $100 billion in the United States.[5] Unfortunately, despite the economic and social burdens associated with chronic back pain, an understanding of the clinical phenomenon of this type of pain remains limited.

Breakthrough pain (BTP) is an important clinical phenomenon that has been well studied in patients with cancer pain.[6,7] BTP has been defined as a transient flare of severe or excruciating pain that occurs in conjunction with well-controlled baseline or persistent pain.[6] It occurs in between 50 and 90 percent of patients with cancer-related pain.[6-10] Though less well studied, BTP is also thought to occur commonly in patients with chronic pain not related to cancer. One fairly recent study reported that 63 percent of patients with various types of non-cancer pain experienced BTP.[11] A survey of the prevalence and characteristics of BTP in 228 patients with chronic noncancer pain was recently completed (findings from this survey have been reported elsewhere).[12] The results of the survey indicated that the prevalence (74 percent) and characteristics of BTP in patients with chronic noncancer pain are similar to those in patients with cancer-related pain. This report is a subgroup analysis of the

Table 1. Characteristics of subjects with chronic back pain according to presence or absence of breakthrough pain		
	BTP present (n = 87)	**BTP absent (n = 30)**
Median (range) age, years	48 (28 to 74)	48 (23 to 71)
Number (percentage) females	51 (59 percent)	16 (53 percent)
Median (range) number of years since diagnosis	7 (0.5 to 30)	5 (0.5 to 40)
Number (percentage) pain pathophysiology		
Somatic nociceptive	44 (51 percent)	20 (67 percent)
Visceral nociceptive	1 (1 percent)	0 (0 percent)
Neuropathic	4 (5 percent)	2 (7 percent)
Mixed pathophysiology	38 (44 percent)	8 (27 percent)

survey and describes BTP in patients with chronic back pain. It also examines both pharmacologic and nonpharmacologic methods used by these patients to manage their back pain.

METHODS

Details of the methodology of the survey have been described elsewhere.[12,13] All subjects provided written informed consent prior to participation in the study, and an institutional review board approved the study prior to its commencement. In summary, eligible subjects participated in a telephone interview approximately one week after demographic information was collected in one of nine pain treatment centers in the United States. Surveys were conducted from February through April of 2004.

Subject selection

Subjects included in this subgroup analysis were between 18 and 75 years of age, had experienced pain for at least six months, were on daily opioid therapy, had a primary pain diagnosis of back pain, and had "controlled" baseline pain (moderate intensity or less). Subjects were excluded from participating in the survey if they had cancer-related pain, had been hospitalized within the previous month for uncontrolled pain, or had a clinically important neurological or psychiatric disorder that could compromise data collection.

Telephone survey

The survey instrument was adapted from a pain assessment algorithm that had been used previously to assess BTP in patients with cancer pain.[6,9] Controlled baseline pain was characterized by assessing its location, the time in weeks since its onset, and the nature of the pain (e.g., sharp; aching; cramping; radiating/shooting; pressing, squeezing, or tight; burning; throbbing; stabbing). Temporary (duration ≤ 12 hours) flares of severe or excruciating BTP were characterized by their duration, frequency (episodes per day), time from onset to maximal intensity, identifiable precipitating factors (if any), and any actions that successfully reduced the pain. Patients could describe up to three different types of BTP. The survey concluded with a series of sociodemographic questions.

RESULTS

Data from 117 subjects with chronic back pain were included in this subgroup analysis. Of the 117 subjects, 87 (74 percent) reported flares of BTP. A total of 93 distinct types of BTP were reported by these 87 subjects, indicating that individuals may experience more than one type of BTP.

Demographic data for each of the groups with or without BTP are shown in Table 1. The median age of subjects with chronic back pain was 48 years and ranged from 23 to 74 years. Fifty-seven percent of the subjects were female. Subjects had experienced back pain for a median of six years (range of 0.5 to 40 years), and the underlying pain pathophysiology could be broken down as follows: nociceptive in 56 percent of subjects, neuropathic in 5 percent, and mixed in 39 percent. There were no apparent differences in characteristics between

Table 2. Characteristics of types of breakthrough pain in subjects with chronic back pain (n = 93 pains)	
	Median (range)
Frequency of breakthrough pain episodes	2/d (1/wk to 12/d)
Time in minutes to maximal pain intensity	10 (1 to 120)
Duration in minutes of episodes	55 (1 to 480)

subjects who reported having episodes of BTP and those who did not.

Characteristics of subjects' BTP are summarized in Table 2. The median number of episodes per day was two (range of less than one to 12). The median time to maximum intensity was 10 minutes (range of one to 120 minutes). Of note, 47 percent of the pains reached a maximum intensity within five minutes, and 59 percent reached maximum intensity within 15 minutes. Figure 1 illustrates the distribution of times to maximum intensity. The median duration of pain was 55 minutes (one to 480 minutes), with 67 percent of pains having a duration of 60 minutes or less (Figure 2). Subjects could identify a precipitant for 76 percent of the pains, and most of the precipitants (96 percent) were activity related. Non-volitional precipitants in subjects without activity-related pain included anxiety or stress (n = 1), change in weather (n = 1), and severe arthritis (n = 1). A precipitant could not be identified for 24 percent of the pains. Onset was unpredictable for 46 percent of BTPs, could sometimes be predicted for 35 percent of the pains, could often be predicted for 7 percent of the pains, and could almost always or always be predicted for 13 percent of the pains. Seventeen pains (18 percent) occurred at the end of the dosing interval of an analgesic medication.

Subjects could identify specific actions that could help reduce the intensity of the pain for 91 of the 93 BTPs (98 percent). Actions that reduced pain included medication (77 percent of pains); rest, lying down, or sitting (56 percent); heat (25 percent); moving, stretching, or physical therapy (14 percent); cold (9 percent); transcutaneous electrical nerve stimulation (5 percent); relaxation (5 percent); distraction (3 percent); massage (2 percent); and spinal cord stimulation (1 percent). Subjects reported that these interventions worked successfully each time they were tried for only 27 percent of the pains.

Medications used by subjects are shown in Table 3. In accordance with the protocol, all subjects were receiving at least one opioid analgesic to manage their back pain, and several were using multiple analgesics. The most commonly used around-the-clock opioids were oral modified-release opioids (39 percent of subjects), methadone (20 percent), and transdermal fentanyl (15 percent). Intrathecal opioids were used by 8 percent of subjects with BTP. Shorter-acting opioids were used by 83 percent of subjects with BTP and included normal-release opioids combined with acetaminophen or a non-steroidal anti-inflammatory agent (NSAID) in 41 percent of subjects, a normal-release opioid that was not combined in 24 percent of subjects, and oral transmucosal fentanyl citrate in 28 percent of subjects.

DISCUSSION

To the best of our knowledge, this is the first study to provide a detailed description of the prevalence and characteristics of BTP in patients with chronic back pain. Understanding the phenomenon of BTP in patients with specific types of chronic pain is important not only in recognizing and diagnosing BTP but also in developing optimal

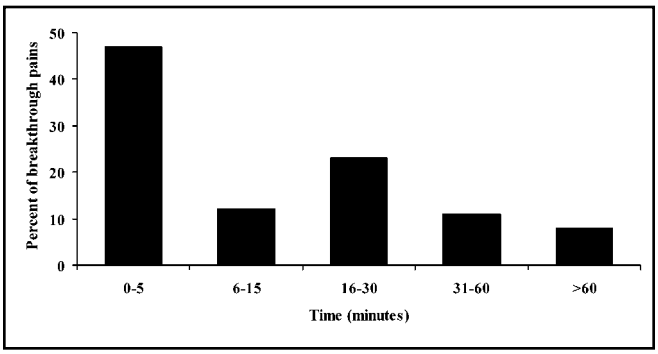

Figure 1. Distribution of times from first perception to peak intensity of breakthrough pain.

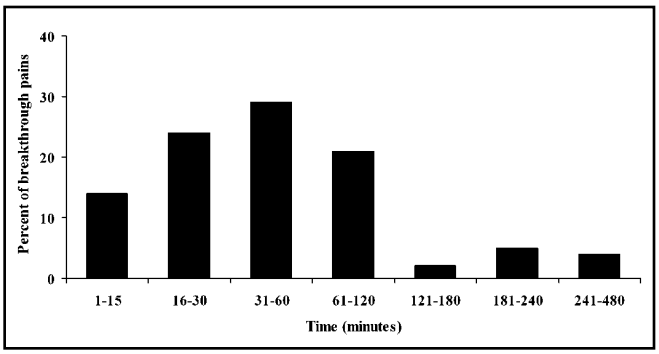

Figure 2. Distribution of durations of breakthrough pain episodes.

Table 3. Analgesics and adjuvant medications of subjects with and without breakthrough pain		
Medication	**BTP present (n = 87)**	**BTP absent (n = 30)**
Opioid analgesics	87 (100 percent)	30 (100 percent)
Oral modified-release opioids	34 (39 percent)	12 (40 percent)
Transdermal opioids	13 (15 percent)	2 (7 percent)
Methadone	17 (20 percent)	5 (17 percent)
Intrathecal opioids	7 (8 percent)	0 (0 percent)
Short-acting opioids (total)	72 (83 percent)	22 (73 percent)
Combined with acetaminophen or NSAID	36 (41 percent)	11 (37 percent)
Not combined	21 (24 percent)	8 (27 percent)
Oral transmucosal fentanyl citrate	24 (28 percent)	3 (10 percent)
NSAIDs	24 (28 percent)	9 (30 percent)
Antidepressants	44 (51 percent)	13 (43 percent)
Anticonvulsants	30 (34 percent)	8 (27 percent)

treatment strategies to manage patients' pain. For example, flares of BTP that reach maximal intensity within minutes, are frequently unpredictable, and are often of relatively short duration may be alleviated by medications that are dosed as needed, have a rapid onset of analgesic effect, and have a relatively short duration. Pain that is relatively constant throughout the day is often better managed with medications that are dosed on a regular schedule around the clock, with the goal of preventing as much pain as possible. Matching the pharmacodynamic profile of medications, such as onset and duration of analgesic effect, with the individual characteristics of pain experienced by the patient offers clinicians a treatment option that may achieve better analgesia with less total medication.

The prevalence of BTP in this group of subjects—74 percent—is similar to that found in both patients with cancer-related pain and patients with noncancer pain.[6-12] Characteristics of the BTPs were also similar to those described by patients with cancer-related BTP. Specifically, they were rapid in onset (from baseline to peak intensity), had a relatively short duration, and were difficult to predict. Typically, longer-acting opioids were dosed around the clock to manage baseline pain, and shorter-acting opioids were dosed as needed to manage flares of BTP. These subjects also required a number of nonopioid and adjuvant analgesics to manage their pain.

The chronic use of opioid analgesia for noncancer pain is controversial and is less well studied than its use for cancer pain.[14-16] However, several studies have demonstrated the efficacy of opioids for chronic back pain, and pain specialists generally support the notion that chronic pain responds to opioid therapy in a manner similar to that of cancer-related pain.[17-20] Recent reviews have also supported the use of opioids for chronic pain not associated with cancer, including low back pain, for carefully selected patients.[21-23] However, some studies have failed to show improved back pain and function in patients using opioids relative to patients not on opioids.[24] Moreover, a comprehensive review of the literature on opioid therapy for chronic pain revealed that most of the literature on opioid therapy consists of reports of surveys and uncontrolled studies.[23] Evidence on long-term opioid therapy is lacking, and well-controlled studies are needed to evaluate the efficacy and safety of opioids in patients with pain not associated with cancer. There is also a need to study the potential adverse impact of BTP in patients without cancer and the role of rapid-onset, short-duration opioids in managing these adverse outcomes.

Physicians' concerns regarding the use of opioids for chronic pain are a frequent barrier to opioid management of back pain. Physicians are often reluctant to prescribe opioids for back pain, not only because of concerns about the safety and efficacy of treatments but also due to concerns about opioid abuse and its legal and regulatory ramifications.[25-27] A recent survey of 230 primary care physicians showed that 35 percent would never prescribe Schedule II opioids on an around-the-clock basis for patients with chronic pain not associated with cancer, and 57 percent would never prescribe them for chronic low back pain, even after exhaustive evaluation and attempts at treatment. Concern about physical dependence was identified as one of the most important barriers to the use of opioids for chronic pain.[26] Another survey of physician attitudes toward opioid use for chronic pain found that 35 percent of general practitioners and 23 percent of physicians with a defined interest in palliative care would never use opioids for noncancer pain, even when the pain was described as severe.[27]

This study has several limitations that warrant comment. First, the survey was based on subject self-report and therefore was dependent on subject recall. Second, our sample comprised subjects who were being seen at a pain clinic and who were receiving opioids for their pain. It is probable that patients who are receiving care outside a pain clinic are less likely to receive opioids for their pain and may therefore have a considerably different pain experience than subjects in our survey. As noted previously, many physicians who are not pain specialists may be reluctant to prescribe opioids, even for patients with severe pain. Indeed, a recent cross-sectional analysis of more than 25,000 patients with spine disorders showed that only 3.4 percent of patients with spine disorders at 23 specialty spine care centers across the United States were recommended, prescribed, or continued on opioid therapy.[28] These limitations notwithstanding, the results of this study suggest that BTP is an important clinical occurrence in patients with chronic back pain.

While pharmacologic management of cancer-related pain has improved considerably over the past 20 years, management of chronic noncancer pain remains a challenge. For noncancer pain management to achieve the same level of success as management of cancer-related pain, the clinical phenomena of specific types of pain must be understood. This article represents an important first step in understanding the prevalence and characteristics of BTP in patients with chronic back pain. Additional, well-controlled studies are needed to more fully elucidate the phenomenon of BTP in chronic pain not associated with cancer, including its impact on patients' lives and the safety and efficacy of various treatment approaches such as rapid-onset, short-duration opioids.

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ORIGINAL ARTICLE

Increasing prevalence of prescription opiate misuse over time among rural probationers

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ABSTRACT

Prescription opiate misuse is a major public health issue, especially in rural areas. The purpose of this analysis was to examine trends in prescription opiate misuse over time in a cohort of community-based rural probationers. Participants (N = 800), recruited over a four-year period, were divided into cohorts according to the year in which they were interviewed. Prescription opiate misuse increased significantly between 2001 and 2004 ($p < 0.001$). After adjustment for changes in demographic characteristics of the cohorts, misuse of prescription opiates was still significantly greater in 2004 compared with 2001. These data suggest changes in drug use patterns among community-based rural probationers from street to prescription drugs. Implications of the findings are discussed.

Key words: opiate misuse, prescription opiates, recreational drugs, rural communities, probationers

INTRODUCTION

Nonmedical use and misuse of prescription opiates has emerged as a major public health problem in recent years.[1] Prescription opiates are second only to marijuana in terms of the number of users who meet abuse or dependence criteria, and the incidence of nonmedical prescription opiate use has increased four-fold since 1980.[2,3] Particularly noteworthy is the intense media coverage that has surrounded OxyContin and reports of dependence, overdose, and diversion related to that substance.[4,5] In addition, government and media reports have indicated that prescription opiate misuse is at epidemic levels in the rural Appalachian regions of Kentucky, Virginia, and West Virginia.[6,7] In fact, in the most recent National Survey on Drug Use and Health, Kentucky ranked first in the number of nonmedical users of prescription opiates ages 12 and older.[8] However, few clinical or epidemiologic data have appeared in the scientific literature characterizing the epidemic. Further, it is unknown whether the prevalence of prescription opiate misuse continues to increase or has leveled off.

More than 4 million Americans are on probation; these individuals make up the largest segment of the criminal justice population, which includes those in prison and on parole.[9] In addition to criminal involvement, probationers are more likely to be drug dependent than members of the general population[10]; however, there is a dearth of literature on drug use by rural probationers. In one of the few published studies, Oser and colleagues[11] noted that drug use was highly prevalent among probationers in Appalachian Kentucky. This is noteworthy, given the subjects were recruited into the study based on their status as probationers, not drug users.

This analysis examined misuse of prescription opiates over time in successive cohorts of community-based rural probationers recruited for participation in a randomized intervention. The purpose of this study was to determine whether changes in misuse of prescription opiates suggested an isolated phenomenon or a secular change from predominantly illicit to prescription drug misuse.

METHODS

Subjects were participants in a National Institute on Drug Abuse (NIDA)–funded study of a brief, randomized HIV intervention for rural probationers. Eligible participants were males and females over the age of 18 who resided in one of 30 target rural or Appalachian Kentucky counties. Participants were eligible regardless of their drug use history, although it should be noted that these probationers were at high risk for drug use/abuse.

A total of 800 rural felony probationers were recruited over a four-year period (2001 to 2004). Study methods are described in greater detail elsewhere.[11] Briefly, after consenting to participation, subjects filled out an interviewer-administered questionnaire that ascertained data pertaining to demographics, drug use, criminal history, and healthcare utilization; the questionnaire was followed

Table 1. Demographic characteristics and drug use among probationers by year								
	2001 Cohort n = 120		2002 Cohort n = 159		2003 Cohort n = 267		2004 Cohort n = 254	
Age, median (IQR) (years)	32.3 (25 to 42.1)		33.2 (25.1 to 41.1)		31.6 (24.7 to 39.7)		32.7 (25.9 to 41.1)	
Education, median (IQR) (years)	11 (8.25 to 12)		11 (9 to 12)		11 (11 to 12)*		11 (9 to 12)	
	n	percent	n	percent	n	percent	n	percent
Male	85	70.8	112	70.4	185	69.3	150	59.1*
Caucasian	107	89.2	153	96.2*	253	94.8	248	97.6**
Married	40	33.3	51	32.1	90	33.7	77	30.4
Recent drug use[1]								
Prescription opiates	32	26.7	40	25.2	106	39.7*	112	44.1**
Benzodiazepines	37	30.8	39	24.5	110	41.2	98	38.6
Cocaine	38	31.7	31	19.5*	85	31.8	68	26.8
Heroin	1	0.8	2	1.3	7	2.6	4	1.6
Marijuana	63	52.5	72	45.3	153	57.3	139	54.7

[1] In the three months prior to most current arrest; * $p < 0.05$ compared to 2001; ** $p < 0.01$ compared to 2001;
IQR = interquartile ratio.

by the HIV-risk-reduction intervention. HIV serostatus was assessed using OraSure (Bethlehem, PA), and pre- and post-test counseling was conducted in accordance with Centers for Disease Control and Prevention standards two weeks post-baseline.[8] Participants randomized to the study condition received an enhanced HIV intervention, while those randomized to the control condition received the NIDA Standard Intervention.[12] The study was approved by the institutional review board at the University of Kentucky.

Participants were recruited from rural probation offices in 30 rural or Appalachian counties encompassing two probation districts. While all of the sample counties are below the US poverty level, 19 of the 30 (63 percent) were classified as "distressed" by the Appalachian Regional Commission (ARC), indicating that the three-year unemployment and poverty rates for the county are at least 150 percent of the US average, and the per capita market income is 67 percent or less of the US average. The other 11 counties were considered to be "at risk" by the ARC, which is defined as having unemployment and poverty rates 125 percent of the US average and a per capita market income of 67 percent or less of the US average.[13]

Variable definitions

The dependent variable of interest was recent prescription opiate misuse. Specifically, participants were asked, "About how often did you use other, nonprescribed opiates (not injected or heroin, but street methadone, morphine, Dilaudid, Darvon, Demerol, Percodan, codeine) in the last three months on the street before you were arrested on the charge that resulted in this probation?" A similar question was posited for OxyContin. These questions were combined to form a variable indicating any prescription opiate misuse in the three months before the participant's latest arrest. Independent variables selected a priori for their association with prescription opiate misuse were age, race, gender, education, employment, and other drug use.

Statistical analysis

Data are presented for the entire cohort and among the four yearly cohorts to examine changes in drug use over time. In order to examine these changes, the prevalence rates of opiate misuse in each cohort (2001 to 2004) were compared using Poisson regression. Rates for

Table 2. Correlates of prescription opiate misuse among 800 rural probationers					
	Prescription opiate misuse (n = 290)		**No prescription opiate misuse (n = 510)**		**p value**
Age, median (IQR) (years)	31.8 (25.3 to 40.2)		32.5 (25.1 to 40.8)		0.858
Education, median (IQR) (years)	11 (9 to 12)		11 (9 to 12)		0.647
	n	**percent**	**n**	**percent**	
Year					
2001	32	26.7	88	73.3	< 0.001
2002	40	25.2	119	74.8	
2003	106	39.7	161	60.3	
2004	112	44.1	142	55.9	
Male	187	64.5	345	67.6	0.392
Caucasian	281	96.9	480	94.1	0.213
Married	76	26.3	182	35.8	0.001
Recent drug use[1]					
Benzodiazepines	202	69.7	82	16.1	< 0.001
Cocaine	138	47.6	84	16.5	< 0.001
Heroin	11	3.8	3	0.6	0.001
Marijuana	217	74.8	210	41.2	< 0.001

[1] In the three months prior to most current arrest; IQR = interquartile ratio.

prescription opiate misuse were calculated by dividing the total number of participants who used prescription opiates by the total number of participants for a given year. Rates for 2002 through 2004 were then compared to the rate for 2001 (referent group). Unadjusted rate ratios and corresponding 95 percent confidence intervals (CI) were calculated using univariate Poisson regression in STATA, version 8.0 (College Station, TX). Demographic and other drug use characteristics were examined by year using contingency table analyses, t-tests, and the Wilcoxon rank-sum test, where appropriate, to determine whether increases in opiate misuse over time could be attributed to changes in the demographic makeup of the cohorts. Correlates of prescription opiate misuse were also examined using contingency table analyses, t-tests, and the Wilcoxon rank-sum test where appropriate. Finally, three multivariable Poisson regression models (2002 versus 2001, 2003 versus 2001, and 2004 versus 2001) were constructed in which rate ratios were adjusted for significant demographic and drug use characteristics, as well as for gender, age, and race. Aside from age, race, and gender, other demographic and drug use characteristics were only retained in the model if they were statistically significant ($p < 0.05$). The goodness of fit for each multivariable model was estimated using deviance statistics.[14]

Table 3. Independent correlates of prescription opiate misuse by year among rural probationers						
	2002 vs. 2001		2003 vs. 2001		2004 vs. 2001	
	Adjusted rate ratio	95 percent CI	Adjusted rate ratio	95 percent CI	Adjusted rate ratio	95 percent CI
Year	1.09	0.68 to 1.76	1.46	0.98 to 2.17	1.51	1.01 to 2.25*
Gender	0.97	0.59 to 1.60	0.98	0.68 to 1.42	1.22	0.87 to 1.71
Median age	0.81	0.51 to 1.30	0.85	0.60 to 1.19	0.95	0.68 to 1.33
Caucasian	2.56	0.62 to 10.57	1.30	0.61 to 2.80	3.02	0.74 to 12.34
Recent cocaine use[1]	3.84	2.39 to 6.17**				

[1] In the three months prior to most current arrest; * $p < 0.05$ compared to 2001; ** $p < 0.001$ compared to 2001.

RESULTS

The majority of participating probationers were male (66.5 percent) and Caucasian (95.1 percent), and the median age was 32.3 years (interquartile range: 25.2 to 40.5). As seen in Table 1, significantly fewer minority probationers participated in the latter years of the study. The proportion of female probationers was also greater in 2004 compared with 2001.

Examination of prescription opiate misuse in the three months prior to the baseline interview revealed that the proportion of probationers misusing prescription opiates rose significantly over time. In 2001 and 2002, approximately one-fourth of the participants reported prescription opiate misuse. By 2004, the proportion of probationers indicating recent opiate misuse was 44.1 percent ($p < 0.001$). Looking at individual years, compared with 2001, rate ratios (RR) for prescription opiate misuse were significantly greater in 2003 (unadjusted [U] RR: 1.49; 95 percent CI: 1.00 to 2.21) and 2004 (URR: 1.65; 95 percent CI: 1.11 to 2.45).

Table 2 shows the differences in sociodemographic and drug use characteristics in prescription opiate misusers versus nonusers. Examination of these factors reveals that in addition to there being a greater proportion of prescription opiate users in 2003 and 2004, prescription opiate misusers were more likely to be married ($p = 0.001$). Also, probationers who reported using prescription opiates were significantly more likely to report having used benzodiazepines, cocaine, and marijuana in the three months prior to their latest arrest. While a greater proportion of respondents reported using heroin, it should be noted that the overall prevalence of heroin use was quite small (3.8 percent among prescription opiate users and 0.6 percent among those not using prescription opiates).

As seen in Table 3, the independent correlates of prescription opiate use differed in 2002, 2003, and 2004 when compared with 2001. In the earlier cohort (2002), recent cocaine use was significantly associated with prescription opiate use after adjustment for year, gender, median age, and race. In 2003, when covariates were added to the multivariable model, year was no longer significant at the $p < 0.05$ level. However, those probationers interviewed in 2004 were significantly more likely to report prescription opiate use, even after adjustment for salient demographic characteristics (adjusted odds ratio: 1.51; 95 percent CI: 1.01 to 2.25). Deviance statistics indicated a good fit ($p > 0.05$) for each of the multivariable models.

DISCUSSION

In this analysis of prescription drug misuse among felony probationers over time, the prevalence of opiate misuse rose considerably as each succeeding cohort entered the study. However, no clear pattern emerged that could explain these increases. Although there were changes in the demographic makeup of the sample (namely more females and Caucasians in the latter years of the study), these changes were not associated with prescription opiate misuse in the multivariable models. While the prevalence of prescription opiate misuse has increased steadily in the general population over the last 20 years,[15] to our knowledge this is the first community-based study examining changes in misuse over time.

Further, national data do not show the rapid increase that was demonstrated in the current analysis.

What the data did show was that those who misused prescription opiates were more drug involved, suggesting that diverted prescription opiates and benzodiazepines are readily available "on the street" in rural and Appalachian Kentucky counties. Also, as the prevalence of prescription opiate use increased over time, the prevalence of other drug use, including of cocaine and marijuana, remained the same or even decreased, while prescription benzodiazepine use, like opiate use, increased. Even after adjusting for salient demographic and drug use characteristics, the rate of prescription opiate misuse was significantly greater in 2004 when compared with 2001, indicating a shift in drug use patterns among rural probationers from illicit to prescription drugs.

Increased availability of prescription opiates may have contributed to the escalating prevalence of misuse over time. Havens and colleagues[16] reported that rates of OxyContin prescription claims in the Medicaid claims for distressed Appalachian Kentucky significantly increased between 1998 and 2002, which suggests the potential for diversion. Further, National Drug Intelligence Center reports indicate that heroin, which is highly prevalent in urban settings, is not readily available in rural settings like Appalachia.[17] The current study supports these findings, as less than 5 percent of respondents reported recent heroin use.

There were several limitations for the current analysis and overall study. A limitation of the current analysis was that there was no measure of chronic pain. Perhaps the increasing rates of prescription opiate misuse could be associated with an increase in the prevalence of chronic pain in this cohort of rural probationers. However, while there was no direct measure of pain, data on the disability status of the respondents were available, and as the prevalence of prescription opiate use rose, the number of subjects reporting being on disability decreased. Another limitation of both the current analysis and overall study is that the findings are not generalizable to all rural people; although this was a community-based study, the study sample is only representative of one segment of the criminal justice system. Finally, all findings were based on self-reported data. However, it has been shown that self-reported drug use is both a reliable and valid measure of actual drug use.[18,19]

Despite these limitations, our findings provide further support that Appalachian Kentucky may be an epicenter of a prescription opiate epidemic. The high prevalence of prescription opiate misuse also has implications for treatment; simply put, there is a lack of viable substance abuse treatment options in most rural areas, including Appalachia. Finally, it appears that additional population-based studies of prescription opiate misuse in rural areas are warranted.

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CASE STUDY

Using methadone to treat opioid-induced hyperalgesia and refractory pain

David J. Axelrod, MD, JD
Barbara Reville, MS, CRNP

ABSTRACT

A patient was treated for several years with high doses of opioids for malignant pain. During a recent hospitalization, the patient's pain remained uncontrolled despite escalating doses of various opioids. We suspected that this patient suffered from the clinical phenomenon of opioid-induced hyperalgesia (OIH). The patient was then rotated from her other opioids to methadone, and her pain was adequately controlled within several days. Methadone, because of its NMDA antagonist properties, offers an effective treatment for OIH. The use of methadone for analgesia is complex and should be undertaken only by practitioners who have appropriate experience.

Key words: opioid-induced hyperalgesia, methadone, opioid rotation, opioid tolerance

INTRODUCTION

Opioids are well established as effective and safe for treating acute and chronic malignant and nonmalignant pain.[1-7] There is no absolute ceiling on opioid dose. Authorities report prolonged and effective analgesia for up to six years while using as much as 195 mg of morphine or the equivalent.[1] If a patient's pain remains uncontrolled, it is reasonable to increase the opioid dose until adequate analgesia is achieved, as long as the side effects are tolerable. As practitioners grow more comfortable with the use of high doses of opioids for the treatment of pain, an increasing number of patients, such as the patient described in this case report, will undergo such therapy for extended periods of time.

Tolerance and dependence are predictable results of long-term opioid use. However, a growing body of clinical and laboratory evidence demonstrates that the use of opioids may lead to another problem—the clinical phenomenon of opioid-induced hyperalgesia (OIH).[8-13] In OIH, opioids intended to abolish pain paradoxically lead to increased pain, particularly during rapid opioid escalation.[14] The mechanism for this hyperalgesia is poorly understood.

This case report describes a patient with suspected OIH whose pain was eventually controlled through an opioid rotation to methadone.

CASE REPORT

The patient was a 45-year-old Jamaican woman diagnosed with multiple myeloma in 2005 after presenting with back pain. Her treatment included chemotherapy, in both 2005 and 2006, and, most recently, radiation therapy to her lumbar spine. On Day 30 of a recent admission for an autologous stem cell transplantation, the palliative care service was consulted for assistance with pain management, which had been an ongoing problem during the hospitalization. The patient described pain in her lower spine with radiating numbness from her back to both thighs and calves. She also described numbness and "tingling pain" in both feet, with particular pain in the soles. Pain severity was rated as 10/10 most of the time. She described herself as "suffering" with the pain since her diagnosis, with little relief from a variety of pain medicines, including opioids such as morphine and oxycodone at increasing doses and adjuvant medications.

Imaging studies revealed multiple skeletal metastases, most significantly the complete loss of height of the fourth lumbar vertebral body, with left-sided bony retropulsion; mild disc herniation at L3-L4; and numerous lytic metastases along the lumbar spine, right femur, sacrum, and occipital regions. There was no evidence of cord compression. Physical examination was unremarkable.

Analgesic medications included gabapentin 1,200 mg every eight hours, five 100 µg transdermal fentanyl patches every 72 hours, hydromorphone 25 mg/h via IV infusion, and lorazepam 1 to 2 mg orally as needed for muscular discomfort.

We decided to rotate the patient from IV hydromorphone to methadone. After discontinuing the hydromorphone, the patient was started on methadone 60 mg every six hours by mouth. Hydromorphone at a dose of 8 mg IV bolus was available for breakthrough pain as needed.

Within 48 hours, the patient experienced significant improvement, with pain severity scores dropping to 6/10 and no signs of excessive sedation. Some nausea and vomiting were noted, so an oral antiemetic was given 30 minutes prior to methadone administration. At this point, the patient was weaned off of the transdermal fentanyl. After removal of the fentanyl patches, we waited an additional 12 hours before increasing methadone to a dose of 95 mg every six hours. For breakthrough pain, methadone 5 to 10 mg was available in lieu of hydromorphone.

By Day 6 on methadone, the patient felt remarkable improvement and rarely requested medication for breakthrough pain, though a premethadone antiemetic was still required to control nausea. Although there were no signs of sedation, the methadone dose interval was decreased to every eight hours based on the potential for drug accumulation. The patient was followed for an additional 48 hours, and no change was noted in her status. At discharge on Day 8 of methadone treatment, the dose was further tapered to 80 mg every eight hours, and the patient was told to follow up with the pain service within one week. The patient was extremely satisfied and felt adequate pain control for the first time in months.

DISCUSSION

In situations where pain is refractory to high doses of opioids, a common strategy is to rotate to a different opioid.[15] With OIH, methadone may be the optimal medication for opioid rotation. The advantages for methadone in treating OIH include its incomplete cross-tolerance with opioid receptors and its action as an NMDA receptor antagonist.[13]

We believed the patient suffered from chronic malignant pain that was complicated by extreme opioid tolerance, refractory pain, and OIH. The patient had been treated with opioids continuously for two years and continued to experience 10/10 pain despite treatment with escalating doses of transdermal fentanyl and parenteral hydromorphone, as well as adjuvant pain medications. We implemented the rotation to methadone by first calculating the parenteral hydromorphone to an equianalgesic dose of oral morphine. As the oral morphine-equivalent daily dose exceeded 12 g, we used a conversion ratio of 20:1 when converting to methadone.[16]

Converting other opioids to methadone is complex. When converting from high doses of opioids, lower conversion ratios of methadone are advised. In this case, a conversion rate of approximately 20:1 of morphine equivalents to methadone was sufficient to achieve adequate pain control. Methadone should be used cautiously, and only by practitioners who are experienced with the drug. Methadone has a long half-life—up to 190 hours—and therefore oral methadone dosage should not be increased more frequently than every four days.[17]

At high doses, methadone has been associated with Torsades de Pointes syndrome. Therefore, when treating with high doses of methadone an EKG should be obtained at dosing changes to monitor the Q-T interval. Despite these cautions, with the growing recognition of OIH and refractory pain uncontrolled by opioids, methadone may become an increasingly utilized and necessary option for chronic pain.

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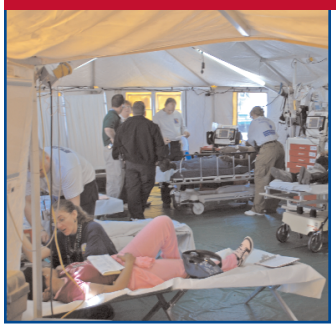

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