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A medical journal for proper and adequate use

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

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

Books—

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

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

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LABOPHARM AND PURDUE PARTNER ON ONCE-DAILY TRAMADOL

A definitive licensing and distribution agreement has been made between Labopharm Inc. and Purdue Pharma LP for the once-daily formulation of tramadol. Labopharm is actively seeking commercialization of the analgesic, and has completed two Phase III clinical studies in the United States, with a third already in progress. It is anticipated that a New Drug Application will be submitted to the US Food and Drug Administration before the end of 2005. Tramadol is currently available in the United States only in immediate-release form, which requires four to six doses per day for analgesic maintenance. Labopharm is based in Quebec, Canada; Purdue is based in Stamford, Connecticut. (Source: Purdue Pharma press release, August 15, 2005.)

NEW STUDY RESULTS FOR EXTENDED-RELEASE OXYMORPHONE

In a Phase III trial conducted under the special protocol assessment process of the US Food and Drug Administration (FDA), extended-release oxymorphone (Endo Pharmaceuticals, Chadds Ford, PA) was shown to make a statistically significant ($p < 0.0001$) difference in pain scores, as compared with placebo. The trial, lasting 12 weeks, involved 205 opioid-naïve patients with moderate to severe low back pain.

Extended-release oxymorphone was initially approved by the FDA on October 20, 2003. However, the FDA made the approval with the condition that Endo provide additional clarification and information, in addition to a trial confirming the safety and efficacy of the product beyond what had already been demonstrated. This supplemental study will be part of the response submitted to the FDA by Endo, anticipated to be finished in early 2006. (Source: Endo Pharmaceuticals press release, August 22, 2005.)

ONLINE PHARMACY OWNER INDICTED

Christopher William Smith, 25, owner and operator of Xpress Pharmacy Direct, was arrested at his home in Prior Lake, MN this week. Dr. Philip Mach, of Franklin Park, NJ, and Bruce Jordan Lieberman, 45, of Farmingdale, NY, were also charged in a multiple-count federal indictment. The indictment features more than a dozen charges related to the operation of Smith's online business. Smith was ordered held without bond; his attorney, Joe Friedberg, would not comment.

The grand jury alleged that Smith provided prescription drugs without verifying customer prescriptions. Orders were obtained through spam e-mails, Internet sites, and telemarketing. Smith is considered one of the world's worst spammers, according to the Spamhaus Project, an international antispam organization based in the United Kingdom.

The indictment includes counts of conspiracy to dispense controlled substances, wire fraud, money laundering, distribution of controlled substances, and introducing of misbranded drugs into interstate commerce. It also claims that from March 2004 to May 2005, Xpress Pharmacy Direct generated sales of more than $20 million from medications containing hydrocodone. In May 2005, a federal judge shut down the business and appointed a receiver to take control of the assets. Federal authorities seized $1.8 million in luxury cars, two homes, and $1.3 million in cash.

Prosecutors allege that Smith had Dr. Mach issue approximately 72,000 prescriptions from July 2004 to about May 2005. Dr. Mach is registered to practice medicine in New Jersey, but allegedly wrote prescriptions for patients throughout the United States without having any contact with them or their primary care physicians.

The US Attorney's Office said that Mach was represented by Bruce Levy of New Jersey. A call to his office was not immediately returned.

Smith's former accountant, Bruce Lieberman, was accused of helping Smith hide the origin of money earned from the prescription drug business. He also allegedly helped Smith process credit cards. Marvin Zevin, Lieberman's attorney, declined to comment until his client had made his first court appearance. (Source: *Houston Chronicle*, August 25, 2005.)

THE BRAIN AND PLACEBO EFFECT

A new brain-imaging study published in the *Journal of Neuroscience* suggests that just thinking you are receiving treatment is enough to make you feel better. This phenomenon, known as the placebo effect, involves release of endorphins, the body's natural painkillers.

Previous studies showed general changes in brain activity associated with the placebo effect by using functional magnetic resonance imaging, and scientists therefore

hypothesized that the brain's opioid system was involved. The new study uses positron emission tomography (PET) brain scans, and the researchers were able to focus on a specific type of brain receptor and track its response to a placebo.

The PET scans used by Jon-Kar Zubieta of the University of Michigan and his colleagues measured the activity of mu opioid receptors, an integral part of the body's natural painkilling system. The receptors help transmit pain signals from one nerve cell to the next. In a randomized trial, 14 healthy male volunteers were asked to undergo the slightly painful but harmless procedure of having salt water injected into their jaws. For the next 20 minutes, volunteers documented the intensity of participants' pain every 15 seconds and then summarized the experience afterward. Some subjects received analgesic medication, whereas others were told they were being given medication but actually received none.

All participants who were told to expect medicine but given the placebo instead showed an increase in the activity of their endorphin system. Four brain regions were involved, and activity in specific areas was also associated with the subjects' own descriptions of pain. As an example, dorsolateral prefrontal cortex activity correlated to the effectiveness the volunteers anticipated from the "pain medicine."

The results from this study offer the first direct evidence that endorphins can help explain the placebo effect. "This deals a serious blow to the idea that the placebo effect is a purely psychological, not physical, phenomenon," Zubieta says. "We were able to see that the endorphin system was activated in pain-related areas of the brain, and that activity increased when someone was told they were receiving a medicine to ease their pain." It was noted, however, that the results may not apply to all groups; further investigation is needed to determine variations based on age, gender, and confounding factors such as illness. (Source: *http://www.scientificamerican.com*, August 24, 2005.)

HIGH RISK IN ULTRA-RAPID DETOXIFICATION

Online advertisements for pain-free anesthesia-based withdrawal from heroin and prescription painkillers are misleading and the actual technique is life threatening, according to a study appearing in the August 24, 2005, issue of the *Journal of the American Medical Association.*

The study of 106 patients, the most rigorous to date on the method, showed that patient withdrawal was as severe as those of addicts undergoing various other detoxification approaches. It was not pain free, and had no distinct advantage over other methods.

"Anyone who tells you it's painless can only honestly be referring to the period the person is under anesthesia," said coauthor Dr. Eric Collins of Columbia University Medical Center.

Study participants, all addicted to heroin, were divided into three treatment groups. Those receiving ultra-rapid detoxification were anesthetized for approximately four hours while receiving a large dose of a drug that blocks the brain's opioid receptors. The anesthesia is meant to mask the symptoms that would normally occur in an awake patient.

Patients still underwent withdrawal on awakening, despite being given additional medications for withdrawal symptoms that included anxiety, insomnia, achy muscles and joints, diarrhea, and vomiting. In addition, 80 percent of the anesthesia patients dropped out of followup treatment, a rate slightly higher than for another method in the study.

Since its introduction approximately 15 years ago, ultra-rapid detoxification has been linked with several deaths. In one case, New Jersey regulators fined and gave two-year license suspensions to two doctors practicing the method, although the doctors were cleared of negligence in seven deaths.

"Some doctors have put their financial interests way ahead of the well-being of their patients," said Dr. Thomas Kosten, professor of psychiatry at Yale University School of Medicine. He recommends maintenance with methadone or buprenorphine, instead of detoxification, for narcotics addiction. Methadone and buprenorphine create physical dependence themselves, however, and must be tapered gradually to avoid withdrawal or else continued indefinitely.

Some people choose detoxification because they do not want to exchange one drug for another, said Jake Epperly, who runs ultra-rapid detoxification programs in Chicago and Los Angeles. His company, Midwest Rapid Opiate Detoxification Specialists, treats approximately 250 addicts annually at $9,200 each.

"We've had no problems," Epperly said, adding that the study mentioned here used a different ultra-rapid method than the one in his programs.

The American Society of Addiction Medicine's policy statement on ultra-rapid detoxification says the method should be paired with counseling services and should be done only by trained staff with access to emergency medical equipment. In addition, patients should be informed of risks and benefits of the method compared with other options. (Source: Associated Press, August 24, 2005.)

METHYLNALTREXONE AND OPIOID-INDUCED CONSTIPATION

Progenics Pharmaceuticals, Inc., has announced additional positive data from a previously completed Phase III clinical trial of methylnaltrexone (MNTX) for the treatment of opioid-induced constipation in patients with advanced medical illness. Final data analysis of the MNTX 301 study showed significant improvements in measures

of constipation distress, bowel movement difficulty, and consistency, and global impressions of clinical change. No increases occurred in pain scores or opioid withdrawal symptoms in any treatment group. At both doses of MNTX that were tested, all prospectively defined secondary endpoints exhibited statistically significant differences compared to placebo. The findings will be presented at the International Association for the Study of Pain, 11th World Congress on Pain in Sydney, Australia.

In March 2005, Progenics announced positive top-line results from the MNTX 301 study. The primary efficacy endpoint, laxation within four hours, was highly statistically significant at both MNTX doses that were tested. In addition, statistically significant results were reported for both MNTX doses for two secondary endpoints, laxation within 24 hours and median time to laxation. In the study, 154 patients were randomized to receive one of three blinded single doses of study medication: placebo, MNTX 0.15 mg per kg, or MNTX 0.30 mg per kg. The MNTX doses were generally well tolerated in patients with advanced medical illness. In addition, there were no meaningful changes in pain levels or opioid withdrawal symptoms at four or 24 hours after double-blind dosing in any treatment group.

MNTX represents a broad treatment platform, and Progenics has ongoing clinical programs using three dosage forms. Subcutaneous MNTX is the subject of a second Phase III clinical trial (MNTX 302) in opioid-induced constipation in patients with advanced medical illness. Intravenous MNTX has successfully completed a Phase II trial for treatment of postoperative bowel dysfunction. Finally, oral MNTX has successfully completed two Phase I studies in healthy volunteers. (Source: Progenics Web site, *http://www.progenics.com*, August 22, 2005.)

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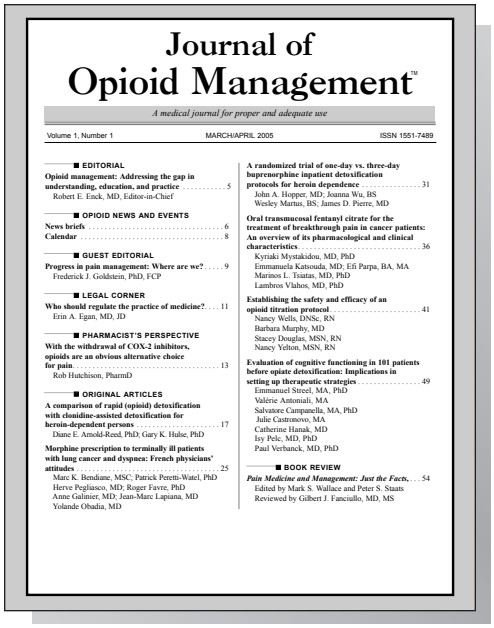

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NOTE! The current FDA and DEA focus on curbing opioid abuse makes this journal a *must read* for all healthcare providers including primary care and palliative care physicians, oncologists, pharmacists, hospices and palliation centers. Because there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

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Taking back your turf: Understanding the role of law in medical decision making in opioid management (Part II—Putting legal/regulatory materials to work for you)

Jennifer Bolen, JD

In Part I of this series, I discussed the basic role of the law in the decision-making process for opioid management. I set out three basic rules: 1) read and learn applicable federal and state legal/regulatory materials on using controlled substances to treat pain, 2) stay current on accepted clinical standards of care, and 3) use a compliance program to minimize the potential for abuse and diversion of controlled substances. Here in Part II, I focus on the third rule and offer a few suggestions on developing and maintaining a compliance program. I also discuss using language from legal/regulatory materials in your practice forms in a manner that, once again, allows you to "take back your turf" and prescribe opioids without fear of legal/regulatory sanction (see Disclaimer). Take a minute to review the self-audit questions that follow and see where you stand on your knowledge and use of legal/regulatory matters in your daily practice. More "yes" answers indicate better knowledge of key compliance and documentation issues. More "no" and "I don't know" answers indicate that more work should be done to minimize potential legal/regulatory compliance problems in your practice.

SELF–AUDIT QUESTIONS[1]

1. Do you live in a state with an Intractable Pain Treatment Act and/or guidelines, position statements, or regulations on using controlled substances to treat pain?

   If your answer is yes, have you read and educated your staff on these materials?

2. Have you compared your office forms with your state's legal/regulatory materials on prescribing controlled substances to treat pain?

3. Do you use these forms consistently, are they drafted in relatively simple language, and are the terms and words you use internally consistent?

   If your answer is yes, do you modify your forms as needed to stay current with the law and accepted medical practice?

   If your answer is still yes, do you leave that modification to someone else in your practice, or do you take an active role in the process to ensure compliance?

4. Do you know the key elements of medical record documentation when it comes to prescribing controlled substances for the treatment of pain?

   If your answer is yes, list them here as a reminder for the rest of this self-audit.

USING CONTROLLED SUBSTANCES TO TREAT PAIN: KEY PRESCRIBING GUIDELINES

It is not practical to discuss each state's legal/regulatory materials and documentation requirements in this article. Moreover, some states do not have legal/regulatory materials on this subject matter, the absence of which may actually promote abuse and diversion of controlled substances and leave providers subject to the whim of federal and state authorities, not to mention hurt patients who have a legitimate medical need for this type of medication. Consequently, I use the Federation of State Medical Boards' Model Policy for the Use of Controlled Substances for the Treatment of Pain (May 2004)[2] when discussing the key elements and documentation areas for guidelines on using controlled substances to treat pain.[3]

The Model Policy contains seven key compliance and documentation elements on the use of controlled substances for the treatment of pain.[4] When comparing the Model Policy with your state's materials on the use of controlled substances for the treatment of pain, look for differences in directive language, such as "shall" versus "should" or "must" versus "may." Directive language

gives you a good idea where the state draws its boundaries relative to controlled-substance prescribing and key documentation requirements and what it expects of you to keep your license and controlled drug registration.

The seven elements from the Model Policy are as follows:

1. History and physical evaluation
2. Treatment plan
3. Informed consent and treatment agreement
4. Periodic review
5. Consultations (and referrals)
6. Medical records
7. Compliance with controlled substance laws and regulations

As with most state legal/regulatory materials, including guidelines and position statements, key elements like those set forth here come with basic instructions. Using a checklist format from my review of the Model Policy, here are the basic instructions for the seven Model Policy elements. You might consider using this to compare the Model Policy with a self-constructed checklist of your state's materials. By doing so, you will have a very complete list to use when you examine your current compliance and risk management status.

History and physical evaluation

Physicians:

- Must evaluate the patient's medical history and perform a physical examination and document these efforts.
- Should document the nature and intensity of the patient's pain.
- Should document the patient's current and past treatments for pain.[5]
- Should document underlying or coexisting diseases or conditions.
- Should document the effect of the pain on the patient's physical and psychosocial function.
- Should document the patient's history of substance abuse (including alcohol).
- Should document the presence of one or more recognized medical indications for the use of a controlled substance.

Based on my review of licensing board and law enforcement investigations on controlled-substance prescribing, I have a few of my own recommendations[6] to add to this element of the Model Policy:

- Physicians should verify the patient's self-report of medication usage with prior providers and should attempt to do so before prescribing more than a couple of days' worth of that same medication to a new patient.
- Physicians should talk to the patient about his/her reluctance to try a different medication or combination of medications and document their efforts in the patient's medical record. Sometimes the reluctance stems from a fear of addiction or simply the process of "change" in general. Other times, the reluctance stems from an abuse and/or diversion problem. In either case, the physician's role is to determine how the patient's reluctance plays into his/her medical history and the development of the treatment plan.
- Physicians should review all documentation from prior prescribing healthcare providers and talk to that provider about the patient's case. Of course, this raises Health Insurance Portability and Accountability Act (HIPAA) issues, but your attorneys should be able to tell you that HIPAA permits communication between healthcare providers about the "treatment" of the patient, among other things such as "payment" and "healthcare options." This recommendation is especially important if a patient comes to you on high doses or combinations of controlled substances for pain management. This is just as important when a patient comes to you after having been discharged by the prior provider for whatever reason. Your job is to find out why the patient wants you to review his/her case, what the prior provider has documented about the patient's case, and what the answers to those questions mean in light of your obligations—ethical, legal/regulatory, and professional.
- Physicians may want to request an initial drug screen (blood or urine) from patients to verify patient self-reports and ensure proper patient assessment and selection in light of the obligation to follow accepted clinical care standards

and minimize the potential for abuse and diversion of controlled substances.

In saying all this, I by no means mean to suggest that you should not prescribe high doses or unusual combinations of controlled substances to your patients when there is a legitimate medical reason to do so within the usual course of professional practice. Instead, I want you to make sure you are evaluating and documenting the patient's case in the manner intended by your professional care standards, licensing board, and your Drug Enforcement Administration (DEA) registration obligations.

Treatment plan

Physicians:

- Should use a written treatment plan.[7]
- Should use the written treatment plan to state objectives that will be used to determine treatment success, such as pain relief and improved physical and psychosocial function.
- Should use the written treatment plan to indicate if any further diagnostic evaluations or other treatments are planned.

After treatment begins, physicians:

- Should adjust drug therapy to the individual medical needs of each patient.
- Should realize that other treatment modalities or a rehabilitation program may be necessary depending on the etiology of the pain and the extent to which the pain is associated with physical and psychosocial impairment.

One of the most problematic documentation issues I see in the audits I have done is the continued prescribing of the same controlled substances (sometimes even at higher levels) in the face of pain levels that are always the same, lack of improved functioning (on physical and psychosocial levels) according to treatment plan goals, and even in the face of aberrant drug-related behaviors. No doubt patients react differently to pain medications, but the measure of how each patient is doing must be guided by the treatment plan and the later element of "periodic review."

Informed consent and treatment agreements

Physicians:

- Should discuss the risks and benefits of the use of controlled substances with the patient, persons designated by the patient, or with the patient's surrogate or guardian if the patient is without medical decision-making capacity.
- Should require the patient to receive prescriptions from one physician and one pharmacy whenever possible.

If the patient is at high risk for medication abuse or has a history of substance abuse, physicians:

- Should consider the use of a written agreement between physician and patient outlining patient responsibilities, including
  - urine/serum medication levels screening when requested;
  - number and frequency of all prescription refills; and
  - reasons for which drug therapy may be discontinued (e.g., violation of agreement).

This element of the Model Policy reads as if informed consent and treatment agreements are the same. In pain policy, they typically are; in the law, however, they are not.[8] In fact, the Federation, and consequently many states and professional medical organizations, have blended informed consent elements with treatment agreement language, unintentionally resulting in the circulation of many "go-by" office forms that fall short of meeting legal/regulatory standards and fail to accurately document a physician's compliance in these areas. For these reasons, it is critical that you understand the legal/regulatory distinctions between informed consent and treatment agreements.

Informed consent relates to your ethical and, in most states, legal/regulatory obligation to discuss with the patient the risks, benefits, and treatment alternatives for use of controlled substances. Informed consent is not new. It is done when you perform procedures or surgery, and routinely as part of a general consent for treatment. While the Model Policy suggests that informed consent is a "should," you must remember that policy language is about "minimum standards," and this is not the same as a standard of care or obligation imposed on you by a state law or regulation/rule. Remember, too, that I view informed consent from a "more than minimum effort" perspective, because legal compliance and risk management incorporates a broader perspective—one that faces a different level of scrutiny when challenged, such as malpractice based on provider negligence. Thus, to ensure a solid compliance and risk management program, I

encourage you to adopt a must- or shall-do attitude and expand your use of the informed consent process when you recommend pain medications to your patients.[9] In saying this, I am primarily speaking to those of you located in states that use policy language similar to that of the Model Policy. However, some of you are located in states where a law or a regulation/rule requires you to use informed consent when you prescribe controlled substances. Make sure you understand your state's position here. In addition, do not forget to search your state for a general patient "bill of rights," as these bills often designate informed consent as a key issue in all aspects of healthcare. A good example of a state with these materials is California, which has not only an Intractable Pain Treatment Act and Patient Bill of Rights, but also an organization, funded by state agencies, that publishes a Patient Rights handbook that includes a discussion on informed consent.[10]

A *treatment agreement* is meant to be a boundary document—a form setting forth office policies and limits relating to controlled substances. Treatment agreements typically remain the same over the term of care with all patients and change only when office policies change.

Treatment agreement terms include those listed in Figure 1. Of course, you can modify treatment agreements to your specific patient population so it reflects what you do when you treat the patient, what you expect in return from the patient, and what you do to minimize the potential for abuse and diversion of controlled substances.

As the Model Policy states, treatment agreements are something a physician "should" consider when handling patients with a high risk for medication abuse, or one with a history of substance abuse. Although the Model Policy and many states say "should," this does not mean you cannot use a treatment agreement with every patient. If you want to read more about the distinctions between informed consent and treatment agreements and view sample forms, you may do so on my Web site.[11]

Periodic review

Physicians:

- Should periodically review the course of pain treatment and any new information about the etiology of the pain or the patient's state of health.
- Should remember that the continuation or modification of controlled substances for pain management therapy depends on your evaluation of progress toward treatment objectives.
- Should remember that satisfactory response to treatment may be indicated by the patient's decreased pain, increased level of function, or improved quality of life.
- Should monitor the patient for objective evidence of improved or diminished function.
- Should consider information from family members or other caregivers in determining the patient's response to treatment, subject to HIPAA considerations.

If the patient's progress is unsatisfactory, physicians:

- Should assess the appropriateness of continued use of the current treatment plan and consider the use of other therapeutic modalities.

In most states, licensing boards rightly give physicians discretion on the timing of periodic review based on the documented, individual circumstances of the patient's case. However, states like New Jersey[12] and Louisiana[13] have regulations that set boundaries on the physician's discretion, obligating the physician to see his/her chronic controlled substances users every 12 weeks at a minimum. Currently, because of the DEA's Interim Policy Statement of November 2004, it appears that federal law may impact the timing for patient followups, particularly when they involve the issuance of a Schedule II controlled substance. Some states, like California, have issued some guidance on this issue.[14] Check with your licensing board to see how it interprets the DEA's Interim Policy Statement regarding the issuance of multiple Schedule II prescriptions with "do not fill before" language on them in light of patient followup policies/regulations. You should also determine the appropriate followup period and criteria using current clinical care standards and document your reasons for the follow up period and criteria that you ultimately use.

Periodic review relates to patient monitoring and is a tough subject, because many patients are good and not a threat when it comes to handling controlled substances responsibly. You must remember, however, that when you use your DEA registration number, you do so under these conditions: 1) you will issue controlled-substance prescriptions for a legitimate medical purpose within the usual course of professional practice, and 2) you will minimize the potential for abuse and diversion of controlled substances. You must also consider the fact that the abuse and diversion of prescription controlled substances is a growing problem in the United States.

There are many ways to meet your periodic review obligations. Determine what your state says about the matter and decide how the language in your state's legal/regulatory materials can help you establish patient

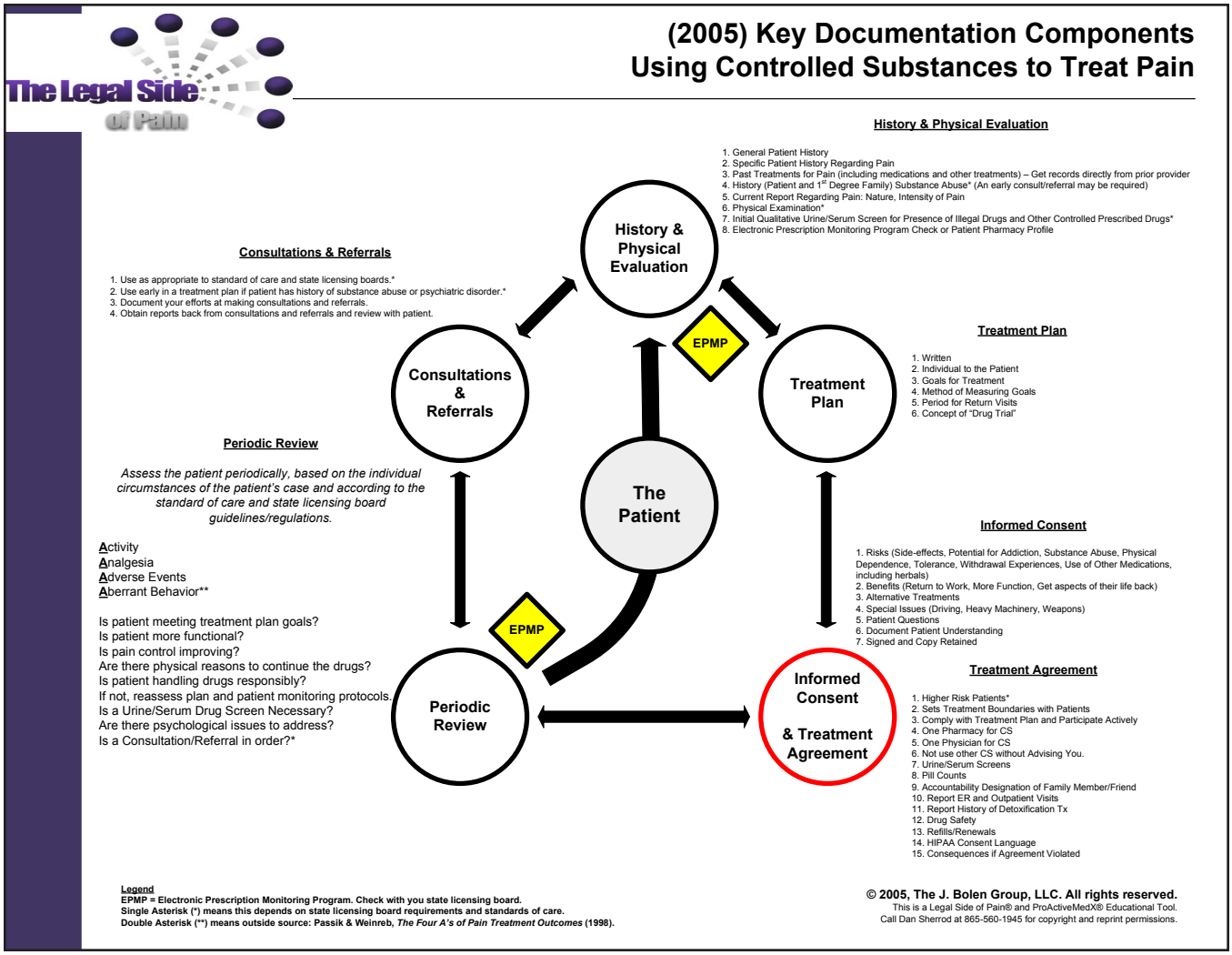

Figure 1.

monitoring forms and office policies.[15] You might also consider using language from these materials to advocate for your patients when a healthcare plan wants you to do something inconsistent with clinical care standards and/or the state's legal/regulatory materials. Figure 1 makes some suggestions about periodic review concerns, as does the work of Passik and Weinreb, titled *The Four A's of Pain Treatment Outcomes* (1998).

Consultations and referrals

Physicians:

- Should be willing to refer the patient as necessary for additional evaluation and treatment to achieve treatment objectives.
- Should give special attention to those patients with pain who are at risk for medication misuse, abuse, or diversion.

Remember, "the management of pain in patients with a history of substance abuse or with a comorbid psychiatric disorder may require extra care, monitoring, documentation and consultation with or referral to an expert in the management of such patients."[16] For this reason, and as a matter of smart compliance, I recommend you take an active role in obtaining documentation of all consultations and referrals directly from the healthcare provider. When you receive these items, review them and determine whether the results support the continuation of your current treatment plan or a change relating to both treatment in general and controlled substances specifically. After you make your decision, document your rationale, together with the corresponding consultation/referral documentation, in the patient's medical record.

Typical medical records required

Physicians:

- Should keep accurate and complete records to include
    - the medical history and physical examination,
    - diagnostic, therapeutic and laboratory results,
    - evaluations and consultations,
    - treatment objectives,
    - discussion of risks and benefits,
    - informed consent,
    - treatments,
    - medications (including date, type, dosage and quantity prescribed),
    - instructions and agreements, and
    - periodic reviews.
- Should keep records current and maintain them in an accessible manner so they are readily available for review.

This policy statement is simple in words, but often difficult in deed. Check your state materials to make sure you are keeping the appropriate records. Audit yourself periodically and get help if necessary. Finally, if you are registered with the DEA to dispense controlled substances from your practice, you must comply with additional federal and state law record-keeping requirements.

Compliance with controlled-substance laws and regulations

Physicians:

- Must be licensed in the state where you practice medicine.
- Must comply with applicable federal and state regulations governing the prescribing, dispensing, and administering of controlled substances.
- Should read the *Physician's Manual* of the DEA and (any relevant documents issued by the state medical board) for specific rules governing controlled substances as well as applicable state regulations.

It should be noted that the *Physician's Manual* is not available at this time because the DEA is revising it. However, the DEA has an excellent *Pharmacist's Manual*, which can be obtained on their Web site, free of charge.[17] I recommend that you or someone on your staff download a copy of this and read it. In doing so, you will have a better understanding of the DEA's role in monitoring the flow of controlled substances.

ADDITIONAL CONSIDERATIONS

The Model Policy contains several definitions relevant to your daily interactions with patients. As you read them, think about which of your office forms need these definitions and how you might incorporate them into patient educational materials. When you use the correct definitions of terms like addiction, physical dependence, and tolerance, even when your state does not, you will be giving your patients proper information and informed consent. You might also help a few understand that it is okay to use opioids and, assuming no history of chemical or substance abuse, dispel a few addiction myths. Here are the Federation's Model Policy terms and corresponding definitions:

Acute pain. The normal, predicted physiological response to a noxious chemical, thermal, or mechanical stimulus. It typically is associated with invasive procedures, trauma, and disease. It is also generally time limited.

Addiction. A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestation. It is characterized by behaviors that include the following: impaired control over drug use, craving, compulsive use, and continued use despite harm. Physical dependence and tolerance are normal physiological consequences of extended opioid therapy for pain and are not the same as addiction.

Chronic pain. A state in which pain persists beyond the usual course of an acute disease or healing of an injury, or that may or may not be associated with an acute or chronic pathologic process that causes continuous or intermittent pain over months or years.

Pain. An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

Physical dependence. A state of adaptation that is manifested by drug class-specific signs and symptoms that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Physical dependence, by itself, does not equate with addiction.

Pseudoaddiction. The iatrogenic syndrome resulting from the misinterpretation of relief-seeking behaviors as though they are drug-seeking behaviors that are commonly seen with addiction. The relief-seeking behaviors

resolve on institution of effective analgesic therapy.

Substance abuse. The use of any substance(s) for nontherapeutic purposes or use of medication for purposes other than those for which it is prescribed.

Tolerance. A physiologic state resulting from regular use of a drug in which an increased dosage is needed to produce a specific effect, or a reduced effect is observed with a constant dose over time. Tolerance may or may not be evident during opioid treatment and does not equate with addiction.

If your state's definitions are out of date, then encourage your licensing board to consider updating them. If your state uses definitions that appear to conflict with the Federation's definitions, then check with your licensing board and ask for clarification, probably best done through a professional medical organization. If all else fails, use your state's definition, but do not forget your ethical obligation to abide by accepted, current standards of care, which likely includes using appropriate and current definitions.

USING LEGAL/REGULATORY MATERIALS TO YOUR ADVANTAGE

Now that you have reviewed the Model Policy's key elements, go back and review your state materials with my comments in mind. When you do this, make notes on key legal/regulatory terms and make it a point to incorporate this language into your office forms. This sounds simple, but I have rarely audited a practice that did this before my teaching them why it is important and how to do it. When you use language from legal/regulatory materials in your practice forms and documentation practices, you signal that you know what the boundaries are and how to follow them. You can also do so without compromising patient care.

I do not believe the law is designed to prevent you from using controlled substances to treat pain. The law sets forth boundaries within which you must operate to preserve a medical license or DEA registration. As physicians, I want you to understand the legal/regulatory materials in your state and see how they actually protect those who prescribe within the state's legal/regulatory framework. Use key phrases from legal/regulatory materials in your office forms. Use these phrases when you write healthcare plans to explain your prescribing rationale. Use these phrases routinely and in connection with practices that meet or exceed accepted clinical care standards. When you do, you will have minimized the potential for abuse and diversion of controlled substances and the likelihood of any unfavorable legal/regulatory intrusion. None of this can stop the event of a board or DEA inquiry, but it can sure help determine the outcome—in your favor. Finally, it is important for you to know that thanks to the work of the Pain & Policy Studies Group at the University of Wisconsin Comprehensive Cancer Center and the Federation of State Medical Boards, many states continue to work to improve existing pain policy and, where possible, other state legal/regulatory materials.

CONCLUSION

There is no way that I can cover all aspects of the issues mentioned previously in the space allotted for this article. I intend to continue this series with a Part III, in which I will focus on handling common patient challenges, responding to healthcare plans that ask you to do things inconsistent with accepted clinical care standards and legal/regulatory materials, and discharging patients. For now, however, after reading this article you are in a good position to make legal/regulatory materials work for you and your patients. Do your homework and revise your office forms and policies as necessary. Finally, in your documentation efforts, remember that patients are individuals, and your medical records should reflect that you have treated them as such.

DISCLAIMER

I do not intend for this paper to serve as specific legal advice. Instead, this paper contains a general outline of legal/regulatory responsibilities and assumes that the clinician will only prescribe controlled substances for a legitimate medical purpose within the usual course of professional practice. If you have a specific legal question, make sure you get legal advice from an expert in this area.

Jennifer Bolen, JD, founder, The Legal Side of Pain®, Knoxville, Tennessee.

NOTES

1. I do not intend for this section to cover every question relevant to compliance for controlled-substance prescribing.
2. You may obtain a copy of the Model Policy on the Federation's Web site: *http://www.fsmb.org.*
3. To determine where your state stands, visit *http://www.fsmb.org.*
4. It is important to remember that as a "policy," the Federation's Model Policy does not have the force of law in a state unless the state incorporates the document into a licensing board regulation or rule. Likewise, a "policy" does not itself set a standard of care. Instead, a "policy" typically sets forth minimum standards of medical practice as defined by a state licensing board, meaning that you should follow them or have a good and well-documented reason for not doing so.
5. This is commonly referred to as "verification." A good way to do this is to get records directly from prior providers instead of simply relying on the patient's self-report or delivery of his/her own medical records.
6. Remember, these are only my recommendations based on my experience. Your state's position on these issues is in control. If you have a specific legal question in this area, make sure

to ask your attorney or expert counsel.

7. In some states this is a "must," and I believe personally that it is best to use a written treatment plan.

8. I am not attacking the Federation's efforts here. I was privileged to participate in the drafting of the Model Policy, and I think that the Federation's work product has had a very positive effect on furthering pain management policy in the United States. However, I also believe that it is important to emphasize the difference between pain policy and legal/regulatory standards, especially when it comes to educating physicians about compliance and risk-management issues. Not only do I look at documents like the Model Policy from the "how are we balancing pain care and legal/regulatory interests" perspective, but also from a "what can and does happen when legal and regulatory suits are filed in civil and criminal courts, or before licensing boards" perspective. I mean only for my comments here to help physicians think about the different approaches to these matters as they make decisions about their approaches to compliance and risk management.

9. I actually believe that informed consent is required any time you prescribe any medication to a patient. Take, for example, the anticoagulation drug, Coumadin. If you had to prescribe this to a patient, no doubt you would talk to the patient about the risks of not taking the drug at all, the risks of taking too much or too little, the risks of taking certain other medications in addition (e.g., aspirin), the effects of alcohol, etc. You would also discuss the benefits of using the drug, especially when the patient has a history of a Factor V Leiden mutation, as I do. And, finally, you would discuss the treatment alternatives to using Coumadin. I will discuss extended informed consent issues, including informed consent for off-label use of medications for pain management, in a future article.

10. As of August 22, 2005, the Web site for the Patient Rights handbook is *http://www.calpatientguide.org*. The American Medical Association Code of Ethics describes informed consent as a process, whereby the physician covers the elements described above with the patient and then allows the patient to ask him/her directly questions about these matters. If, at any time, your treatment recommendations involve the use of different drugs or drugs in off-label ways, then a new informed consent process is in order.

11. *http://www.legalsideofpain.com*.

12. New Jersey Administrative Code Title 13, Chapter 35, Subchapter 7, section 7.6, available online at: *http://www.state.nj.us/lps/ca/bme/statreg/bmeregulations2.doc*.

13. Louisiana Administrative Code Title 46, Vol. 45, Chapter 69, Subchapter B, Section B-6921, available online at: *http://www.lsbme.org/documents/laws_rules/rules/46V45069PrescriptionDispensationandAdministrationofMedicatio.pdf*.

14. In April 2005, the California Medical Board issued a statement about the DEA's Interim Policy Statement that suggested to some that the statement itself required physicians to see their patients every month, prior to issuing a new Schedule II prescription. In July 2005, the California Medical Board issued a "clarifying" statement about this matter, stating that the board did not mean to suggest that physicians must personally see their patients each month and referred CA physicians back to the CA guideline on using controlled substances to treat pain. To read these two items, go to the board's Web site at *http://www.medbdca.gov* and look under Controlled Substances in the April and July Action Reports.

15. Of course, doing everything I mention in this paper does not guarantee that you will be problem free when it comes to issues surrounding the abuse and diversion of controlled substances. Nonetheless, you will be able to show that you understand the legal/regulatory boundaries and use them to guide your documentation process.

16. Federation of State Medical Boards' Model Policy for the Use of Controlled Substances for the Treatment of Pain, May 2004.

17. To obtain the DEA's Pharmacist's Manual, go to *http://www.deadiversion.usdoj.gov* and click on "Publications" and then "Manuals."

Opioids: The role in headache pharmacotherapy

Rob Hutchison, PharmD

INTRODUCTION

Opioid pharmacotherapy in the treatment of headaches may be viewed from dichotomous perspectives. The most common clinical application of opioids is for acute, symptomatic rescue in migraine headache. The second, more controversial application, is their use in a daily scheduled regimen to remediate intractable chronic daily headaches (CDH). The goal of this article is to describe the diagnostic criteria, cautions, and/or outcome measures for these opioid treatment modalities.

OPIOIDS FOR ACUTE, SYMPTOMATIC HEADACHE RELIEF

Opioids for short-term, symptomatic rescue therapy for migraine should be used with caution and vigilant monitoring for potential medication overuse headache (MOH). Opioids are a risk factor for MOH and transformed migraine, and patients who overuse opioids have high headache relapse rates after initially successful withdrawal.[1-4] In June of 2005, the International Headache Society (IHS) redefined the diagnostic criteria for an opioid overuse headache as the following[5]:

- headache present ≥ 15 days/month;
- opioid intake ≥ 10 days/month on a regular basis for > three months;
- headache markedly worsened during opioid overuse; and
- headache resolves or reverts to its previous pattern within two months after discontinuation of opioid.

MOH is being recognized more often in headache, neurology, and primary care clinics, but is still frequently overlooked. A lack of awareness by the clinician and patient is the primary contributor to the development of MOH.

OPIOIDS FOR REFRACTORY CHRONIC DAILY HEADACHES

The use of daily scheduled opioids (DSO) in treatment of CDH is a complex and controversial pharmacotherapy approach. A long-term (≥ three years) structured DSO clinical headache program analyzed the effectiveness, prevalence of problematic drug behavior, and predictors of long-term benefit.[6] To be eligible for the program, the patient must have failed to improve with aggressive, comprehensive care (i.e., hospitalization, detoxification, aggressive pharmacotherapy, and behavioral management) or else had medical conditions in which standard therapy is contraindicated. The DSO treatment program consisted of frequent follow-up office visits at four- to eight-week intervals. Effectiveness of DSO was measured by the Severe Headache Index (SHI). The SHI formula is determined by multiplying the frequency times duration of severe headaches per week.

Only 26 percent of patients benefited from DSO (defined as 50 percent improvement over baseline). The age, gender, and diagnosis of anxiety or depression had no association with success rate of DSO. Response to DSO during the first month was a strong predictor (67 percent) of which patients would continually benefit at the end of three years. The use of DSO was not associated with a decrease in the number of other prophylactic or abortive medications. All patients signed an agreement on entry to the clinical headache program clearly stating an understanding that the dose would not be self-modified, opioids would be prescribed from one headache center only, and opioids would be dispensed from one pharmacy only. Of the patients who stayed in the DSO program for at least three years, 50 percent committed one or more agreement violations.

SUMMARY

Optimal acute opioid management involves a continual awareness of the potential for development of MOH. Both the clinician and patient should be aware of the IHS MOH diagnostic criteria. Prophylactic medications should be initiated for patients having two

headache days per week. Reduction in headache risk factors should include behavioral modification approaches to headache control earlier in the natural history of migraine.

DSO therapy may provide significant long-term relief to a small percentage of patients suffering from intractable chronic daily headaches. A one-month DSO trial may provide a fair indication whether long-term DSO will be of benefit in the otherwise intractable cases.

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ORIGINAL ARTICLE

Opioid contract use is associated with physician training level and practice specialty

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ABSTRACT

Opioid contracts are widely used to manage opioid prescribing in the treatment of pain conditions, but they are not well studied. A notable gap in our knowledge of opioid contracts involves the factors that determine their use. As an initial inquiry, this study evaluated the responses of a Web-based survey of trainees and faculty in an academic medical training context to determine correlates of opioid contract use.

All paid faculty, third- and fourth-year medical students, and residents in The University of Oklahoma College of Medicine were invited via email to participate in a Web-based survey of their attitudes and prescribing practices related to controlled prescription drugs. Respondents composing a subgroup of those who replied to the survey were identified by their prescription of opioids and by their designation that pain was the most likely diagnosis for which they would prescribe a controlled drug. Chi-square analysis was used to determine any correlation between contract use and respondents' demographic variables and categorical survey responses. Analysis of variance was used to determine any correlation between contract use and survey responses that involved continuous variables.

Our results showed that opioid contract use was significantly associated with resident status, primary care specialty, participant estimation of alcohol and illicit drug abuse by patients, and the participant's assessment of the risks in general of prescribing controlled drugs. A majority of contract users reported that the use of this tool increased their sense of mastery and comfort with prescribing controlled drugs.

The factors associated with opioid contract use found in this study suggest there are significant prescriber-specific determinants of the use of the tool, including training level, medical specialty, and risk appraisals. Opioid contracts' effects on mastery and comfort of the physician with prescribing opioids suggest that they may play an important role in facilitating appropriate pain management with opioids. Further study is needed to elucidate environmental and patient-specific factors that may influence opioid contract use.

Key words: opioids, contract use, prescription, academic medicine

INTRODUCTION

The management of pain with opioid analgesics holds the promise of significantly alleviating suffering and improving quality of life for patients. However, opioid prescribing is attended by a number of concerns that may significantly impact clinical practice. To name a few, these issues include practitioner concerns regarding rising prescription drug abuse, fear of causing addiction, and uneasiness with regulatory oversight of and potential censure for opioid prescribing practices.[1,2] Mindful of these issues, the thoughtful practitioner may be understandably hesitant to prescribe opioids, or he or she may prescribe opioids at suboptimal levels for appropriate pain control. On a broader public health level, such prescriber concerns may significantly contribute to inadequate medical treatment of pain.[3]

A widely used but poorly studied method for addressing prescriber concerns is the opioid contract.[4] Recent research has begun to characterize these tools. Fishman and colleagues analyzed opioid contracts from 39 academic medical centers and reported their most common features.[5] These features included common goals of facilitating informed consent, improving patient care through education, and fostering patient-prescriber agreement on the treatment. Also noted were frequently identified statements outlining terms of treatment, proscribed behaviors, and conditions for patient dismissal. Other research has attempted to identify the prevalence of opioid contract use, with one study reporting the use of opioid contracts by 42 percent of practitioners in a primary care setting.[6] Others have identified potential problems

with opioid contracts, including the risk of stigmatizing patients with substance abuse, patients' perceiving the contracts as punitive, and practitioners' equating a signed contract with adequate patient compliance.[5] Differences of opinion among medical professionals exist about the appropriateness of using opioid contracts, but, generally, such contracts are considered useful tools in managing opioid prescriptions for some patients.[7] In recognition of such, the American Academy of Pain Medicine published a sample agreement form.[8]

Despite the growing knowledge about opioid contracts, important questions about these tools remain. Such questions include whether opioid contracts are efficacious for the purposes for which they are used. Additionally, it is not known whether they are binding or whether they may increase prescriber liability risk.[5] Furthermore, it is not clear what factors might be associated with their use. In the face of a lack of demonstrated efficacy of opioid contracts, answering this latter question may be particularly important because it may help uncover the determinants of contract use. Knowledge from this avenue of inquiry may be useful for a number of reasons. Determining the factors associated with the use of opioid contracts may assist with providing a descriptive context for their use. Such topography could help frame or guide future research aimed at studying opioid contracts. Understanding factors linked to opioid contract use may also broaden understanding of physician behavior, particularly regarding concerns, beliefs, and motivations about opioid prescribing. Such knowledge may hold the potential ultimately to enhance physicians' clinical performance and care of patients. As a preliminary investigation, this study examined the prevalence and determinants of opioid contract use among medical faculty and trainees in a large university-based health system.

METHODS

A Web-based survey assessing medical trainee and faculty attitudes and prescribing practices regarding controlled drugs, including opioids, was administered to third- and fourth-year medical students, residents, and paid physician faculty at The University of Oklahoma College of Medicine. The participants were practicing or training in various locations across Oklahoma, representing a broad range of primary care and specialty groups. Their patients were drawn from rural and urban areas and included those who were insured and uninsured. Participation was solicited via email, and participants submitted their responses anonymously through a link to a Web-page survey. Demographic information gathered included age cohort (five-year increments); gender; and training status as medical student, resident (with specialty training program), or faculty (with specialty). The study population was acquired by focusing analysis on participants whose responses indicated a co-occurrence of opioid prescription and the diagnosis of pain as the most likely condition for which they prescribe controlled drugs. The chi-square test was used to perform several analyses. These included examining the relations between contract use and factors such as participant's demographic variables and their assessment of the risks of controlled drugs. Analysis of variance was used to examine the relationship between contract use and participants' estimation of their patients' abuse of alcohol and illicit drugs and of prescription drugs. Age and gender were examined as possible confounders by examining their relationship to contract use via chi-square analysis. Finally, contract users' evaluation of the effects of contract use on their sense of mastery and comfort level with prescribing opioids was assessed. A p value of 0.05 was considered statistically significant.

RESULTS

A total of 196 surveys were submitted by participants. Of this number, 52.6 percent were faculty, 26.0 percent were medical students, and 21.4 percent were residents. Representation by 10-year incremented age cohorts was 37.8 percent for ages 20 to 30 years, 24 percent for ages 31 to 40 years, 17.3 percent for ages 41 to 50 years, 16.8 percent for ages 51 to 60 years, and 4 percent for ages 61 to 70 years. One hundred ninety-three participants identified their gender. Of this group, 54.4 percent were male. Ninety-eight faculty members identified their practice specialty. Of this group, 30.6 percent were medical specialists, 52.0 percent were primary care physicians (e.g., general internal medicine, pediatrics, family medicine), and 17.3 percent were surgical specialists. The total number of paid faculty, residents, and third- and fourth-year medical students in The University of Oklahoma College of Medicine at the time of the survey was 1,419. The survey response rate was calculated to be 14 percent.

The study population was composed of those participants who indicated they prescribed opioids (directly or under supervision) and were most likely to prescribe controlled drugs for a pain diagnosis in their practice or training activities. This group numbered 122 (Figure 1). All of these participants identified their gender and training status. Of this group, 59 faculty identified their practice specialty. Age distribution was similar to that of the total survey response group.

There were no statistically significant differences in gender distribution across training status groups ($n = 122$, chi-square = 4.832, $df = 2$, $p = 0.09$) or across faculty specialty groups ($n = 59$, chi-square = 0.514, $df = 2$, $p = 0.77$). Faculty specialty groups did not differ from each other in age distribution ($n = 59$, chi-square = 14.841, $df = 16$, $p = 0.54$); however, training status groups differed significantly by age ($n = 122$, chi-square = 104.083, $df = 18$, $p < 0.0001$). The

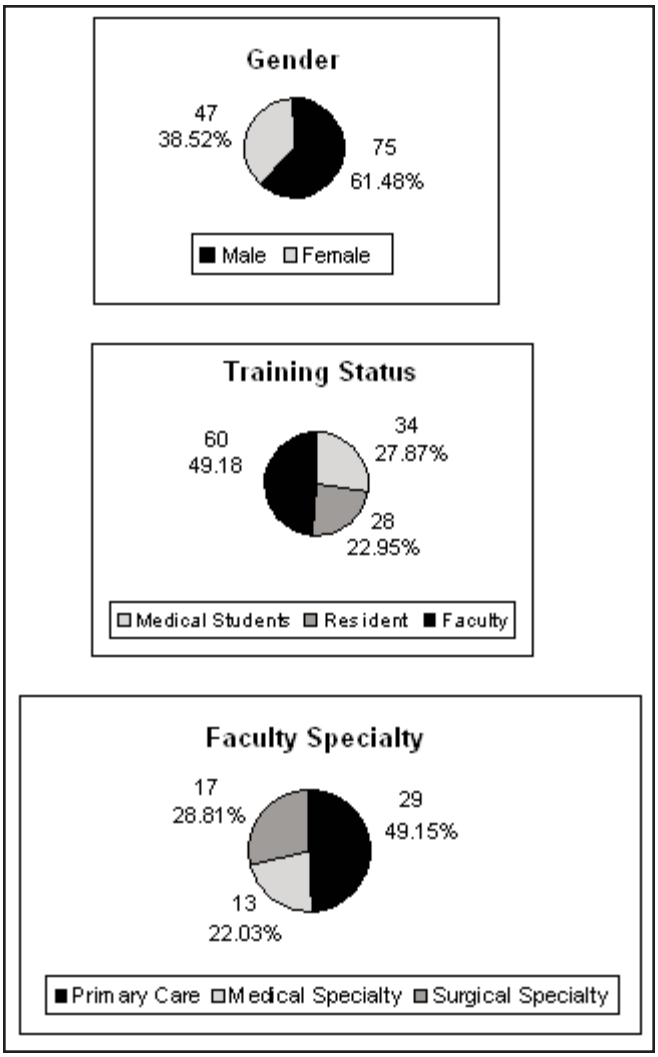

Figure 1. Participant distribution by gender, training status, and faculty specialty.

majorities of students (86.1 percent) and residents (60.7 percent) were at or below 30 years of age, whereas most faculty (75.0 percent) were 36 to 60 years of age.

Regarding contract use, residents were more likely than medical students or faculty to use a drug contract ($n = 122$, chi-square = 6.125, $df = 2$, $p = 0.047$) (Figure 2). Among faculty members, primary care physicians were more likely than medical or surgical specialists to use a drug contract ($n = 59$, chi-square = 25.9, $df = 2$, $p < 0.0001$) (Figure 3). Users and nonusers of drug contracts significantly differed in how they assessed the risks and benefits of prescribing controlled drugs ($n = 121$, chi-square = 6.843, $df = 2$, $p = 0.033$). Contract users were more likely to view risks and benefits as varying significantly with each case, whereas contract nonusers were more likely to endorse the idea that benefits outweigh risks in most cases. Also bearing on the use of contracts is the participant's assessment of the prevalence of alcohol and drug abuse among his or her patients. Contract users tended to estimate such rates as higher than contract nonusers ($n = 105$, $p < 0.001$) (Figure 4). Interestingly, participants' estimation of the prevalence of their patients' abuse of prescription drugs did not correlate with contract use ($n = 106$, $p = 0.201$).

Because age and gender were considered as possible confounders, their relationship to contract use was examined. There were no correlations between opioid contract use and participant age ($n = 122$, chi-square = 9.928, $df = 9$, $p = 0.36$) or gender ($n = 122$, chi-square = 0.744, $df = 1$, $p = 0.39$).

The majority of contract users indicated that contract use improved their sense of mastery (54 percent) and comfort level (64 percent) with prescribing controlled drugs.

DISCUSSION

This preliminary study demonstrates several findings that may shed light on the determinants of opioid contract use. Within the context of an academic medical training system, residents are more likely than faculty or medical students to use opioid contracts. One explanation may be a cohort effect. Residents as a group may be more familiar with opioid contracts as a recent tool in pain management. Resident use of contracts may also be influenced by their training demands. Resident physicians carry a relatively large load of patient care responsibility and are still honing their clinical skills. They may find the use of such tools especially helpful in managing opioid prescribing in their frequently complex patients. In contrast, faculty members, who have acquired clinical competency and experienced judgment, may not feel they require the structured assistance an opioid contract provides. Faculty members typically apply expert skills in an automatic fashion that may negate the perceived need for a contract. Medical students, who typically function at a more basic skill level, may not be aware of the availability of or need for contracts. Furthermore, because medical students do not have prescriptive authority, they are somewhat removed from managing opioid analgesics and may have little motivation for using opioid contracts. Finally, the lack of correlation between age and contract use would contend with arguments that residents' preferential contract use owed to age effects.

Another major finding of this study is that, among faculty, opioid contracts are more likely to be used by primary care physicians than by medical or surgical specialists. A possible explanation is that primary care faculty members are more likely than specialists to provide continuous care over time for patients with pain conditions. Longer-term care may promote a more in-depth doctor-patient relationship, with all of its attendant rewards and potential complications. In this context, opioid contract use may facilitate positive and predictable doctor-patient

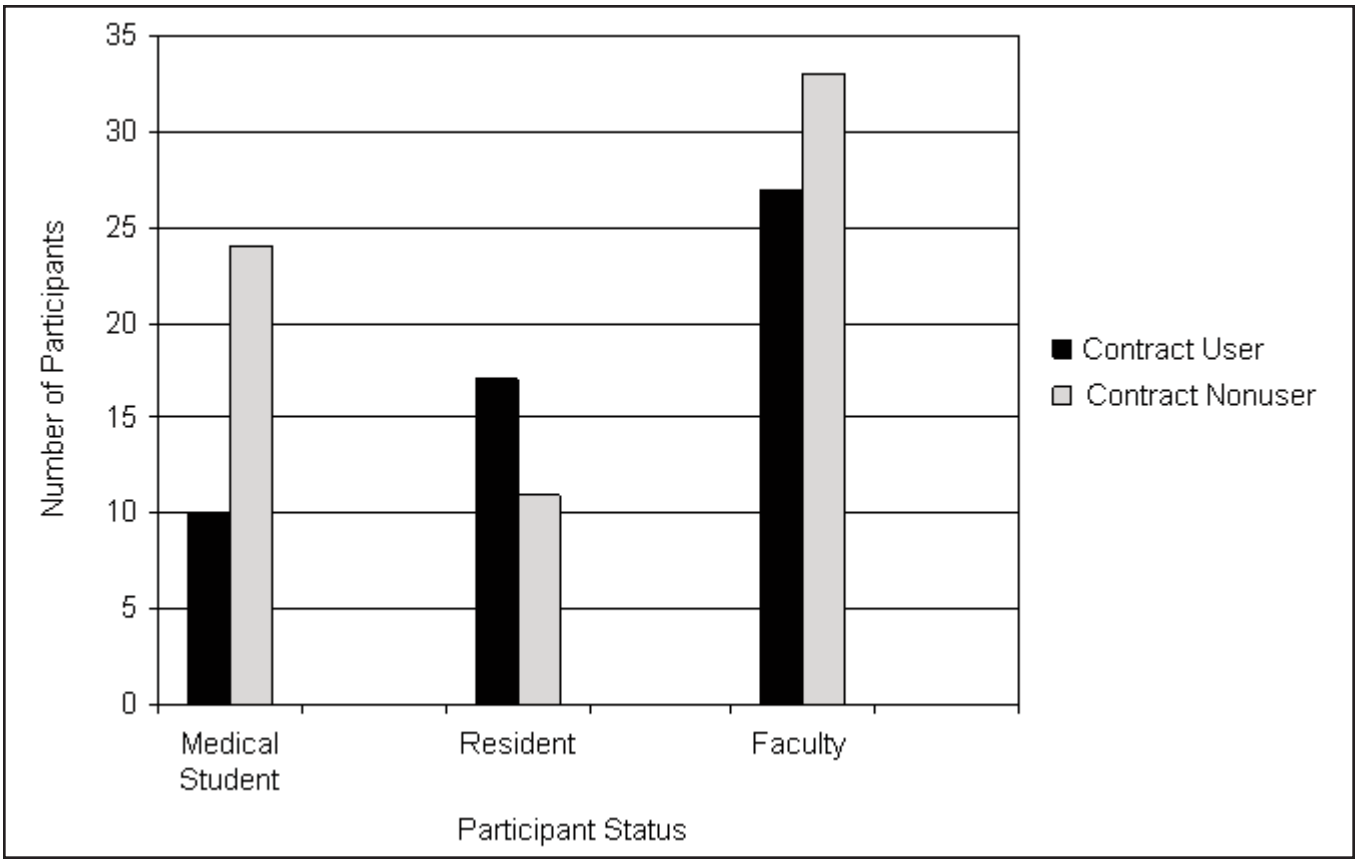

Figure 2. Opioid contract use among medical students, residents, and faculty.

interactions, potentially smoothing the sometimes-difficult course of treating pain.

How a prescriber assesses the risk/benefit ratio of prescribing opioid analgesics is correlated with opioid contract use. Specifically, contract users are more likely to see risks and benefits as varying significantly case by case. By comparison, contract nonusers tend to view benefits as outweighing risks in most cases. This finding suggests that contract use may be influenced by a physician's priority of awareness of the risks of opioids vis-à-vis their benefits. Indeed, contracts may be viewed by users as an important method of containing risks while retaining benefits. As such, contracts may improve physicians' comfort levels with prescribing opioids, thus supporting and promoting opioid prescribing. This idea is supported by our finding that a majority of contract users reported contract use as having improved their comfort with and mastery of prescribing opioids. This implies that opioid contracts have a significant role to play in overcoming physician concerns that may prevent appropriate opioid prescribing for pain.

Related to the previously described evaluation of risk is prescriber estimation of patient abuse of alcohol, illicit drugs, and prescription drugs. This study found that contract users estimated significantly higher rates of alcohol and illicit drug abuse in their patients than contract nonusers. This finding further supports the idea that contract use may be motivated, at least in part, by prescriber awareness and concerns regarding addiction as a potential problem among patients. As previously noted, contract use may be perceived as helping the prescriber manage addiction risks as they may arise in the context of opioid prescribing. However, there were no significant differences in how contract users and nonusers estimated the prevalence of their patients' abuse of prescription drugs. This would seem to contend with the view of the opioid contract as a risk management tool. A potential explanation may, however, lie with differences in how physicians anticipate their patients will use opioids based on their estimation of those patients' abuse of alcohol/illicit drugs and prescription drugs. Physicians may perceive that alcohol and illicit drug abuse raises the risk of abuse of opioids relatively higher than it does their similar estimate of risk regarding prescribed drugs. In other words, the perceived likelihood of alcohol and illicit drug abuse may promote opioid contract use more effectively than the perceived likelihood of prescription drug abuse. There is some support in the literature for these perceptions. For example, some studies report that among chronic pain patients, the risk of drug abuse, dependence, and addiction is comparable to that in the general population.[9,10] However, studies examining the

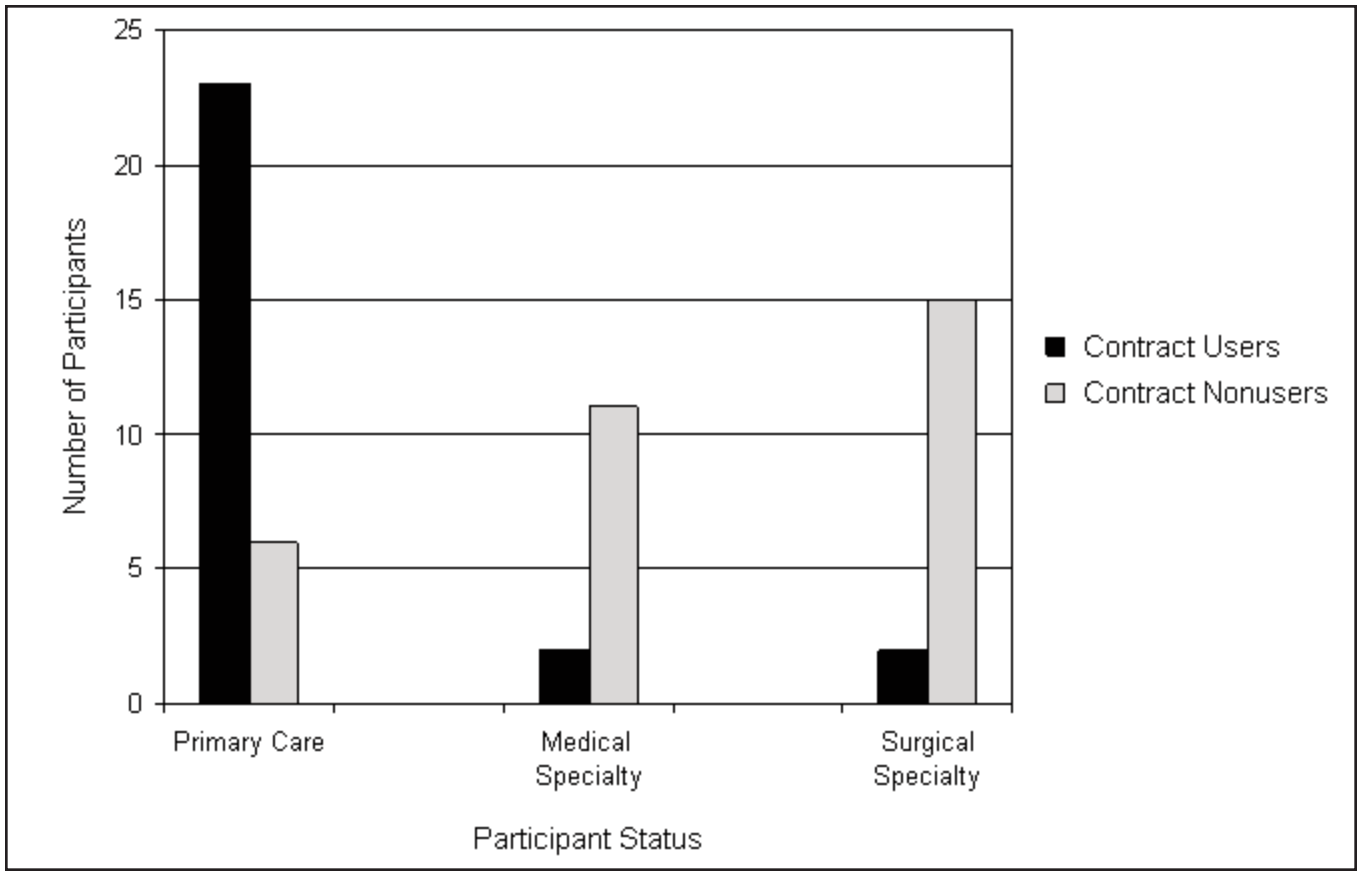

Figure 3. Opioid contract use differences by faculty.

comorbidities associated with alcohol disorders have indeed demonstrated an increased risk of other drug dependencies.[11]

The limitations of this study center on sampling issues. This study solicited participants voluntarily through university email using preconfigured contact lists. Because the sampling method was not random, self-selection bias is a possibility. Nonresponders might have declined participation for a number of reasons. They might have been uninterested, felt they were too busy to participate, or might have been excluded from participating by email filters or by nonuse of their university email. On the basis of these selection factors, however, it is unclear that nonresponders would necessarily differ significantly from responders in how they answered the survey questions. It is possible that some faculty elected not to participate owing to the nature of their academic pursuits; that is, these faculty members may not be involved in direct patient care, and may devote their time exclusively to administrative and/or research pursuits. This assumption is reasonable and has the net effects of reducing the pool of potential survey participants and raising the survey response rate.

The survey response rate was calculated to be 14 percent; however, for reasons noted previously, the actual response rate is likely higher. We might reasonably estimate our response rate to actually be in the 20 to 30 percent range. Two sources suggest that this response rate is within the range of expectation. One source reports that samples drawn from a consumer email database of those opting in for contact will have response rates in the 20 to 50 percent range.[12] Another source, a review of studies using email surveys, reports an average response rate of 31 percent.[13] Thus, the response rate to our survey appears comparable to those of other online surveys. Nevertheless, it is probably wise to interpret the findings of this study with caution. Given the response rate to the survey, the results may not provide a complete picture of

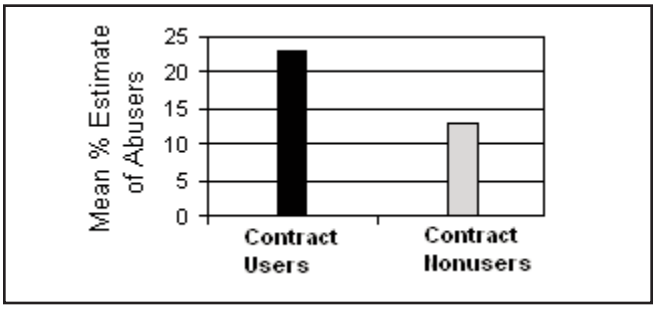

Figure 4. Opioid contract use as a function of the estimated percentage of patients abusing alcohol and drugs.

the university-based population it samples. Additionally, the study findings may not be generalizable to nonacademic practice settings.

Despite its limitations, this study offers important insights into the possible determinants of opioid contract use. Our findings suggest that these include the physician prescriber's level of training, assessment of alcohol and illicit drug abuse prevalence among one's patients, and practice specialty. Furthermore, opioid contract use may be reinforced by the increased sense of mastery and comfort they provide to users and might be viewed as vehicles for promoting and sustaining appropriate pain management with opioids. These findings suggest the use of opioid contracts is a complex behavior influenced by several prescriber-specific factors. Our study focused on prescriber-specific factors, but patient-specific or environmental factors, such as patient age or regulatory oversight of opioid prescribing, may also influence opioid contract use. In addition to replicating and expanding on the findings of this study, further research might examine these external factors. Ultimately, a better understanding of physician behaviors involved in prescribing opioids may allow for improved physician confidence in and understanding of opioid prescribing, potentially enhancing the management of pain.

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ORIGINAL ARTICLE

Factors associated with willingness to participate in a heroin prescription program among injection drug users

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ABSTRACT

Randomized controlled trials of prescription heroin have shown success in reducing drug-related harm among chronic opiate injection drug users (IDUs) in several European nations. We sought to explore willingness to participate in a heroin trial among a well-characterized North American cohort of IDUs, and therefore performed analyses of factors associated with willingness to participate in a prescription heroin trial among IDUs enrolled in the Vancouver Injecting Drug Users Study (VIDUS). Of 410 current heroin injectors followed between May and November 2002, injecting heroin frequently (more than once daily) [odds ratio (OR) 1.33; 95 percent confidence interval (CI) 1.06 to 1.69] and being enrolled in methadone maintenance therapy (MMT; OR 1.33, 95 percent CI 1.06 to 1.69) were associated with willingness to participate in a trial. In subanalyses, statistical associations with willingness to participate in a trial among current MMT users were frequent injection of heroin (OR 2.12, CI 1.16 to 3.88) and speedballs (OR 2.57, CI 1.02 to 6.48), frequent crack cocaine use (OR 1.84, CI 1.11 to 3.06), lending of syringes (OR 3.22, CI 1.08 to 9.65), and requiring help to inject (OR 1.83, CI 1.01 to 3.33). Among IDUs, willingness to enroll in a heroin prescription program was associated with high-intensity heroin injection and high-risk behaviors and was particularly prevalent among individuals who have been unable to significantly reduce their injection drug use on MMT alone. These findings indicate that a clinical trial of prescribed heroin should be able to enroll an appropriate sample of drug users and properly assess the treatment potential of prescribed opiate pharmacotherapy.

Key words: prescription heroin, methadone maintenance therapy, injection drug use, treatment

INTRODUCTION

Clinical controlled trials of prescription heroin in Europe have shown success in reducing drug-related harm among chronic opiate injection drug users (IDUs) while showing no elevated health risks or evidence of having increased the number of IDUs.[1,2] The findings from these studies have prompted the expansion of existing heroin prescription programs and the addition of new trials.[3,4] Despite the rapid spread of human immunodeficiency virus (HIV) infection that has occurred in cities across North America, the effects of heroin prescription remain unknown in this setting.[5,6] However, Canadian investigators have developed a protocol to test the feasibility of a prescription heroin program in North America through the establishment of several clinical control trial sites in cities with a high prevalence of IDUs.[7] The Vancouver, British Columbia prescription heroin trial began in the spring of 2005.

Although heroin prescription programs are being considered in other settings, we are aware of no study investigating willingness among IDUs to enroll in such programs. We therefore undertook this study to investigate the acceptability of prescription heroin among a well-characterized cohort of IDUs at the Vancouver trial site.

METHODS AND MATERIALS

We investigated correlations with willingness to participate in a heroin prescription trial among IDUs enrolled in the Vancouver Injection Drug User Study (VIDUS), a prospective study of IDUs who have been recruited through self-referral and street outreach from Vancouver's Downtown Eastside since May 1996. To date, over 1,500 participants have been enrolled. The cohort has been described in detail previously.[5,8] Ethical

approval for the project was provided by the University of British Columbia's Ethics Committee on Human Experimentation.

The current analyses were restricted to VIDUS participants who were current heroin injectors at the time of interview and who were followed between May 2002 and November 2002 and replied to the following question asked of participants during this period: "If a structured prescription heroin program similar to methadone was available, would you use it?" We used contingency table analysis to compare sociodemographic and risk variables between participants who were willing and those unwilling to participate in a prescription heroin trial.

For the current analyses, variables of interest included baseline sociodemographics of gender and ethnicity (aboriginal vs. other), as well as continuous variables referring to the previous six months at the time of interview, including unstable housing, heroin, cocaine and speedball injection, crack cocaine smoking, sex-trade involvement, binge use of drugs, requiring help to inject, public injecting, and syringe borrowing and lending. To be consistent with our previous work, unstable housing was defined as living arrangements that included single-room occupancy hotels and homelessness, and sex-trade involvement was measured as having sexual partners with whom sex was traded for money, drugs, or shelter. "Borrowing" refers to the use of used syringes, and "lending" refers to lending used syringes. "Speedball" refers to a mixture of heroin and cocaine. Binge drug use is well understood by local IDUs and generally refers to compulsive high-intensity injection drug use that differs from normal patterns of consumption, often very frequent cocaine and/or polydrug injection for periods ranging from a few days to a few weeks. Requiring help with injecting is a common practice among many IDUs whereby others are relied on to inject the drugs due to collapsed veins and/or difficulty accessing veins. All continuous variables were elicited in reference to the six months preceding the interview.

RESULTS

Of 410 IDUs who met eligibility criteria, 256 (62 percent) reported willingness to participate in a prescription heroin program. Willingness was associated with sex-trade involvement (OR 1.88, 95 percent CI 1.08 to 3.27), frequent (more than once daily) heroin (OR 2.89, 95 percent CI 1.90 to 4.40) and speedball injection (OR 2.13, 95 percent CI 1.13 to 4.03), and current use of methadone maintenance therapy (MMT) (OR 1.77, 95 percent CI 1.18 to 2.65).

We were aware that a substantial proportion of opiate addicts in the cohort may have been excluded from the study because they were currently on MMT and not actively injecting heroin. We therefore performed subanalyses of the 301 individuals who were followed between May 2002 and November 2002 and who reported being currently on MMT. Willingness was associated with lending used syringes (OR 3.22, 95 percent CI 1.08 to 9.65), requiring help to inject (OR 1.83, 95 percent CI 1.01 to 3.33), and frequent heroin (OR 2.12, 95 percent CI 1.16 to 3.88), crack (OR 1.84, 95 percent CI 1.11 to 3.06), and speedball use (OR 2.57, 95 percent CI 1.02 to 6.48).

DISCUSSION

Vancouver, British Columbia, has been the site of an explosive outbreak of HIV infection among IDUs. To respond to the growing public health concerns in this population, MMT services have been revised and expanded in recent years to increase the availability of MMT to Vancouver-area IDUs. MMT in this setting is available free of charge, prescribed primarily by community physicians, and dispensed by community pharmacists. Average daily dosages range from 75 to 80 mg, and while efforts have been made to expand the program, waitlists still exist. Currently, there are no regulatory requirements to discharge MMT patients for infractions, including ongoing illicit drug use.[9]

Our finding of an association between current MMT users, ongoing heroin injection, and willingness to participate in a heroin trial suggests that MMT may not be a sufficient treatment for some heroin injectors and corroborates similar findings in other studies of IDUs.[1,10,11] Prescription heroin and heroin combined with MMT in other trial settings has been found to be more effective than MMT on its own in reducing continued frequent injection, as well as illegal activities and cocaine use.[1,12] The types of potential benefits that could occur in this high-risk population include a reduction in drug-related harm and blood-borne infections.

As would be expected, participants that were willing to participate in a heroin trial were those with uncontrolled addictions and who were injecting heroin and speedballs on a frequent basis, often despite the use of MMT. This finding underscores the fact that many IDUs, particularly high-intensity polydrug users, are willing to engage in therapeutic treatment programs to gain control over or change their addictive behavior. Sex-trade involvement, requiring help to inject, and frequent crack and speedball use in this setting have been associated with a number of high-risk practices, including syringe borrowing and lending.

In summary, willingness to enroll in a heroin prescription program was associated with high-intensity heroin and cocaine injection, sex-trade involvement, and use of MMT. Among individuals currently on MMT, willingness was associated with ongoing high-risk behaviors that have been associated with HIV incidence, criminal activity, and community harm. These findings provide evidence that the initiation of a heroin prescription trial may

be associated with substantial public health and community benefits and support the rationale for heroin prescription in Vancouver and potentially other settings in North America.

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ORIGINAL ARTICLE

Comparison of transdermal fentanyl with codeine/paracetamol, in combination with radiotherapy, for the management of metastatic bone pain

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ABSTRACT

Radiotherapy (R/T) is frequently used for palliative treatment of painful bone metastases; however, complete alleviation of pain is not always achieved. This study was designed to evaluate pain management outcomes and quality of life (QoL) measures in cancer patients with metastatic bone pain receiving a combination of R/T and either transdermal therapeutic fentanyl (TTS-F) patches or codeine/paracetamol.

A total of 460 palliative care patients with bone metastases who received R/T were enrolled in this prospective, open-label study. The patients were randomized to initially receive a total dose of 120 mg codeine/paracetamol per day or TTS-F patches releasing 25 μg fentanyl per hour. Pain measures were assessed on the basis of selected questions from the Greek-Brief Pain Inventory. Overall treatment satisfaction (scale, 1 to 4), QoL, and European Collaborative Oncology Group status were also recorded.

Among the 460 patients, 422 were eligible for evaluation. Pain measures in the TTS-F group demonstrated statistically significant improvements during the study that were superior to those in the codeine/paracetamol group ($p < 0.05$). Likewise, there was a significantly greater increase ($p < 0.05$) in the mean satisfaction score for patients in TTS-F group at every visit between baseline and month two. The vast majority (95.8 percent) of patients in the codeine/paracetamol group increased their medication dosage until the end of the study, whereas in the TTS-F group the respective percentage was only 6.1. Both treatments were generally well tolerated, with constipation as the most common side effect followed by sleep disturbances and nausea. The overall frequencies of side effects were higher in the codeine/paracetamol group.

The results therefore indicate that TTS-F offers more effective pain relief than codeine/paracetamol, in combination with R/T, in patients with metastatic bone pain, obtaining complete treatment satisfaction matched by improvements in their QoL.

Key words: bone metastases, pain, radiotherapy, fentanyl, codeine/paracetamol, palliation

INTRODUCTION

Moderate to severe pain is experienced by one-third of cancer patients receiving active therapy and by 60 to 90 percent of patients with advanced disease.[1,2] Bone pain is the most common type, and approximately 70 percent of patients with bone metastases experience pain at some point during the course of their disease. Advances in the diagnosis and treatment of cancer, coupled with advances in our understanding of anatomy, physiology, pharmacology, and pain perception, have led to improved care of the patient with metastatic bone pain.[3] Such patients are managed most effectively by a multidisciplinary approach with local radiotherapy (R/T) and the use of many analgesic agents, such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and biphosphonates, which provide additional benefit in the adjuvant setting. Moreover, the expertise of a wide range of healthcare professionals is of great significance in the management of pain attributable to bone metastases. Nevertheless, the ideal therapy for metastatic bone pain remains a subject of considerable debate among clinicians.

The transdermal therapeutic fentanyl system (TTS-F) (Duragesic, Janssen Pharmaceutical Products, LP, Titusville, NJ) has been used in the management of cancer

pain with promising results.[4,5] Open-label and prospective evaluations of efficacy, tolerability, and toxicity in cancer pain management have indicated that TTS-F is safe, with toxicities similar to those reported for other opioids. Constipation, nausea, and vomiting are the most common side effects.[6-11] Pain relief is rated as good by 49 to 82 percent of patients, and many as 63 percent of patients prefer TTS-F.[6,10] One large, randomized, open, two-period crossover study and a cross-sectional quality-of-life (QoL) study of TTS-F versus sustained-release oral morphine demonstrated more sustained pain relief and a lower frequency and severity of side effects, making TTS-F the preferred analgesic among participants.[12,13]

However, although the analgesic efficacy and tolerability of TTS-F has been established, until now there has been only one small study that demonstrated its efficacy and safety profile in combination with R/T in the management of metastatic bone pain.[14]

The present study was conducted to examine the efficacy and safety of TTS-F with that of codeine/paracetamol, in combination with R/T, in the palliative care setting in patients with metastatic bone pain. In addition, this study was designed to investigate pain management outcomes and QoL measures in these patients.

PATIENTS AND METHODS

From 1996 to 2003, a total of 460 palliative care patients with bone metastases experiencing moderate to severe chronic cancer pain were enrolled in this study. The local Ethics Committee approved the study, and each patient provided informed consent. The study was performed in accordance with the Helsinki Declaration of 1975, as revised in 1983, and according to European guidelines for good clinical practice.

Eligible patients were aged at least 18 years, able to communicate effectively with study personnel regarding the nature of their pain and their QoL, and adequate communication and cooperation could be had from the patient's family. Inclusion criteria also included histologically confirmed malignancy with bone metastases, chronic moderate to severe cancer pain requiring strong opioid analgesics, and patient informed consent. Bone metastases were confirmed from computed tomography, magnetic resonance imaging, simple x-rays, or bone scintigraphy. Exclusion criteria included a history of opioid abuse, contraindications to opioids, and opioid use outside of the designated treatment regimen. Patients with the following conditions were excluded: cardiac, respiratory, or mental dysfunction; hepatic insufficiency (aspartate aminotransferase, alanine aminotransferase > 200 U per L); and renal failure (creatinine > 2.5 mg per dL).

All participants underwent palliative radiotherapy and then were randomized to initially receive the TTS-F 25 μg per hour patch applied every 72 hours or codeine/paracetamol at a total dose of 120 mg per day. No significant difference was detected between the two groups for pain measurements at baseline, confirming the homogeneity between the two groups. This was the reason that in both groups, approximately equianalgesic doses were given. Medication doses could be escalated during the trial for sufficient relief of emerging pain. All patients had already received palliative radiotherapy at the site of their painful bony metastases in 10 daily fractions (total dose of 30 Gy, 3 Gy per fraction, five days a week) with one or two radiation fields, by linear accelerator or 60Co. All patients that were included in the study had moderate to severe bone pain refractory to common analgesics and were naïve to mild or strong opioids. The type of this pain, called "nociceptive," is perceived with evidence of neuroradiologic tissue damage.

Data were collected on diary cards at the following time points of the study: baseline; 72 hours; seven, 14, and 28 days; and two months. Only patients with complete data for all relevant time points were included in the final analysis. Standard information collected on the patient's diary card at every visit included QoL, Greek-Brief Pain Inventory (G-BPI), overall treatment satisfaction, European Collaborative Oncology Group (ECOG) status, side effects, and use of concomitant medications. At baseline, both demographic and clinical characteristics were obtained, including family and educational status. A detailed medical history was also obtained and a complete physical examination was performed for each patient. Additional data included cancer location(s); type and etiology of pain; use of concomitant analgesic medications (NSAIDs or SAIDs); type, frequency, and grade of any side effects (i.e., constipation, nausea, sleep disturbances, vomiting, rashes/pruritus and sweating); ECOG status (0 to 4), and concurrent use of adjuvant hormonal therapy. Side effects were graded according to the Common Toxicity Criterion.[15]

For QoL assessment, a Visual Analog Scale (VAS) from 0 to 10 was used [highest (0) to worst (10)]. Three questions contained within the G-BPI (5, 9i, and 9ii) were used as an assessment of the patient's pain index.[16] These scores are shown in Figure 1. The Brief Pain Inventory (BPI) is a reliable yet simple pain assessment tool, which has been translated into Greek and validated.[16] Patients were also asked to rate their treatment satisfaction during the study by using a self-assessment scale (1 to 4), with 1 corresponding to "not at all satisfied," 2 to "fairly satisfied," 3 to "satisfied," and 4 to "completely satisfied."[17,18] The increment of the dose was dependent on the patient's needs. When the self-assessment scale was 1 or 2 and their pain score was ≥ 3, the drug dose was increased.

Changes in measurable scores between the TTS-F and codeine/paracetamol groups and their potent correlations were assessed using the chi-square test and analysis

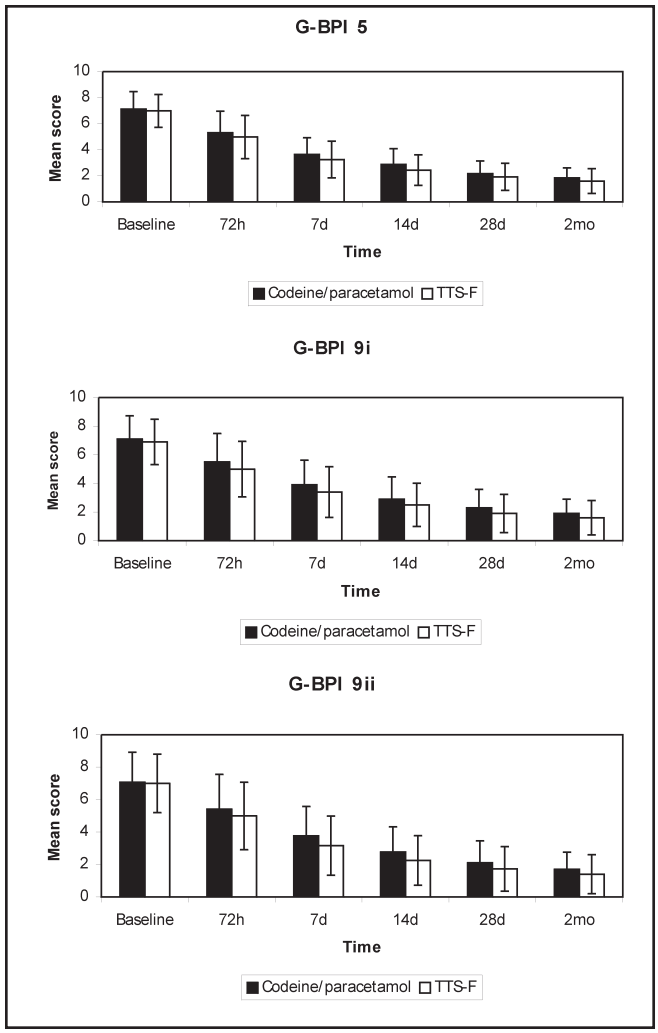

Figure 1. Pain measures: Results for questions GBPI-5, -9i, and -9ii for the two groups from baseline to month two.

of variance (ANOVA) for categorical and continuous variables, respectively. All tests were two-sided; $p < 0.05$ was considered statistically significant.

RESULTS

A total of 460 patients were enrolled in the study and were randomly assigned to the two treatment groups. Table 1 summarizes the patient population's general characteristics and demographics, primary and metastatic cancer site, and types of pain and adjuvant hormonal therapy. A total of 11 patients in the TTS-F group did not adhere to the protocol from baseline and five were excluded due to severe anemia, whereas in the codeine/paracetamol group nine and two patients, respectively, were also excluded for the same reasons. Ten patients in the TTS-F group did not receive palliative R/T, and three were excluded due to acute intestinal obstruction (ileus). These exclusions made 201 patients from the TTS-F group and 221 from the codeine/paracetamol group eligible for the study. During the course of the study, 17 (4.0 percent) patients withdrew. Nine (2.1 percent) withdrew as a result of uncontrolled pain relief, and one (0.24 percent) owing to side effects. The seven (1.7 percent) other patients died during the study.

Patients in TTS-F group started with an initial dose of 25 µg per hour; the codeine/paracetamol group with a total dose of 120 mg per day. In the TTS-F group the patients were allowed to take paracetamol/codeine with the onset of TTS-F application and, therefore, every six hours for the first 12 hours as rescue.

At the end of the study (month two), among the 215 patients in the codeine/paracetamol group who completed the study, only nine (4.2 percent) continued to receive the initial dose of 120 mg per day. Twenty (9.3 percent) patients increased their dose to 240 mg, 186 (86.5 percent) to 360 mg, and five (2.3 percent) withdrew because of uncontrollable pain, whereas in the TTS-F group, the vast majority of patients (184 out of 188; 97.9 percent) maintained their medication at the initial dose, and only four (6.1 percent) increased their dose to 50 µg per hour.

The summary statistics showed a progressive improvement in QoL, ECOG score, pain management, G-BPI (questions 5, 9i, and 9ii), and in overall treatment satisfaction for the two groups. Mean VAS QoL score 28 days post-baseline decreased gradually from 7.33 ± 1.09 to 4.43 ± 1.35 in the codeine/paracetamol group and from 7.28 ± 1.00 to 4.23 ± 1.31 in the TTS-F group. Likewise, ECOG score in the codeine/paracetamol group decreased from 2.33 ± 0.49 to 1.91 ± 0.59 and from 2.33 ± 0.63 to 1.98 ± 0.82 in the TTS-F group, showing a similar improvement between two groups. G-BPI scores (questions 5, 9i and 9ii) for the two groups are shown in Figure 1. All three G-BPI parameters decreased gradually during the study until month two in both groups, but patients in the TTS-F group experienced greater decrease, indicating greater pain relief, than patients in the codeine/paracetamol group ($p < 0.05$). For patients in the TTS-F group, the mean differences from baseline to study end (month two) in G-BPI questions 5, 9i, and 9ii were 5.39 ± 1.54, 5.38 ± 1.65, and 5.60 ± 1.87, respectively. For patients in the codeine/paracetamol group the mean differences were 5.26 ± 1.46, 5.22 ± 1.40, and 5.33 ± 1.63, respectively. Similarly, there was a significant greater increase ($p < 0.05$) in the mean satisfaction score for patients in the TTS-F group at every visit between baseline and month two (Figure 2).

Overall, both analgesic therapies were well tolerated. Table 2 indicates the percentage of side effects, expressed as the number per patient per visit. The most common side effect was constipation, with the highest incidence within patients in the codeine/paracetamol (28.5 percent) and TTS-F groups (18.4 percent) on the day seven visit. Respective highest rates for sleep disturbances were 20.4 percent in the codeine/paracetamol group and 18.4

Table 1. Patient characteristics and demographics			
Patients		**R/T + TTS - F**	**R/T + C/P**
Number		201	221
Gender	Male	95 (47.3)	124 (56.1)
	Female	106 (52.7)	97 (43.9)
Age (yr)		60.7 ± 13.2	60.9 ± 12.1
Age range (yr)		25 to 88	33 to 80
Family status	Married	139 (69.5)	158 (71.5)
	Single/divorced	61 (30.5)	63 (28.5)
Education	Primary	46 (23.0)	84 (38.0)
	Secondary	89 (44.5)	86 (38.9)
	University	65 (32.5)	51 (23.1)
Primary cancer location	Lung	58 (28.9)	86 (38.9)
	Kidney/bladder	61 (30.3)	54 (24.4)
	Gastrointestinal	33 (16.4)	31 (14.0)
	Breast	29 (14.4)	18 (8.1)
	Unknown	8 (4.0)	15 (6.8)
	Other	12 (5.9)	17 (7.7)
Site of bony metastasis	Thoracic spine	38 (18.9)	43 (19.4)
	Lumbar spine	47 (23.4)	52 (23.5)
	Cervical spine	36 (17.9)	39 (17.6)
	Thoracic + lumbar	24 (11.9)	31 (14.0)
	Pelvis	26 (12.9)	24 (10.9)
	Femur	9 (4.5)	10 (4.5)
	Scapula	21 (10.4)	22 (10.0)
Other metastases	Brain	29 (14.4)	38 (17.2)
	Gastrointestinal	23 (11.4)	9 (4.1)
	Lung	16 (8.0)	2 (0.9)
	Adrenal	12 (6.0)	7 (3.2)

Numbers in parentheses are percentages; C/P, codeine/paracetamol; R/T, radiotherapy; TTS-F, transdermal therapeutic fentanyl.

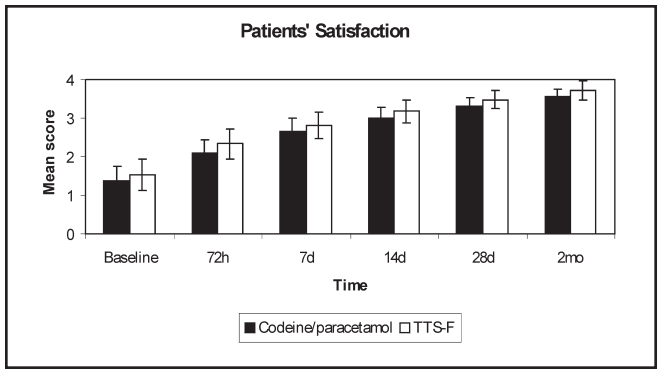

Figure 2. Mean patient satisfaction scores for the two groups from baseline to month two.

percent in the TTS-F group on the same visit. The highest incidences for nausea emerged only 72 hours post-baseline, and were 10.0 percent and 8.0 percent for the codeine/paracetamol and TTS-F groups, respectively. The overall frequencies of side effects showed a steady decline from an initial increase after the first doses of medications (baseline to 72 hours or day seven), and these side effects were successfully treated with appropriate medications (i.e., antiemetics, laxatives).

DISCUSSION

The vast majority of patients who die of cancer have tumor metastasis. Bone is the third most common organ involved by metastasis, behind lung and liver.[19] The increasing age and size of the population leads to an increased number of cases of cancer; this, coupled with longer patient survival, increases the incidence of metastatic lesions to bone. Patients with bone metastases most often present with pain as the principal symptom. As more patients are living with bone metastases, the main challenge for healthcare providers is to provide sufficient analgesia to improve patient QoL. Current management of painful bone metastases involves a multimodality approach, including systemic therapies—chemotherapy, hormone therapy, analgesics, and other medications (i.e., bisphosphonates)—and R/T.[20-22]

External-beam palliative R/T is an important technique for treatment of metastatic bone pain. Irradiation achieves at least partial relief of pain in 80 to 90 percent of patients, with better outcome in those with a limited number of well-localized bony metastases.[23-26] The optimal dose and fractionation regimen for palliative therapy of metastatic bone lesions has been debated.[24,26,27] It can be given as a single fraction or in multiple fractions over several days.[28]

Table 2. Side effects during study period

Time	Group	Constipation	Nausea	Sleep disturbances	Vomiting	Rash/pruritus	Sweating
Baseline	TTS-F	6 (3.0)	2 (1.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
	C/P	15 (6.8)	5 (2.3)	6 (2.7)	3 (1.4)	0 (0.0)	0 (0.0)
72 hours	TTS-F	37 (18.4)	16 (8.0)	37 (18.4)	13 (6.5)	3 (1.5)	9 (4.5)
	C/P	66 (29.9)	22 (10.0)	40 (18.1)	3 (1.4)	0 (0.0)	2 (0.9)
7 days	TTS-F	37 (18.4)	20 (10.0)	37 (18.4)	11 (5.5)	3 (1.5)	9 (4.5)
	C/P	63 (28.5)	19 (8.6)	45 (20.4)	3 (1.4)	1 (1.5)	2 (0.9)
14 days	TTS-F	36 (17.9)	19 (9.5)	31 (15.4)	6 (3.0)	3 (1.5)	9 (4.5)
	C/P	54 (24.4)	16 (7.2)	37 (16.7)	1 (0.5)	2 (0.9)	1 (0.5)
28 days	TTS-F	29 (14.7)	11 (5.6)	17 (8.6)	2 (1.0)	1 (0.5)	2 (1.0)
	C/P	46 (21.0)	11 (5.0)	16 (7.3)	2 (0.9)	6 (2.7)	0 (0.0)
2 months	TTS-F	30 (16.0)	12 (6.4)	5 (2.7)	2 (1.1)	1 (0.5)	0 (0.0)
	C/P	43 (20.0)	6 (2.8)	5 (2.3)	1 (0.5)	2 (0.9)	0 (0.0)

Numbers in parentheses are percentages; C/P, codeine/paracetamol; TTS-F, transdermal therapeutic fentanyl.

Opioid analgesics remain the cornerstone of pharmacotherapy for pain, with morphine long being the gold standard for cancer-associated pain. Short-lived drugs are generally favored because they are easier to titrate than those with a long half-life. The optimal route of administration of opioids is oral; however, bowel obstruction, severe vomiting, or coma may preclude this route. The TTS-F system is a long-acting, controlled-released opioid preparation that limits the inconvenience of 24-hour administration of other drugs. Several studies have examined its effectiveness and safety as an analgesic,[4,5,10,29,30] for which it was recently added to the WHO Step III ladder for chronic and intractable pain.[11] More recently, attention has been drawn to the use of opioids for the treatment of carefully selected patients with chronic cancer pain, especially in the palliative care setting.[9,31]

In our study we have investigated the combined analgesic effectiveness and safety profile of the two treatments in cancer patients with strong intolerable or chronic pain. We demonstrated that in combination with R/T, TTS-F was superior to codeine/paracetamol in improving the three G-BPI parameters and the mean satisfaction score from baseline to study end. Both analgesic therapies improved VAS QoL and ECOG scores similarly and were generally well tolerated and safe with patients in the TTS-F group, which experienced marginally fewer side effects. It should be noted that for reasons of providing best analgesic treatment, dose escalation was permitted during the study period. The majority of patients (95.8 percent) in the codeine/paracetamol group increased their medication dosage from 120 mg to 240 mg and 360 mg per day, whereas only four patients (6.1 percent) in the TTS-F group increased their dosage from 25 μg per hour to 50.0 μg per hour for adequate pain alleviation. Considering this, the final differences in the improvement of G-BPI, QoL, ECOG, and satisfaction scores would have been greater between the two groups if we had maintained the initial doses throughout the study.

TTS-F has been available in Greece since 1996, from which point we have continued to monitor and study the safety profile and effectiveness in cancer patients admitted to the palliative care and pain relief clinic. We have previously investigated the possibility of direct conversion to TTS-F in a population of cancer patients (n = 130) previously receiving codeine/paracetamol for cancer pain relief and requiring strong opioids for adequate analgesia.[9] We demonstrated that with careful patient selection and under controlled conditions, TTS-F is a feasible option. More recently, interest has centered on a generally held perception that is possible to use TTS-F as a single opioid in cancer patients naïve to mild or strong opioids with intractable or chronic pain (pain index scores ≥ 6), that is, on Step I of the WHO ladder.[32,33] In a clinical trial conducted in our center, we examined 113 patients with high pain index scores and demonstrated the safety and efficacy of bypassing Step II for carefully selected populations.[9] In another recent study conducted in our center (n = 1,828), we showed that TTS-F offers a safe, well-tolerated pain relief treatment for carefully monitored patients with cancer pain experiencing difficulties in their pain management while progressing up the WHO ladder.[34]

The present study investigated the analgesic efficacy and the safety profile of TTS-F with those of codeine/paracetamol in combination with R/T for metastatic bone pain. The results support a previous small, multicenter, randomized study in which TTS-F was compared with oral codeine/paracetamol in combination with R/T,[14] but the present study enrolled a greater number of patients with bone metastases (n = 460 vs. n = 26), and escalation of medication doses was permitted during the study for optimal pain alleviation. Moreover, because this study was conducted in a single center in which there is an integrated and experienced pain relief and palliative care team, conformity in patient management was assured during the study period.

In conclusion, our study showed that TTS-F in combination with R/T offers a greater degree of pain relief for cancer patients with painful bone metastases than codeine/paracetamol with the use of a single 25 μg per 72 hours patch in the majority of patients. Patients with moderate to severe persistent intolerable or chronic pain who had not been previously prescribed with a strong opioid will obtain complete treatment satisfaction matched by improvements in their QoL without serious side effects as a result of the pain relief provided by TTS-F.

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Methadone-related deaths

Lynn R. Webster, MD

INTRODUCTION

The increasing involvement of methadone in accidental overdose deaths is the subject of several recent reports. The federal government reported more methadone-related deaths in 2001 alone—61—than occurred in the entire 1990s. By 2002, that number had doubled to 123.[1] Individual states are seeing a similar spike, causing state and local medical examiners to publish data seeking to alert the public to the potential danger.[2-8] While the actual numbers may look small, the increases are startling.

To examine this issue, a literature search was conducted for studies related to methadone deaths in the 1990s and 2000s. Available for review was a report from the US Substance Abuse and Mental Health Services Administration (SAMHSA), an additional report covering 11 states, and another six separate state studies containing analyses of state medical examiner data. An email message also was sent to the medical examiner offices of all 50 states and the District of Columbia to request access to any further published studies. Only six replies were received, none of which yielded any further published studies for inclusion.

Of immediate interest to clinicians is whether the increase in methadone-related deaths is tied to the drug's recent emergence as an analgesic to manage chronic, nonmalignant pain. The SAMHSA report draws such a parallel, even concluding that the increase in methadone deaths cannot be traced to doses provided to narcotic addicts by clinics specializing in methadone maintenance treatment (MMT).[9]

While the state reports do not contain data adequate to determine whether the bulk of decedents were abusing methadone, combining it with other substances, or taking methadone as directed for pain, it appears clinicians and patients may underestimate the risk of respiratory depression associated with methadone. Some of this risk arises from methadone's pharmacologic properties, which include a long, variable half-life.

The purpose of this paper is fourfold: 1) to alert clinicians to the rising number of reports of methadone-related deaths, 2) to discuss the relative contribution of methadone prescribed for pain to the incidence of accidental overdose, 3) to consider the possibility that opioid tolerance does not provide as much protection against respiratory depression as often assumed, and 4) to suggest safe methadone prescribing guidelines for use in clinical pain practice. A particular urgency drives this latter need, as methadone's use as an agent for treating chronic pain continues to widen.

RISE IN METHADONE–RELATED DEATHS

SAMHSA data

A 2002 SAMHSA report showed methadone as ranking in the top 10 drugs involved in deaths in 19 US cities. This puts methadone ahead of hydrocodone and oxycodone (in the top 10 for 15 cities each) but behind benzodiazepines (26 cities).[10] This is striking, considering the much higher availability of hydrocodone and oxycodone compared to methadone. The US Drug Enforcement Agency (DEA), using the Automation of Reports and Consolidated Orders System (ARCOS), reports that the amount of methadone manufactured and distributed commercially in the United States grew from 194 g per 100,000 population to 954 g between 1997 and 2002. To compare, oxycodone distribution for the same years grew from 1,668 g to 8,056 g, and hydrocodone increased from 3,249 g to 6,777 g.[8]

In 2004, SAMHSA reported that the increase in methadone-related deaths did not appear to stem from the liquid issued by methadone treatment centers, but instead from an increase in solid tablets or diskettes used to treat pain.[9] Hospital emergency-department visits involving methadone rose 176 percent from 1995 to 2002 and 50 percent from 2000 to 2002, according to SAMHSA's Drug Abuse Warning Network (DAWN).[9] The report names three scenarios as common for methadone deaths: The first is through illicitly obtained methadone used to achieve euphoria. The second is methadone (either illicit or licit) used in combination with other prescription medications, alcohol, opioids, or benzodiazepines. The last scenario is "an accumulation of

methadone to harmful serum levels in the first few days of treatment for addiction or pain, before tolerance is developed."[11] It is this latter possibility that especially concerns pain clinicians and calls for a re-examination of methadone prescribing guidelines.

State data

Several states have noted a rise in methadone-related deaths and have issued reports quantifying its involvement in drug-related deaths overall. In a study of 11 states from 1990 to 2001, death rates from poisonings that were unintentional or of undetermined cause increased by an average of 145 percent.[2] Of the 11 states studied, eight states identified the top poisoning substances for 1999 and 2000. Methadone was among the six most common poisoning substances, involved in 5 percent of unintentional/undetermined poisoning deaths. It should be noted, however, that nonspecific categories such as "other opioids" were common.

Six states (Florida, Maryland, Maine, New Mexico, North Carolina, and Utah) have all issued recent reports that analyzed state medical examiner data regarding recent drug deaths, including methadone's contribution.[3-8] These reports are similar in structure, although differing in some details. Of particular interest are the data detailing the change in drug-related overdose deaths overall, the change in methadone-related deaths, and methadone's percentage of all drug-related deaths (Table 1).

Decedent characteristics

The extent of analysis regarding decedent characteristics varied greatly from state to state. New Mexico investigators performed extensive, bivariate analyses in which methadone-related deaths were significantly associated with the following covariates: being white (non-Hispanic), death caused by prescription drugs, absence of heroin as a cause of death, absence of alcohol as a cause of death, and the year 1998.[6]

Middle age appears to be a vulnerable period for drug overdose, particularly involving prescription drugs. In the study of 11 states, death rates from unintentional/undetermined poisonings were greatest for persons aged 45 to 54 years (average increase, 359 percent) and 35 to 44 years (average increase, 195 percent).[2] Other states showed similar risk for middle-age patients.

Multiple drug interactions

Some of the states reported the extent to which methadone was found in toxicology reports to be the sole cause of death or one of several contributing factors combined with other prescription drugs, alcohol, or illicit drugs. It should be noted, however, that a single-drug death does not mean no other drugs were present, but that one drug was judged to cause the death. For the year 2002, Florida reported 89 methadone-only deaths and 467 deaths attributed to methadone in combination.[3] New Mexico reported 143 methadone-related deaths from 1998 to 2002, 32 (22.4 percent) of which were single-drug mentions.[6] New Mexico deaths in which methadone was found in combination included 34 (23.8 percent) with prescription drugs and 72 (50.3 percent) with illicit drugs. North Carolina reported a 729 percent increase in single-drug deaths involving methadone, from seven in 1997 to 58 in 2001. Of 316 polydrug deaths in North Carolina, methadone was involved in 51 (16 percent).[7]

The data are intriguing but fail to clarify how often the methadone implicated in drug deaths was instrumental in causing the fatality or was just one factor in a polydrug interaction. At least two states—Maine and Maryland—reported an increase in the trend of overdose deaths attributed to single-drug mentions.[4,5] However, DAWN data point to frequent polydrug involvement: In 43 major US metropolitan areas, nine out of 10 deaths involving narcotic analgesics, including methadone, were multiple-drug deaths.[10]

When a polydrug interaction is documented, benzodiazepines and alcohol are frequently listed as co-causes of death. The exact mechanisms of the interaction of benzodiazepines with methadone, whether additive or synergistic, have been studied[12,13] but need to be better understood. In addition to their sedative effects, some benzodiazepines can alter the rate at which methadone is metabolized in the system. This drug interaction can make interpretation of postmortem results difficult.[13]

Non–United States studies

The 1990s also saw an increase in studies from non-US countries documenting a rise in methadone overdose deaths.[14-16] Most studies from Australia, the United Kingdom, and elsewhere in Europe focused on heroin addicts maintained on methadone. An exception is an Australian study that links a jump in methadone deaths in 1994 to its increased availability as a chronic-pain treatment.[17]

SOURCES OF MISUSED METHADONE

Where most overdose victims obtain the methadone that contributes to their deaths is still unclear. The evidence, although incomplete and sometimes contradictory, indicates a fairly high level of prescription involvement. For example, in Utah, 40 percent of decedents held a valid prescription at the time of death. In New Mexico, of 143 methadone-related decedents from 1998 to 2002, 68 (47.5 percent) had a prescription; 31 had been issued methadone for MMT, 27 for managing pain, and 10 for an unknown reason.[6] Nevada claimed an even higher degree of prescription involvement. In an email message

Table 1. State data: Overall change in drug-related deaths,[a] methadone-related deaths, and methadone's percentage of total drug-related deaths

	Years studied	Change in total drug-related deaths	Change in methadone-related deaths	Methadone percent of total drug-related deaths
Florida	2003 – 2004	N/A	Up 56 percent[b]	7.8 (2004)
Maine	1997 – 2002	up > 400 percent	Up 450 percent[b]	18
Maryland	1997 – 2001	Up 16 percent	Up 950 percent	4 (2001)
New Mexico	1998 – 2002	N/A	Down 35 percent	12.8
North Carolina[c]	1997 – 2001	Up 110 percent	Up 729 percent	19
Utah	1991 – 2003	Up ~ 500 percent[d]	Up 1,358 percent[e]	7.8 (1991 – 1998) 32.7 (1999 – 2003)[e]

[a] A drug was either the direct cause of death or a significant underlying factor; [b] Methadone increase as a cause of death; [c] Unintentional overdose deaths only; [d] Increase from 1991 to 2003; [e] Compared the intervals of 1991–1998 to 1999–2003.

dated May 10, 2005, the Washoe County Coroner said Nevada had experienced approximately a fourfold increase in methadone-related deaths in the past two years, with the majority of victims holding valid prescriptions for methadone. North Carolina found that 73 of 92 decedents for whom information could be documented had held a valid prescription written for them by a physician.[7] In contrast to these reports, Oklahoma showed that close to two-thirds of methadone-related overdose victims in 2001 and 2002 held no valid prescription, leading state medical officials to blame black-market purchases for many of the deaths.[1] Exactly how popular methadone is as a drug of abuse is unknown; however, methadone's unique pharmacologic properties make it relatively ineffective in producing the type of high sought by addicts. Methadone's use by narcotic addicts to medicate withdrawal symptoms is well known and can increase the risk of overdose.

One wonders whether greater distribution at the end of the 1990s contributed to the spike seen in some states in methadone-related overdose deaths. As mentioned previously, SAMHSA's report points to the drug's increased availability by means of prescriptions for chronic pain. Some states reported a rise in deaths paralleling the rise in quantities of methadone shipped to the state. Utah, for example, from 1997 to 2002, saw a sixfold increase in methadone distribution not explained by the needs of addiction treatment programs.[8] The higher quantities of trafficked methadone did indeed coincide with a higher incidence of fatality. In a conversation with the author in March 2005, Utah's state medical examiner traced most of the prescription methadone involved in accidental deaths to the offices of general practitioners across the state rather than pain specialists, highlighting the need for the wider publicizing of sound, safe prescribing guidelines to nonspecialists.

However, availability cannot explain everything, and the factors contributing to methadone overdose appear complex. In North Carolina, the 2001 average of retailed methadone per DEA registrant was 47 g (36 percent above national average). However, counties with above-average retailed methadone did not have a concurrently high overdose rate, perhaps indicating under-treated pain in low-retail areas. Just how much fraud is involved in the obtainment of methadone will likely remain unclear in the absence of a statewide prescription monitoring program, North Carolina investigators concluded.[7]

METHADONE AS PAIN TREATMENT

Methadone has proved to be an effective treatment for several chronic pain conditions, and many clinicians consider its long-acting pharmacologic properties especially valuable in treating patients at high risk for abusing prescription opioids. This characteristic, along with its being relatively inexpensive and a good match with most short-acting opioids used to treat breakthrough pain, make methadone an attractive choice for treating chronic pain. There is increasing pressure from third-party payers to prescribe methadone as a first-choice opioid analgesic due to its relative low cost.

Methadone's profile as a long-acting agent brings with it certain cautions, however. The drug's long and variable half-life contributes to a clinical picture in which physiologic response can vary greatly from one person to the next. Its half-life can range from four to 91 hours, and clearance from a person's system can vary by a factor of almost 100.[7] At the International Conference on Pain and Chemical Dependency in February 2004, Richard Payne, MD, then-president of the American Pain Society, warned that these properties of methadone bring the potential for multiple drug interactions and named rising safety concerns about its use as one of the barriers to effective pain medicine.

TOLERANCE AND RESPIRATORY DEPRESSION

The protection offered by opioid tolerance against the risk of opioid-induced respiratory depression has been an accepted fact of chronic opioid therapy for pain. This treatment principle is presented in a consensus statement from the American Academy of Pain Medicine and the American Pain Society:

> It is now accepted by practitioners of the specialty of pain medicine that respiratory depression induced by opioids tends to be a short-lived phenomenon, generally occurs only in the opioid-naive patient, and is antagonized by pain. Therefore, withholding the appropriate use of opioids from a patient who is experiencing pain on the basis of respiratory concerns is unwarranted.[18]

This view has been bolstered by several researchers, including Fohr, who performed an exhaustive literature review to demonstrate that the belief opioids hasten death via respiratory depression is "more myth than fact."[19]

However, other research—some of it methadone specific—has found that tolerance to respiratory depression is incomplete and outpaced by tolerance to other opioid effects such as euphoria, even in long-term opioid users. Australian researchers White and Irvine, who examined the pharmacologic basis of respiratory depression after opioid administration, found that tolerance to the respiratory-depressant effects of methadone was incomplete as related to the hypoxia-sensitive chemoreceptor mechanism. This contrasted with the carbon dioxide-sensitive chemoreceptor mechanism, which the research suggested was complete.[20]

Further support for this finding comes from a study of the chemical control of breathing, performed before and after the administration of the daily dose of methadone in 14 former heroin addicts. The former addicts were enrolled in an MMT program and were taking 60 to 100 mg per day. Subjects in one group had taken methadone for less than two months, while members of a second group had taken the drug from eight to 43 months. The study found that during the first two months of MMT, patients showed continual alveolar hypoventilation owing to depression of central (CO_2) and peripheral (hypoxia) chemoreception. Then, after five months, alveolar hypoventilation was eliminated as the CO_2-sensitive chemoreflex acquired full tolerance to methadone at the maintenance dose level. Also, they found that tolerance of the hypoxia-sensitive chemoreflex developed more slowly and is never complete.[21]

Further cautions arise not from errors in application, but from the potential that certain patient characteristics, as yet minimally studied and poorly understood, amount to risk factors for accidental overdose death. Utah data, for instance, show a predominance of overdose deaths in overweight individuals, perhaps implicating sleep apnea.[8]

While undue fear of inducing respiratory depression should not be allowed to interfere with appropriate delivery of effective pain relief via opioid therapy, attention should be paid to the research that warns against considering opioid tolerance an absolute protection against respiratory depression.

STUDY CAVEATS

The literature review methods used for this report could not be considered exhaustive, and additional data may exist covering methadone-related deaths. Only published works were included, and no data were analyzed that reported on limited geographic areas within states. The limitations in the data-gathering and analysis methods of initial death investigators raise several serious issues not to be minimized. First, the assignment of a cause of death is a tricky business, particularly when multiple substances are present in the body and their relative contributions are unclear. Second, bias may exist toward assigning an opioid as the cause of death whenever it is present in a toxicology report. Third, difficulty exists in pinpointing a blood level of methadone that would be toxic in most individuals.[12,13,22,23] The lowest postmortem concentrations of methadone given as fatal in several studies ranged from 0.06 to 0.32 mg per L.[13] The lethal level is subject to a number of variables such as the decedent's history of opioid use, the presence of chronic pain, and the action of polydrug combinations. Levels of methadone reported as the cause of death may actually be therapeutic in some chronic pain patients on long-term methadone therapy for pain.

Yet, if methods used by state medical examiners to investigate overdose deaths are imperfect, it is reasonable to surmise that they are, at least, fairly consistent from year to year. The rise in overdose deaths related to methadone—and, indeed, to other categories of prescription drugs—during the preceding decade and beyond has been well documented and would appear to be independent of the data-gathering methods used.

This information suggests the need to review safe

guidelines for methadone prescribing. The process of designing safe, effective dosing guidelines is complicated by the difficulty in pinpointing any reliable, lethal dose of methadone. It is difficult to determine whether the methadone blood levels found after death reflect the medication taken as prescribed or in excess of the prescribed quantity. The time of day methadone is taken may also have an effect. Because methadone's distinct contribution to overdose death is difficult to isolate, it is better for clinicians to err on the side of caution.

PRESCRIBING GUIDELINES: LOOKING FOR SAFETY

The sources and means by which misused methadone becomes available will doubtless become clearer as evidence accumulates. In the meantime, it is obvious that the misuse of methadone by patients who held valid prescriptions is responsible for at least a segment of the deaths observed. Therefore, it is imperative that the medical establishment responds to any clinical misapplications that are occurring. Arresting preventable deaths is of paramount importance. This also throws the discussion open to a certain amount of theorizing until more evidence is available.

When accidental death does occur as a result of methadone that was legally prescribed, two sources of error are suspect. One is error introduced by clinicians while initiating methadone therapy for pain, making the conversion from other medications to methadone, or escalating the methadone dose while feeling falsely secure in the belief that a patient's opioid tolerance or pain status ensures safety. The second source of error can be introduced by patients in their consumption of methadone in ways not directed by the physician or in combination with other substances. Patient error may stem from escalating doses of methadone tablets against medical orders while seeking greater pain relief. Patients seeking optimal pain relief sometimes think, in essence, "If one tablet is good and two are better, then three must be great." A patient may have done this in the past with a different opioid medication, not realizing that methadone's long, variable half-life makes any deviation from the treatment plan extremely dangerous.

Methadone conversion tables

Clinicians, perhaps over-reliant on published conversion tables, may not be taking into account the long and widely variable half-life of methadone as they convert from what is believed to be equianalgesic doses of other opioids. During this process, clinicians may overestimate the protection afforded by a patient's previous opioid tolerance and underestimate the risk of overdose.

Most conversion tables use a ratio to estimate the equianalgesic dose of one opioid to another. It is often assumed that the tolerance achieved by a patient on a current regimen of opioids allows the clinician to begin methadone at a rate equal to the exact morphine equivalent. However, cross-tolerance is incomplete, even for individuals currently prescribed high doses of other opioids. Therefore, it is potentially dangerous to use the equianalgesic dosing guidelines published in available conversion tables when determining the starting dose of methadone.

These tables—designed for a single use, not for chronic administration—may also imply that no upper limit exists for the starting methadone dose. This is belied by evidence that patients are at risk for overdose during the conversion period. One table suggests a conversion rate of 5 to 10 percent of the oral morphine dose. This may be far too high. For example, if the opioid-tolerant individual were taking up to 500 mg per day of pharmaceutical narcotics, the starting methadone dose could be as high as 50 mg per day. This might not be problematic for one dose, but could prove too high for the accumulation that occurs with multiple doses when considering methadone's wide variability of half-life. The doses recommended by conversion tables fail to take into account the potential for accumulated toxicity and for polydrug interactions that can occur with around-the-clock methadone.

New guidelines: Start low, titrate slow

Speaking at the California Society of Addiction Medicine Conference in October 2004, Mary Jeanne Kreek, MD, recommended a starting dose of methadone for chronic pain of 10 mg, bid. She suggested this be titrated slowly to an analgesic, still-low dose, delivered twice a day—thrice at the most. If patients have been taking high doses of other opioids, they may be quite opioid tolerant. Still, the starting dose should be low and the titration slow, Kreek recommended.

As with all opioids, the starting dose of methadone depends on the patient's age, degree of opioid tolerance, severity of pain, concomitant medications, and general health. Yet methadone's pharmacologic properties call for a conservative approach for even the most opioid-tolerant patients. Because such large variability exists in the responses of individuals, it is always necessary to start with a low dose and titrate slowly to an analgesic effect. For this reason, the guidelines that follow do not differ much between opioid-tolerant and opioid-naïve individuals. Careful monitoring of individual patient response is key. Keeping these thoughts in mind, the guidelines recommended for initiating methadone therapy are shown in Table 2.

For now, safe practice supports starting the conversion with a ceiling dose of no more than 20 mg per day, 10 mg per day for elderly or infirm patients. Dose changes should not occur more often than weekly to

Table 2. Suggested guidelines for initiating methadone for pain		
Total daily morphine	**Starting methadone dose**	
	Healthy adults aged < 70 yr	**Adults with chronic illness or aged > 70 yr**
Opioid naïve	5 mg tid	2.5 mg bid
60 mg to 100 mg	5 mg tid	5 mg bid
> 100 mg	5 mg qid	5 mg bid

allow a steady state of methadone to develop and for the peak side effects to become clear. If patients are taking concomitant benzodiazepines, the starting dose and speed of titration may need to be adjusted downward.

For patients who are being converted from another opioid to methadone, clinicians should slowly titrate downward the other opioid as they slowly titrate methadone upward. This practice will minimize the risk of withdrawal and of overdose involving methadone or a combination of the two opioids.

Patient counseling must include an emphasis on following all medical instructions to the letter: no escalation of doses and no mixing of methadone with other prescriptions, alcohol, or illicit substances. Patients should be warned that any deviation in this regard can be dangerous, even fatal.

These guidelines represent a more conservative recommendation than seen elsewhere. Certainly, some patients are able to tolerate a much more rapid conversion or titration. Nevertheless, given the reports of deaths associated with methadone, these starting guidelines should help clinicians ensure patient safety and give methadone pain therapy a greater chance of success. Safety must come first. More aggressive pain control may follow once the mechanisms behind the increase in methadone-related deaths are further researched and better understood.

CONCLUSION

Methadone has unique properties that may make it subject to overdose, especially during its initial use. It is important to clarify these properties to all practitioners who use methadone to treat pain. These problems must be swiftly dealt with. Many thousands of people are still under-treated for pain. The quickest way for practitioners, many of whom already fear treating pain with opioids, to lose confidence in opioid therapy is for pain specialists to fail to acknowledge problems with opioid toxicity when they arise.

Many questions must still be answered in future research: What is the primary source—or sources—of misused methadone? Is it possible to reach a medical consensus on the doses, combinations, or other factors that turn methadone lethal? Which patient characteristics are also risk factors for accidental overdose when prescribed methadone for pain? Does the time of day at which methadone is consumed influence the potential for a fatal dose? Is there opioid-specific tolerance to respiratory depression? How much cross-tolerance between opioids can be developed? What factors will influence the degree of cross-tolerance? Is tolerance to respiratory depression reduced with concomitant medications commonly used in treating chronic pain? If so, how much and which concomitant medications pose the greatest risk?

Until these questions are answered, physicians must adopt a cautious, conservative approach to the use of methadone and closely monitor patient response. Continued trust in the principles of pain management depends on the widespread availability of dosing guidelines that do no harm. In the case of methadone prescribing for pain, a certain urgency exists in this respect.

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Methadone-related deaths

Lynn R. Webster, MD

INTRODUCTION

The increasing involvement of methadone in accidental overdose deaths is the subject of several recent reports. The federal government reported more methadone-related deaths in 2001 alone—61—than occurred in the entire 1990s. By 2002, that number had doubled to 123.[1] Individual states are seeing a similar spike, causing state and local medical examiners to publish data seeking to alert the public to the potential danger.[2-8] While the actual numbers may look small, the increases are startling.

To examine this issue, a literature search was conducted for studies related to methadone deaths in the 1990s and 2000s. Available for review was a report from the US Substance Abuse and Mental Health Services Administration (SAMHSA), an additional report covering 11 states, and another six separate state studies containing analyses of state medical examiner data. An email message also was sent to the medical examiner offices of all 50 states and the District of Columbia to request access to any further published studies. Only six replies were received, none of which yielded any further published studies for inclusion.

Of immediate interest to clinicians is whether the increase in methadone-related deaths is tied to the drug's recent emergence as an analgesic to manage chronic, nonmalignant pain. The SAMHSA report draws such a parallel, even concluding that the increase in methadone deaths cannot be traced to doses provided to narcotic addicts by clinics specializing in methadone maintenance treatment (MMT).[9]

While the state reports do not contain data adequate to determine whether the bulk of decedents were abusing methadone, combining it with other substances, or taking methadone as directed for pain, it appears clinicians and patients may underestimate the risk of respiratory depression associated with methadone. Some of this risk arises from methadone's pharmacologic properties, which include a long, variable half-life.

The purpose of this paper is fourfold: 1) to alert clinicians to the rising number of reports of methadone-related deaths, 2) to discuss the relative contribution of methadone prescribed for pain to the incidence of accidental overdose, 3) to consider the possibility that opioid tolerance does not provide as much protection against respiratory depression as often assumed, and 4) to suggest safe methadone prescribing guidelines for use in clinical pain practice. A particular urgency drives this latter need, as methadone's use as an agent for treating chronic pain continues to widen.

RISE IN METHADONE–RELATED DEATHS

SAMHSA data

A 2002 SAMHSA report showed methadone as ranking in the top 10 drugs involved in deaths in 19 US cities. This puts methadone ahead of hydrocodone and oxycodone (in the top 10 for 15 cities each) but behind benzodiazepines (26 cities).[10] This is striking, considering the much higher availability of hydrocodone and oxycodone compared to methadone. The US Drug Enforcement Agency (DEA), using the Automation of Reports and Consolidated Orders System (ARCOS), reports that the amount of methadone manufactured and distributed commercially in the United States grew from 194 g per 100,000 population to 954 g between 1997 and 2002. To compare, oxycodone distribution for the same years grew from 1,668 g to 8,056 g, and hydrocodone increased from 3,249 g to 6,777 g.[8]

In 2004, SAMHSA reported that the increase in methadone-related deaths did not appear to stem from the liquid issued by methadone treatment centers, but instead from an increase in solid tablets or diskettes used to treat pain.[9] Hospital emergency-department visits involving methadone rose 176 percent from 1995 to 2002 and 50 percent from 2000 to 2002, according to SAMHSA's Drug Abuse Warning Network (DAWN).[9] The report names three scenarios as common for methadone deaths: The first is through illicitly obtained methadone used to achieve euphoria. The second is methadone (either illicit or licit) used in combination with other prescription medications, alcohol, opioids, or benzodiazepines. The last scenario is "an accumulation of

methadone to harmful serum levels in the first few days of treatment for addiction or pain, before tolerance is developed."[11] It is this latter possibility that especially concerns pain clinicians and calls for a re-examination of methadone prescribing guidelines.

State data

Several states have noted a rise in methadone-related deaths and have issued reports quantifying its involvement in drug-related deaths overall. In a study of 11 states from 1990 to 2001, death rates from poisonings that were unintentional or of undetermined cause increased by an average of 145 percent.[2] Of the 11 states studied, eight states identified the top poisoning substances for 1999 and 2000. Methadone was among the six most common poisoning substances, involved in 5 percent of unintentional/undetermined poisoning deaths. It should be noted, however, that nonspecific categories such as "other opioids" were common.

Six states (Florida, Maryland, Maine, New Mexico, North Carolina, and Utah) have all issued recent reports that analyzed state medical examiner data regarding recent drug deaths, including methadone's contribution.[3-8] These reports are similar in structure, although differing in some details. Of particular interest are the data detailing the change in drug-related overdose deaths overall, the change in methadone-related deaths, and methadone's percentage of all drug-related deaths (Table 1).

Decedent characteristics

The extent of analysis regarding decedent characteristics varied greatly from state to state. New Mexico investigators performed extensive, bivariate analyses in which methadone-related deaths were significantly associated with the following covariates: being white (non-Hispanic), death caused by prescription drugs, absence of heroin as a cause of death, absence of alcohol as a cause of death, and the year 1998.[6]

Middle age appears to be a vulnerable period for drug overdose, particularly involving prescription drugs. In the study of 11 states, death rates from unintentional/undetermined poisonings were greatest for persons aged 45 to 54 years (average increase, 359 percent) and 35 to 44 years (average increase, 195 percent).[2] Other states showed similar risk for middle-age patients.

Multiple drug interactions

Some of the states reported the extent to which methadone was found in toxicology reports to be the sole cause of death or one of several contributing factors combined with other prescription drugs, alcohol, or illicit drugs. It should be noted, however, that a single-drug death does not mean no other drugs were present, but that one drug was judged to cause the death. For the year 2002, Florida reported 89 methadone-only deaths and 467 deaths attributed to methadone in combination.[3] New Mexico reported 143 methadone-related deaths from 1998 to 2002, 32 (22.4 percent) of which were single-drug mentions.[6] New Mexico deaths in which methadone was found in combination included 34 (23.8 percent) with prescription drugs and 72 (50.3 percent) with illicit drugs. North Carolina reported a 729 percent increase in single-drug deaths involving methadone, from seven in 1997 to 58 in 2001. Of 316 polydrug deaths in North Carolina, methadone was involved in 51 (16 percent).[7]

The data are intriguing but fail to clarify how often the methadone implicated in drug deaths was instrumental in causing the fatality or was just one factor in a polydrug interaction. At least two states—Maine and Maryland—reported an increase in the trend of overdose deaths attributed to single-drug mentions.[4,5] However, DAWN data point to frequent polydrug involvement: In 43 major US metropolitan areas, nine out of 10 deaths involving narcotic analgesics, including methadone, were multiple-drug deaths.[10]

When a polydrug interaction is documented, benzodiazepines and alcohol are frequently listed as co-causes of death. The exact mechanisms of the interaction of benzodiazepines with methadone, whether additive or synergistic, have been studied[12,13] but need to be better understood. In addition to their sedative effects, some benzodiazepines can alter the rate at which methadone is metabolized in the system. This drug interaction can make interpretation of postmortem results difficult.[13]

Non–United States studies

The 1990s also saw an increase in studies from non-US countries documenting a rise in methadone overdose deaths.[14-16] Most studies from Australia, the United Kingdom, and elsewhere in Europe focused on heroin addicts maintained on methadone. An exception is an Australian study that links a jump in methadone deaths in 1994 to its increased availability as a chronic-pain treatment.[17]

SOURCES OF MISUSED METHADONE

Where most overdose victims obtain the methadone that contributes to their deaths is still unclear. The evidence, although incomplete and sometimes contradictory, indicates a fairly high level of prescription involvement. For example, in Utah, 40 percent of decedents held a valid prescription at the time of death. In New Mexico, of 143 methadone-related decedents from 1998 to 2002, 68 (47.5 percent) had a prescription; 31 had been issued methadone for MMT, 27 for managing pain, and 10 for an unknown reason.[6] Nevada claimed an even higher degree of prescription involvement. In an email message

Table 1. State data: Overall change in drug-related deaths,[a] methadone-related deaths, and methadone's percentage of total drug-related deaths

	Years studied	Change in total drug-related deaths	Change in methadone-related deaths	Methadone percent of total drug-related deaths
Florida	2003 – 2004	N/A	Up 56 percent[b]	7.8 (2004)
Maine	1997 – 2002	up > 400 percent	Up 450 percent[b]	18
Maryland	1997 – 2001	Up 16 percent	Up 950 percent	4 (2001)
New Mexico	1998 – 2002	N/A	Down 35 percent	12.8
North Carolina[c]	1997 – 2001	Up 110 percent	Up 729 percent	19
Utah	1991 – 2003	Up ~ 500 percent[d]	Up 1,358 percent[e]	7.8 (1991 – 1998) 32.7 (1999 – 2003)[e]

[a] A drug was either the direct cause of death or a significant underlying factor; [b] Methadone increase as a cause of death; [c] Unintentional overdose deaths only; [d] Increase from 1991 to 2003; [e] Compared the intervals of 1991–1998 to 1999–2003.

dated May 10, 2005, the Washoe County Coroner said Nevada had experienced approximately a fourfold increase in methadone-related deaths in the past two years, with the majority of victims holding valid prescriptions for methadone. North Carolina found that 73 of 92 decedents for whom information could be documented had held a valid prescription written for them by a physician.[7] In contrast to these reports, Oklahoma showed that close to two-thirds of methadone-related overdose victims in 2001 and 2002 held no valid prescription, leading state medical officials to blame black-market purchases for many of the deaths.[1] Exactly how popular methadone is as a drug of abuse is unknown; however, methadone's unique pharmacologic properties make it relatively ineffective in producing the type of high sought by addicts. Methadone's use by narcotic addicts to medicate withdrawal symptoms is well known and can increase the risk of overdose.

One wonders whether greater distribution at the end of the 1990s contributed to the spike seen in some states in methadone-related overdose deaths. As mentioned previously, SAMHSA's report points to the drug's increased availability by means of prescriptions for chronic pain. Some states reported a rise in deaths paralleling the rise in quantities of methadone shipped to the state. Utah, for example, from 1997 to 2002, saw a sixfold increase in methadone distribution not explained by the needs of addiction treatment programs.[8] The higher quantities of trafficked methadone did indeed coincide with a higher incidence of fatality. In a conversation with the author in March 2005, Utah's state medical examiner traced most of the prescription methadone involved in accidental deaths to the offices of general practitioners across the state rather than pain specialists, highlighting the need for the wider publicizing of sound, safe prescribing guidelines to nonspecialists.

However, availability cannot explain everything, and the factors contributing to methadone overdose appear complex. In North Carolina, the 2001 average of retailed methadone per DEA registrant was 47 g (36 percent above national average). However, counties with above-average retailed methadone did not have a concurrently high overdose rate, perhaps indicating under-treated pain in low-retail areas. Just how much fraud is involved in the obtainment of methadone will likely remain unclear in the absence of a statewide prescription monitoring program, North Carolina investigators concluded.[7]

METHADONE AS PAIN TREATMENT

Methadone has proved to be an effective treatment for several chronic pain conditions, and many clinicians consider its long-acting pharmacologic properties especially valuable in treating patients at high risk for abusing prescription opioids. This characteristic, along with its being relatively inexpensive and a good match with most short-acting opioids used to treat breakthrough pain, make methadone an attractive choice for treating chronic pain. There is increasing pressure from third-party payers to prescribe methadone as a first-choice opioid analgesic due to its relative low cost.

Methadone's profile as a long-acting agent brings with it certain cautions, however. The drug's long and variable half-life contributes to a clinical picture in which physiologic response can vary greatly from one person to the next. Its half-life can range from four to 91 hours, and clearance from a person's system can vary by a factor of almost 100.[7] At the International Conference on Pain and Chemical Dependency in February 2004, Richard Payne, MD, then-president of the American Pain Society, warned that these properties of methadone bring the potential for multiple drug interactions and named rising safety concerns about its use as one of the barriers to effective pain medicine.

TOLERANCE AND RESPIRATORY DEPRESSION

The protection offered by opioid tolerance against the risk of opioid-induced respiratory depression has been an accepted fact of chronic opioid therapy for pain. This treatment principle is presented in a consensus statement from the American Academy of Pain Medicine and the American Pain Society:

> It is now accepted by practitioners of the specialty of pain medicine that respiratory depression induced by opioids tends to be a short-lived phenomenon, generally occurs only in the opioid-naive patient, and is antagonized by pain. Therefore, withholding the appropriate use of opioids from a patient who is experiencing pain on the basis of respiratory concerns is unwarranted.[18]

This view has been bolstered by several researchers, including Fohr, who performed an exhaustive literature review to demonstrate that the belief opioids hasten death via respiratory depression is "more myth than fact."[19]

However, other research—some of it methadone specific—has found that tolerance to respiratory depression is incomplete and outpaced by tolerance to other opioid effects such as euphoria, even in long-term opioid users. Australian researchers White and Irvine, who examined the pharmacologic basis of respiratory depression after opioid administration, found that tolerance to the respiratory-depressant effects of methadone was incomplete as related to the hypoxia-sensitive chemoreceptor mechanism. This contrasted with the carbon dioxide-sensitive chemoreceptor mechanism, which the research suggested was complete.[20]

Further support for this finding comes from a study of the chemical control of breathing, performed before and after the administration of the daily dose of methadone in 14 former heroin addicts. The former addicts were enrolled in an MMT program and were taking 60 to 100 mg per day. Subjects in one group had taken methadone for less than two months, while members of a second group had taken the drug from eight to 43 months. The study found that during the first two months of MMT, patients showed continual alveolar hypoventilation owing to depression of central (CO_2) and peripheral (hypoxia) chemoreception. Then, after five months, alveolar hypoventilation was eliminated as the CO_2-sensitive chemoreflex acquired full tolerance to methadone at the maintenance dose level. Also, they found that tolerance of the hypoxia-sensitive chemoreflex developed more slowly and is never complete.[21]

Further cautions arise not from errors in application, but from the potential that certain patient characteristics, as yet minimally studied and poorly understood, amount to risk factors for accidental overdose death. Utah data, for instance, show a predominance of overdose deaths in overweight individuals, perhaps implicating sleep apnea.[8]

While undue fear of inducing respiratory depression should not be allowed to interfere with appropriate delivery of effective pain relief via opioid therapy, attention should be paid to the research that warns against considering opioid tolerance an absolute protection against respiratory depression.

STUDY CAVEATS

The literature review methods used for this report could not be considered exhaustive, and additional data may exist covering methadone-related deaths. Only published works were included, and no data were analyzed that reported on limited geographic areas within states. The limitations in the data-gathering and analysis methods of initial death investigators raise several serious issues not to be minimized. First, the assignment of a cause of death is a tricky business, particularly when multiple substances are present in the body and their relative contributions are unclear. Second, bias may exist toward assigning an opioid as the cause of death whenever it is present in a toxicology report. Third, difficulty exists in pinpointing a blood level of methadone that would be toxic in most individuals.[12,13,22,23] The lowest postmortem concentrations of methadone given as fatal in several studies ranged from 0.06 to 0.32 mg per L.[13] The lethal level is subject to a number of variables such as the decedent's history of opioid use, the presence of chronic pain, and the action of polydrug combinations. Levels of methadone reported as the cause of death may actually be therapeutic in some chronic pain patients on long-term methadone therapy for pain.

Yet, if methods used by state medical examiners to investigate overdose deaths are imperfect, it is reasonable to surmise that they are, at least, fairly consistent from year to year. The rise in overdose deaths related to methadone—and, indeed, to other categories of prescription drugs—during the preceding decade and beyond has been well documented and would appear to be independent of the data-gathering methods used.

This information suggests the need to review safe

guidelines for methadone prescribing. The process of designing safe, effective dosing guidelines is complicated by the difficulty in pinpointing any reliable, lethal dose of methadone. It is difficult to determine whether the methadone blood levels found after death reflect the medication taken as prescribed or in excess of the prescribed quantity. The time of day methadone is taken may also have an effect. Because methadone's distinct contribution to overdose death is difficult to isolate, it is better for clinicians to err on the side of caution.

PRESCRIBING GUIDELINES: LOOKING FOR SAFETY

The sources and means by which misused methadone becomes available will doubtless become clearer as evidence accumulates. In the meantime, it is obvious that the misuse of methadone by patients who held valid prescriptions is responsible for at least a segment of the deaths observed. Therefore, it is imperative that the medical establishment responds to any clinical misapplications that are occurring. Arresting preventable deaths is of paramount importance. This also throws the discussion open to a certain amount of theorizing until more evidence is available.

When accidental death does occur as a result of methadone that was legally prescribed, two sources of error are suspect. One is error introduced by clinicians while initiating methadone therapy for pain, making the conversion from other medications to methadone, or escalating the methadone dose while feeling falsely secure in the belief that a patient's opioid tolerance or pain status ensures safety. The second source of error can be introduced by patients in their consumption of methadone in ways not directed by the physician or in combination with other substances. Patient error may stem from escalating doses of methadone tablets against medical orders while seeking greater pain relief. Patients seeking optimal pain relief sometimes think, in essence, "If one tablet is good and two are better, then three must be great." A patient may have done this in the past with a different opioid medication, not realizing that methadone's long, variable half-life makes any deviation from the treatment plan extremely dangerous.

Methadone conversion tables

Clinicians, perhaps over-reliant on published conversion tables, may not be taking into account the long and widely variable half-life of methadone as they convert from what is believed to be equianalgesic doses of other opioids. During this process, clinicians may overestimate the protection afforded by a patient's previous opioid tolerance and underestimate the risk of overdose.

Most conversion tables use a ratio to estimate the equianalgesic dose of one opioid to another. It is often assumed that the tolerance achieved by a patient on a current regimen of opioids allows the clinician to begin methadone at a rate equal to the exact morphine equivalent. However, cross-tolerance is incomplete, even for individuals currently prescribed high doses of other opioids. Therefore, it is potentially dangerous to use the equianalgesic dosing guidelines published in available conversion tables when determining the starting dose of methadone.

These tables—designed for a single use, not for chronic administration—may also imply that no upper limit exists for the starting methadone dose. This is belied by evidence that patients are at risk for overdose during the conversion period. One table suggests a conversion rate of 5 to 10 percent of the oral morphine dose. This may be far too high. For example, if the opioid-tolerant individual were taking up to 500 mg per day of pharmaceutical narcotics, the starting methadone dose could be as high as 50 mg per day. This might not be problematic for one dose, but could prove too high for the accumulation that occurs with multiple doses when considering methadone's wide variability of half-life. The doses recommended by conversion tables fail to take into account the potential for accumulated toxicity and for polydrug interactions that can occur with around-the-clock methadone.

New guidelines: Start low, titrate slow

Speaking at the California Society of Addiction Medicine Conference in October 2004, Mary Jeanne Kreek, MD, recommended a starting dose of methadone for chronic pain of 10 mg, bid. She suggested this be titrated slowly to an analgesic, still-low dose, delivered twice a day—thrice at the most. If patients have been taking high doses of other opioids, they may be quite opioid tolerant. Still, the starting dose should be low and the titration slow, Kreek recommended.

As with all opioids, the starting dose of methadone depends on the patient's age, degree of opioid tolerance, severity of pain, concomitant medications, and general health. Yet methadone's pharmacologic properties call for a conservative approach for even the most opioid-tolerant patients. Because such large variability exists in the responses of individuals, it is always necessary to start with a low dose and titrate slowly to an analgesic effect. For this reason, the guidelines that follow do not differ much between opioid-tolerant and opioid-naïve individuals. Careful monitoring of individual patient response is key. Keeping these thoughts in mind, the guidelines recommended for initiating methadone therapy are shown in Table 2.

For now, safe practice supports starting the conversion with a ceiling dose of no more than 20 mg per day, 10 mg per day for elderly or infirm patients. Dose changes should not occur more often than weekly to

Table 2. Suggested guidelines for initiating methadone for pain		
Total daily morphine	**Starting methadone dose**	
	Healthy adults aged < 70 yr	**Adults with chronic illness or aged > 70 yr**
Opioid naïve	5 mg tid	2.5 mg bid
60 mg to 100 mg	5 mg tid	5 mg bid
> 100 mg	5 mg qid	5 mg bid

allow a steady state of methadone to develop and for the peak side effects to become clear. If patients are taking concomitant benzodiazepines, the starting dose and speed of titration may need to be adjusted downward.

For patients who are being converted from another opioid to methadone, clinicians should slowly titrate downward the other opioid as they slowly titrate methadone upward. This practice will minimize the risk of withdrawal and of overdose involving methadone or a combination of the two opioids.

Patient counseling must include an emphasis on following all medical instructions to the letter: no escalation of doses and no mixing of methadone with other prescriptions, alcohol, or illicit substances. Patients should be warned that any deviation in this regard can be dangerous, even fatal.

These guidelines represent a more conservative recommendation than seen elsewhere. Certainly, some patients are able to tolerate a much more rapid conversion or titration. Nevertheless, given the reports of deaths associated with methadone, these starting guidelines should help clinicians ensure patient safety and give methadone pain therapy a greater chance of success. Safety must come first. More aggressive pain control may follow once the mechanisms behind the increase in methadone-related deaths are further researched and better understood.

CONCLUSION

Methadone has unique properties that may make it subject to overdose, especially during its initial use. It is important to clarify these properties to all practitioners who use methadone to treat pain. These problems must be swiftly dealt with. Many thousands of people are still under-treated for pain. The quickest way for practitioners, many of whom already fear treating pain with opioids, to lose confidence in opioid therapy is for pain specialists to fail to acknowledge problems with opioid toxicity when they arise.

Many questions must still be answered in future research: What is the primary source—or sources—of misused methadone? Is it possible to reach a medical consensus on the doses, combinations, or other factors that turn methadone lethal? Which patient characteristics are also risk factors for accidental overdose when prescribed methadone for pain? Does the time of day at which methadone is consumed influence the potential for a fatal dose? Is there opioid-specific tolerance to respiratory depression? How much cross-tolerance between opioids can be developed? What factors will influence the degree of cross-tolerance? Is tolerance to respiratory depression reduced with concomitant medications commonly used in treating chronic pain? If so, how much and which concomitant medications pose the greatest risk?

Until these questions are answered, physicians must adopt a cautious, conservative approach to the use of methadone and closely monitor patient response. Continued trust in the principles of pain management depends on the widespread availability of dosing guidelines that do no harm. In the case of methadone prescribing for pain, a certain urgency exists in this respect.

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Role of gabapentin in postoperative pain

Alparslan Turan, MD

Postoperative pain is a major factor that affects recovery from anesthesia and surgery. Different classes of analgesics have been used alone or in combination for the treatment of postoperative pain. Opioids, although highly effective in managing pain, have a range of side effects such as respiratory depression, central nervous system depression/sedation, and nausea/vomiting.[1] These side effects are common and can limit the use of opioids, despite their analgesic efficacy, in postoperative analgesia. However, a multimodal analgesic concept in which opioids are combined with nonopioids could enhance analgesia, reduce opioid requirements, and decrease opioid-related side effects.

Pain signals from the nociceptors may result in sensitization of secondary nociceptive neurons in the dorsal horn. This is mediated by a decrease in inhibitory input or an increase in synaptic efficacy or membrane excitability, triggered by windup, neurokinin, and N-methyl-d-aspartic acid (NMDA) receptor mechanisms.[2,3] Subsequent activity in nociceptors and non-nociceptive A-β fibers will be amplified, leading to increased pain, hyperalgesia and allodynia.[4]

Gabapentin is a structural analog of γ-aminobutyric acid (GABA), which is an anticonvulsant drug. Gabapentin has been shown to be effective in neuropathic pain,[5] diabetic neuropathy,[6] postherpetic neuralgia,[7] and reflex sympathetic dystrophy.[8] Pretreatment with gabapentin blocked the development of hyperalgesia, suggesting a preventive effect of gabapentin.[9] Recent studies suggest that gabapentin may be useful in the perioperative setting as an adjuvant to parenteral opioid analgesics in the postoperative period.[4,11-13] Different pain models have been used, demonstrating significant analgesic properties and a decrease in opioid consumption in these studies.

A possible mechanism for gabapentin-mediated analgesia is the modulation of glutamate receptors NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate. Gabapentin seems to decrease both NMDA- and non-NMDA-mediated glutamate currents in the superficial lamina of the rat spinal cord,[14] and also inhibits nociceptive responses to intrathecal NMDA and AMPA in vivo.[15] Furthermore, the analgesic effects of gabapentin are antagonized by the NMDA/glycine receptor agonist serine.[16,17] The findings of Suarez et al.[18] suggest that sodium entry through presynaptic NMDA-R channels facilitates axon excitability, and the interaction of gabapentin with this mechanism might contribute to its analgesic benefits. Gabapentin has no direct GABAergic action, and does not block GABA uptake or metabolism.[19] Another suggested mechanism for gabapentin is that it binds to the voltage-dependent calcium channels.[20] All of the suggested mechanisms can be responsible for the analgesic action of gabapentin; however, no consensus has been made. An animal experiment done by Shimoyama et al.[21] showed that intrathecal gabapentin significantly enhanced the effect of an intrathecal subanalgesic dose of morphine in the rat. A recent study[22] also revealed that combined spinal administration of gabapentin and low doses of morphine significantly reduced pain-related behaviors in this acute rat pancreatitis model, whereas these agents were ineffective when used alone in the selected dose range. Regional techniques combined with gabapentin must be the main aim for future studies; interaction with opioids and local anesthetics in different models also needs to be investigated.

Gilron et al.,[23] in a placebo-controlled randomized clinical trial, compared gabapentin individually with rofecoxib, and their combination, on postoperative hysterectomy pain. The combination was superior to the individual agents in pain control, opioid consumption, and accelerated pulmonary recovery. This study is a perfect example of combining different types of drugs in a postoperative pain model setting. Another study by Gilron combining gabapentin with morphine for neuropathic pain also achieved better analgesia with lower doses of a combination of the drugs than either as a single agent.[24]

The main aim in combining different analgesic drugs and techniques is to obtain synergistic or additive analgesia, allowing a lower dose of each agent with an improved safety profile. This can be achieved by combining analgesics acting at different locations, such as centrally and peripherally acting analgesics. Future studies should focus on combining gabapentin with different

NSAIDs and determining the most effective dose to reduce postoperative pain and the potential side effects of opioids.

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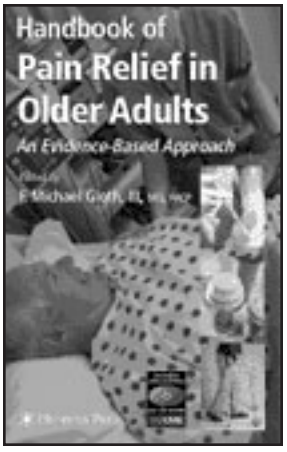

***Handbook of Pain Relief in Older Adults: An Evidence-Based Approach*. Edited by F. Michael Gloth, III, MD, FACP. Published by Humana Press, Totowa, NJ; 2004, 264 pp.**

Handbook of Pain Relief in Older Adults: An Evidence-Based Approach presents healthcare providers, patients that are victimized by pain, and their caregivers a broad survey of negotiating pain in the elderly population. It provides information covering the management of pain, socioeconomic and political issues, and cultural and spiritual issues, including the legal aspects that are requisite to decreasing pain in the elderly population.

Two unique features set this text apart from others. The first is its supplementary materials, including a continuing medical education (CME) certification, a CME posttest and evaluation to be completed and submitted for credit, and an appendix of analgesics with description of initial oral dosing, maximum oral dosing, and some unique considerations for the geriatric patient. A 6.5-hour American Medical Association/Physician's Recognition Award Category I CME credit is provided for the completion of the included test within the book. The second feature is a CD-ROM, which contains a single-license Adobe-format E-book version of the volume. The CD-ROM is viewable on a computer and able to be synchronized to a PDA hand-held device.

Chapter 1 is a well-written introduction, which contains a glossary of terms used in the management of pain along with tables and descriptions of obstacles often encountered in the management of pain in the elderly that are experienced by the patients themselves, healthcare professionals, and the healthcare system.

Chapter 2 discusses appropriate pain scales for the elderly patient in a functional scale model. Also covered are assessment of pain in those patients that are cognitively or communication impaired and discussion of research versus clinical care instruments available as screening instruments, which can be exceeded for the assessment of the pain patients with cognitive deficits.

Chapter 3 covers preventive analgesia evaluation and therapy. The chapter focuses on establishing an introductory pain assessment treatment plan and a pain history, including awareness of the patient and providers, barriers, and listening to as opposed to simply hearing the patient. Patient and family experience and expectations of pharmacotherapeutic risk assessment are discussed. Most importantly, this chapter reflects family and patient needs and expectations during the initial interview.

Chapter 4 is highly unique, discussing spirituality as an adjunct to pain management. This chapter discriminates pain and suffering and cross-cultural issues in spirituality along with pain and spiritual activity and practical applications. Of great significance is the table identifying how one takes a spiritual history with a nomogram.

Chapter 5 describes exercise and physical modalities such as heat vs. cold, cryotherapy, thermal therapy, electrotherapy, manual therapy, creation of physical medicine and rehabilitation descriptions, and kinematic therapy (i.e., static and dynamic body positioning). This chapter presents to the reader that the judicious use of physical medicine and rehabilitation modalities with exercise not only aids in the prevention of chronic illness and impairment, but also provides decrements in pharmacologic intervention.

Chapter 6 discusses the nonopioid pharmacotherapy of pain in older adults and provides an overview of acetaminophen, nonsteroidal anti-inflammatory drugs, and tramadol. Other factors discussed in the chapter are pharmacokinetic (i.e., absorption, distribution, metabolism, and elimination) and pharmacodynamic considerations with the event of comorbid disease states. Much of this information is not that dissimilar to what can be found in the *Physician's Desk Reference* and other standard drug handbooks.

Chapter 7 centers on opioids and adjuvants, with discussion of the mechanism of action of opioids, their place in therapy, adverse events and precautions, and adjuvant analgesics. Also discussed, briefly, are some antidepressants and anticonvulsants.

Chapter 8 looks at interventional strategies for the management of pain. These strategies are primarily invasive and offered by multidisciplinary comprehensive pain centers, to include nerve blocks, facet blocks, sympathetic blocks, stellic ganglion blocks, celiac plexus blocks, lumbar sympathetic blocks, and superior hypogastric plexus blocks. A section of the chapter is devoted to that of nerve destruction, along with information on spinal cord stimulators and drug delivery via epidural and intrathecal routes with a discussion of implantable

intrathecal pumps. Other invasive techniques are also covered, such as verteboplasty, cypoplasty, intradiscal electrothermal anaeroplasty, and nucleoplasty (IDET). Botulinum toxin is also mentioned, focusing on reduction of muscle contraction and spasms. Finally, it should be noted that the illustrations and photographs in this chapter are exceptional.

Chapter 9 deals with pain management and long-term care. A description of the epidemiology of pain is followed by discussion of barriers to successful pain assessment and management, all within the confines of a nursing home. This assessment of pain is composed of a multidisciplinary model as a part of the Omnibus Budget Reconciliation Act (COBRA) of 1987, and the Resident Assessment Instrument, with its minimum data set (MDS), was developed to improve patient care with systematic planning. The MDS evaluates residents for a range of nursing home quality measures, which include pain, and is performed on every resident at a facility that receives federal funding under Medicaid or Medicare when there is a change in patient condition and on a quarterly basis. Data points are entered by a member of the nursing staff who uses a variety of sources of information about the resident to determine the most appropriate response for each item. Results of the MDS are forwarded electronically to the state and the US Department of Health and Human Services.

Chapter 10 gives an interesting discussion on how the healthcare professional may influence representation, joining a professional society, resisting restrictive (and costly) regulatory and manipulation efforts, and reminding all leaders that "all politics are vocal." In addition, some insights for healthcare professionals on using the media to advance the message of pain are provided.

Chapter 11 focuses on use of the Internet and electronic medical records to assist with pain relief. Of US adults over the age of 50 years, 40 percent of them have a computer. Discussion of the use of electronic medical records and a list of Internet sites featuring pain information, along with a brief description of each site, are also included. Some of the sites are sponsored by corporations, societies, the government, and/or institutions. One site of specific interest concerns sickle cell disease. This site is updated on a regular basis, and is sponsored by the Sickle Cell Disease Association of America.

Chapter 12 is also encouraged for review by patients, caregivers, and families. It discusses the patient "bill of rights," opiophobia, compliance and reporting issues, alternative therapies, and information acquisition by the patient and family.

The final chapter in the book presents suggestions for change in education policy and communication, and overview improved educational efforts improving efforts focused at education and research, changes on policy and mechanism for disseminating information. An appendix is included at the end of the text that lists selected analgesics and opportunities for use in older patients. It includes starting oral dose, maximum oral dose, and selected special considerations.

In conclusion, this text offers practical advice to the healthcare provider, patient, and family to achieve a higher degree of relief for those with less than adequate control of nociceptive and/or neuropathic pain. It encourages the reader to work together with the patient and family to ensure that management is a shared event. This fast-reading text is highly recommended for those who treat, manage, or are victimized by pain.

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MEETING REVIEW

The World Institute of Pain: Advancing research and clinical practice

Stephen J. Ziegler, PhD, JD

INTRODUCTION

In September 2004, pain specialists from around the globe attended the Third World Congress of the World Institute of Pain (WIP), held in Barcelona, Spain. The conference ("Pain: Advances in Research and Clinical Practice") was widely attended by scientists, practitioners, pharmaceutical industry representatives, and other interested parties.[1] As a social scientist who studies the medicolegal barriers to the treatment of pain,[2] I was elated when the WIP invited me to speak in Barcelona. I must admit, however, that before receiving my invitation I was largely unaware of the WIP's purpose and mission. Consequently, in an effort to inform the readership about the valuable contribution of the WIP, the following article provides an overview of the organization and its most recent conference, and concludes with a brief comment about how their efforts could actually help depoliticize the regulation of medicine in general and opioids in particular.

WORLD INSTITUTE OF PAIN OVERVIEW

The inadequate treatment of pain remains one of the most significant health problems facing patients and providers in the United States and around the world. Researchers from a myriad of disciplines have identified many of the barriers to the relief of pain such as, but not limited to, inadequate training, insufficient knowledge, and fear of regulatory scrutiny.[3,4] Consequently, in an international collaborative effort to address these barriers and thereby reduce the incidence of pain among chronic, acute, and terminally ill populations, the WIP was formed. Since its formation in 1995 by a group of internationally renowned physicians, its founding members have striven to bridge the gap between theory and practice and enable practitioners "to develop links among international pain centers for patient consultation, physician training, research, protocol development, and pain therapy certification."[1] In addition to its workshop offerings each year, the WIP hosts an international conference every other year (World Congress) with multiple conference panels and exhibits, publishes its own journal (*Pain Practice*), and offers pain specialists the opportunity to become fellows in interventional pain practice (FIPP).[1]

CONFERENCE OVERVIEW: SEPTEMBER 21–25, 2004

The past year's World Congress was held in Barcelona, Spain, at the Palau de Congressos Barcelona Conference Center. The facilities were well staffed with ample room to accommodate the 2,000 or more attendees, and all lectures were in English. In addition to the scientific panels, poster sessions, social events, and vendor exhibits at the Congress, the WIP also provided training courses on the essentials of pain medicine and interventional techniques (followed by an examination for those seeking to become fellows in interventional pain practice). The Congress covered a variety of topics such as pharmacological developments, invasive procedures and surgery, cancer pain and palliative care, diagnosis and assessment, and ethics, as well as medicolegal issues stemming from the treatment of pain. Although many of the lectures focused on cutting-edge clinical techniques, the medicolegal issues of pain treatment were certainly not ignored.

Aside from my own lecture on the fear of prosecution stemming from the aggressive treatment of pain and the regulation of opioids, the keynote speaker was a professor of criminal law whose Presidential Lecture focused on the impact of law and the right to pain relief.[5] Clearly, by inviting me and selecting a criminal law professor to present the Presidential Lecture, the conference organizers rightly recognized the value and need for interdisciplinary collaboration and the role of politics in the treatment of pain. Although the law and political process have undoubtedly raised the standard of care, politics and the lawmaking process have also created barriers to the treatment of pain.[2] Consequently, I would argue that the medical profession should take a more proactive approach and avoid the politicization of medicine by remaining several steps ahead of the regulators and avoiding the political process as much as possible.[6] An example of one such effort is the creation of standards

within the profession, by the profession. Such is the case with the WIP's program in Interventional Pain Practice.

FELLOWS IN INTERVENTIONAL PAIN PRACTICE: BENEFITS BEYOND CLINICAL

Among the many new programs that the WIP has implemented, the organization is particularly proud of their efforts in developing training courses in pain medicine and interventional techniques. The WIP continues to organize workshops on interventional pain practice, and even offers a clinical examination to those interested in becoming an FIPP. These efforts are consistent with the WIP's goal to provide a more focused approach to pain management and the "development of Pain Medicine as a specialty throughout the world."[1] Moreover, all of these efforts to improve the quality of pain treatment come from within the medical community, a bottom-up approach, and consequently avoids the political process associated with regulation and legislation.

At times, the lawmaking process can be a good thing, particularly because it is a very political and public one (as it should be). Although laws and regulations have contributed to improving standards, the larger question is whether we need yet another law or regulation on top of the many we already have. Politicians, particularly legislators, are in the business of making laws and want to retain their positions. Consequently, they must remain in the public spotlight and will often resort to credit claiming and, at times, grandstanding. The "War on Drugs" is a prime example. Becoming a champion of this cause is often too tempting for most politicians to resist. Instead of focusing on the negative impact of law associated with the prescription of opioids, most find political rewards in repeating the same tired rhetoric about crime and drugs.[6] Politicians realize that it is often simpler to scare people with images of drug pushers corrupting our children than discuss the negative impact of law on patients and providers and risk being seen as soft on crime (or terrorism, for that matter). The role of balance somehow gets lost in the translation. Accordingly, internal efforts by the WIP to improve the treatment of pain through its training programs and certification as fellows in interventional pain practice effectively improve the standard of care without involving the political process or increased regulatory oversight.

CONCLUSION

The WIP is a growing organization with laudable goals and a membership dedicated to the reduction of pain. In addition to its many training events and opportunities to confer with colleagues on social and professional levels, the WIP has developed a clinical examination and a fellowship program directed at improving the treatment of pain from within the medical community. Although the eradication of pain will take a collaborative effort among a variety of disciplines, the effort by the WIP to improve the standard of care while avoiding the political process is certainly a step in the right direction.

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