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A medical journal for proper and adequate use

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Journal of Opioid Management™

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LOOKING AHEAD TO 2007

OPIOID
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Dear Colleagues,

Good news! It's now official: the *Journal of Opioid Management* has been accepted for inclusion in ***Index Medicus,*** the principal bibliographic database of the National Library of Medicine—a powerful and unambiguous endorsement of the quality of this journal's content. *Index Medicus* is used nationally and internationally to provide access to the world's biomedical journal literature. Inclusion in *Index Medicus* means that the Journal will also be cataloged in its online counterpart, MEDLINE. Congratulations to one and all!

On another front, last fall the publishers of the *Journal of Opioid Management* joined with members of the Journal's editorial review board and formed the Opioid Management Society—a professional organization dedicated to educating physicians in the proper and adequate use of opioid analgesics.

As you know, opioids may deliver an incomparable level of relief to some patients with severe pain, but they also have a downside that includes diversion, addiction, and possible regulatory action. Faced with these unintended consequences and trying to sort out who's genuinely miserable from those just seeking a fix, doctors have become acutely aware that they must get it right. They want to provide relief, but they also want to keep people safe and stay out of trouble themselves.

Now, here in the fall of 2006, we, the members of the Society, can say we've come a long way in realizing our mission. To date, we have held four very successful, fully accredited conferences—the Opioid Education Program—each designed specifically to inform opioid prescribers in the myriad uses, abuses, and legal ramifications of these powerful painkillers. Judging by the reviews we've received from hundreds of our attendees and the physicians themselves (who, as we all know, are often tough critics), we have been overwhelmingly successful. Clearly, there is a pronounced need for first-rate education around this powerful class of pain medications, and we will continue to strive to provide these educational opportunities.

Thus, armed with the feedback we've received from our attendees and from our faculty of renowned speakers, we are in the process of making our conference curriculum even more relevant and compelling in the new year. Our first conference of 2007 will be in Boston April 14-15 at the Conference Center at Harvard Medical. As for the rest of our 2007 schedule, look for an announcement soon here in an upcoming issue of the Journal as well as at our Society's Web site (*www.opioidmanagementsociety.org*).

As always, I thank you for your interest and consideration.

Very truly yours,

Robert E. Enck, MD

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Opioid Management Society
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GUEST EDITORIAL

Healthcare professionals and the DEA: Restoring the balance

Howard A. Heit, MD, FACP, FASAM

We in the pain community were afraid that, as Yogi Berra once said, it would be "déjà vu all over again" when, on September 6, 2006, the Drug Enforcement Administration (DEA) announced from its office in Arlington, Virginia, its proposed regulations on the issuance of multiple prescriptions for Schedule II controlled substances[1] (CSs) and their policy for dispensing CSs for the treatment of pain.[2] But my colleagues and I were pleased when we could say, "Not this time, Yogi!"

The DEA proposes to amend its regulations to allow practitioners to provide individual patients with multiple prescriptions, to be filled sequentially, for the same Schedule II CS; such multiple prescriptions allow a patient to receive up to a 90-day supply of the CS. This will allow the return of the "Do Not Fill Until _____" prescription. This proposal, along with the clarification of the DEA's policy on dispensing CSs for the treatment of pain, reopens the dialogue between the DEA and healthcare professionals, a move that is to the benefit of prescribers, patients, and society as a whole. In my opinion, it also reflects recognition that the DEA and healthcare professionals who are treating pain have the shared goal of "balance"—to ensure that those who need Schedule II CSs for pain or other medical conditions receive them, while preventing misuse and diversion.[3]

The DEA announced the following:

> 1. The refilling of a prescription for a CS listed in Schedule II is prohibited. This is not a change from existing regulation (21 CFR 1306.2).
>
> 2. An individual practitioner may issue multiple prescriptions authorizing the patient to receive a total of up to 90 days' worth of a Schedule II CS, provided the following conditions are met:
>
> a. The individual practitioner properly determines that there is a legitimate medical purpose for the patient to be prescribed that CS, and the individual practitioner is acting in the usual course of professional practice. This is not a change from existing regulation (21 CFR 1306.04).
>
> b. The individual practitioner writes instructions on each prescription (other than the first prescription) regarding whether he or she intends for that prescription to be filled immediately or indicating the earliest date on which a pharmacy may fill the prescription.
>
> c. The individual practitioner concludes that providing the patient with multiple prescriptions in this manner does not create an undue risk of diversion or abuse.
>
> d. The issuance of multiple prescriptions as described in this section is permissible under the applicable state laws.
>
> e. The individual practitioner complies fully with all other applicable requirements under the act and these regulations, as well as any additional requirements under state law.
>
> 3. This new policy shall not be construed as mandating or encouraging individual practitioners to issue multiple prescriptions or to see their patients only once every 90 days when prescribing Schedule II CSs. Rather, individual practitioners must determine on their own, based on sound medical judgment and in accordance with established medical standards, whether it is appropriate to issue multiple prescriptions and how often to see the patient when doing so.
>
> 4. When a prescription has been prepared with instructions from the prescribing practitioner indicating that the prescription shall not be filled until a certain date, no pharmacist may fill the prescription before that date.

Based on these new regulations, it appears to me that the DEA has listened to the medical community and addressed many of our concerns.

A prescriber, if he or she deems it appropriate, can now write any number of sequential prescriptions providing up to a 90-day supply. All of the prescriptions must be dated, usually in the upper right corner, on the date of issue. "Do Not Fill Until _____" must be written on all prescriptions that are to be filled after the date of the first prescription. (All prescriptions for CSs shall be dated as of, and signed on, the date when issued. One must ***never*** postdate a prescription [21 CFR 1306.05]).

The return of the "Do Not Fill Until _____" prescription allows stable patients to be evaluated and prescribed their CSs at intervals that are determined by the patients' individual treatment plans. The stable patient is happy because he or she does not have to bear the unnecessary cost of frequent office visits, the insurance company is happy because it is receiving a co-payment for each prescription (usually a 30-day supply), and the prescriber is happy because he or she has fewer administrative tasks and more open slots to see patients—a win-win for everyone.

Being able to use a "Do Not Fill Until _____" format also allows a prescriber who is seeing a new patient or a patient with a comorbid condition (or conditions) to make the clinical decision to see the patient every two weeks but prescribe one week's worth of a CS at a time.

I believe the DEA has recognized that allowing a prescriber to have more control over the amount and interval of a prescription for a Schedule II medication may lead to less abuse and diversion of CSs, a goal shared by the medical community and the DEA.

The DEA's policy for dispensing CSs for the treatment of pain states that the DEA's charge is to enforce existing regulations and to clarify existing regulations upon request.[2] The DEA does not want to write or endorse guidelines, or to be perceived as practicing medicine. Therefore, it is the prescriber's responsibility to know and follow all federal regulations for prescribing a CS. However, it is the DEA's responsibility to ensure that all DEA agents, from the national to the local level, be knowledgeable about the agency's regulations, enforce the regulations, and follow the policies as written. If all parties accept their responsibilities, the result should be less-fearful healthcare professionals who are able to appropriately prescribe CSs, as well as reduced suffering and increased productivity for millions of patients who do not currently have access to pain management.

Howard A. Heit, MD, FACP, FASAM, assistant clinical professor, Georgetown University, Fairfax, Virginia.

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Science at the mercy of the mob: Dr. Hurwitz's legal problems in perspective

Siobhan Reynolds, MA, MFA

> Socrates is an evil-doer, and a curious person, who searches into things under the earth and in heaven, and he makes the worse appear the better cause; and he teaches the aforesaid doctrines to others.
>
> —Socrates in Plato's *Apology*[1]

As most members of the pain management community are aware, Dr. William Hurwitz's drug-trafficking conviction was recently overturned in the Fourth Circuit, after it was proven that the jury had not been correctly instructed on the issue of "good faith" related to the prescription of controlled substances. This was hailed at the time as a victory for all of us. When the legal implications are examined, however, one can see the victory unearths more problems than it solves.

Mainstream legal thinkers laud the Fourth Circuit's ruling because they expect Dr. Hurwitz's retrial to provide the pain management community with the opportunity to overcome future government accusations by successfully asserting its own medical standards. This didn't occur in the first trial, and those following the case are mistaken if they think the inclusion of a good faith jury instruction will make the difference this time around.

In Dr. Hurwitz's case, as well as in each of the other cases that my organization, Pain Relief Network, has assisted on, the defense teams have presented overwhelming evidence that the accused physician's conduct fell well within the medical standard of care. Regardless of the issuance of a good faith jury instruction, such testimony has had no positive effect on the outcome in any of our other cases. Juries are routinely convinced by the government's accusation—despite what defense experts say to the contrary—that what the doctor did was criminal in nature. This is because the government's characterization is consistent with the layman's view of how opioids ought to be prescribed, i.e., rarely or never.

The average American doesn't view opioids as "real" medicines like antidepressants or insulin. Rather, he or she imagines them to be substances imbued with evil powers that enslave their victims, transforming them into drug-addicted, crime-committing zombies. Such a powerful and irrational image can not be entirely defeated by reason or science. To believe that Dr. Hurwitz's retrial will be fair is to utterly fail to grasp the profound disadvantage that medical science suffers in federal criminal courts under the existing statutory scheme.

The Controlled Substances Act (CSA) was never intended to create a "battle between experts" such as we saw in Dr. Hurwitz's first trial, as well as in all the other cases currently making their way up through the appellate process. Justice Kennedy addressed this issue when he wrote for the majority in *Gonzales v. Oregon*.[2] While this case was ostensibly about physician-assisted suicide, it more importantly defined the limits of the attorney general's authority over medical practice: "The statutory references to 'control' . . . [make] clear that the Attorney General can establish controls against diversion . . . but do not give him authority to define diversion based on his view of legitimate medical practice."

So the arguments currently being had in Federal courts all over the country as to whether or not the medicine practiced by the defendant doctor was "legitimate" or not are, quite simply, badly off point. Kennedy[2] adds further,

> Congress regulates medical practice in so far as it bars doctors from using their prescription-writing powers as a means to engage in illicit drug dealing and trafficking as conventionally understood . . . . [T]he Act [the CSA] manifests no intent to regulate the practice of medicine generally, which is understandable given federalism's structure and limitations.

One might ask how, given these limitations, we arrived at a point so profoundly disadvantageous to the autonomy of medical practitioners, as this was clearly not the intent of the authors of the CSA. As it turns out, the Department of Justice itself added the phrase "legitimate medical purpose" to the federal rule giving force to the CSA, thereby accomplishing an end run around the restrictiveness of the statute they were purporting to merely interpret.

Effectively, government lawyers during the Nixon administration wrote themselves a new power—namely, to criminally prosecute physicians whose practices they believed were inconsistent with how they thought pain management ought to be practiced. In other words, they empowered themselves to establish standards for the practice of medicine based on their own preferences, rather than on medical science or compassion. Blessedly, the Supreme Court in *Gonzales v. Oregon* disallowed the Justice Department's attempt to outlaw physician-assisted suicide, which was premised on the same expansive legal theory. Justice Kennedy devoted quite a bit of his argument to this problem, using extremely strong and precise language in denouncing the government's exercise of its power under these terms[2]:

> By this logic, however, the Attorney General claims extraordinary authority. If the Attorney General's argument were correct, his power to deregister necessarily would include the greater power to criminalize even the actions of registered physicians, whenever they engage in conduct he deems illegitimate. ***This power to criminalize***—unlike his power over registration, which must be exercised only after considering five express statutory factors—***would be unrestrained***. [Italics added for emphasis.] It would be anomalous for Congress to have so painstakingly described the Attorney General's limited authority to deregister a single physician or schedule a single drug, but to have given him, just by implication, authority to declare an entire class of activity outside "the course of professional practice" and therefore a criminal violation of the CSA.

Unfortunately, the court has yet to apply this analysis to delimit the power of federal prosecutors in the cases of pain-treating physicians, and, oddly, mainstream legal thinkers do not seem to perceive the legal connection between the *Gonzales* case and the government's misconduct in its pursuit of pain-treating physicians.

The Fourth's concession that Dr. Hurwitz's good faith was indeed relevant to whether or not he had committed a crime demonstrates just how far down the rabbit hole pain doctors and their patients really are after nearly four decades of case law developed on what amounts to no more than a rhetorical sleight of hand. When we are dependent upon courts to rule that actual innocence might reasonably figure into a jury's deliberations in deciding the fate of a man who no one disputes was practicing medicine in good faith, we have no reason for celebration.

Mainstream legal thinkers in this area need to take off their rose-colored glasses and take a hard look at the CSA and how it actually functions. Because if, as Justice Kennedy noted in the *Gonzales* opinion,[2] "[t]he CSA's structure and operation presume and rely upon a functioning medical profession regulated under the state's police powers," then it is incumbent upon the pain-treating community to ask itself whether working in terror, prescribing "anything but opioids," and allowing patients to deteriorate in order to "stay under the radar" really constitutes a functioning medical profession. Dr. Hurwitz was applying the current science in his ethical practice of clinical medicine to patients in chronic pain, and it was this behavior which provoked the wrath of the mob. That he did so in good faith is not likely to protect him from further punishment.

Siobhan Reynolds, MA, MFA, President, Pain Relief Network, New York City, New York, and Santa Fe, New Mexico.

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A patient-activated iontophoretic transdermal system for acute pain management with fentanyl hydrochloride: Overview and applications

Kevin T. Bain, PharmD, BCPS, CGP, FASCP

ABSTRACT

Opioid administration by patient-controlled analgesia (PCA) is the standard therapy for acute postoperative pain. Despite its utility in this setting, limitations of this modality do exist. Consequently, noninvasive PCA systems, including an iontophoretic transdermal system (ITS) with fentanyl hydrochloride, are under development to circumvent many of these limitations. This preprogrammed, self-contained, compact, needle-free system provides pain control superior to that of placebo and comparable to morphine PCA in the first 24 hours after major surgical procedures. The objectives of this article are to describe the method of transdermal iontophoretic medication administration and to review the literature pertaining to the fentanyl ITS.

Key words: iontophoresis, transdermal, fentanyl, opioid analgesics, patient-controlled analgesia, noninvasive method, postoperative pain, acute pain, breakthrough pain

INTRODUCTION

Opioids are the most commonly used analgesics for the management of moderate to severe acute pain in the postoperative setting[1]; the most frequently used opioids are morphine and fentanyl.[2] Acute pain can be managed using a variety of modalities; however, since its introduction two decades ago,[3] patient-controlled analgesia (PCA), which is usually administered via the intravenous (IV) or epidural route, has become the most common method of postoperative opioid delivery. Postoperative pain management has evolved over the last 20 years through the application of new knowledge and technology to existing opioids and the development of new methods of medication administration, such as PCA and spinal administration, rather than through the introduction of new medications.[4]

Although PCA with opioids has become one of the most effective techniques in the management of acute postoperative pain and a number of studies indicate that patients prefer this method of analgesic administration over more conventional methods (e.g., intramuscular [IM] injections on an as-needed basis),[5] a number of drawbacks are associated with its use. The administration of PCA requires equipment that is costly, cumbersome, and invasive. The typical PCA delivery system requires the technical expertise of involved nursing and pharmacy staff.[6] Problems that compromise patient safety, such as programming errors, uncontrolled delivery of syringe contents, pump failures, syringe mix-ups, and inappropriate use of the system (e.g., patient tampering or family administration of doses by proxy), have all been reported.[7,8] Failures of this delivery method secondary to IV line occlusions and catheter infiltration into the subcutaneous tissue are also possible.[7,9,10] Consequently, noninvasive PCA systems that could circumvent many of these problems are under development, with the aims of maximizing efficacy and minimizing risks to the patient. If proven successful, an effective, noninvasive PCA system would be an attractive alternative for the control of postoperative pain.

Recently, a noninvasive patient-activated transdermal system that uses the iontophoretic drug delivery process known as E-TRANS® (ALZA Corporation, Mountain View, CA) to deliver fentanyl hydrochloride has been developed (fentanyl iontophoretic transdermal system [ITS]; IONSYS™; Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ). Formerly, the transdermal delivery of fentanyl has been limited to a commercially available patch formulation (Duragesic®; Janssen Pharmaceutica, L.P., Titusville, NJ); however, this transdermal therapeutic system (TTS) is contraindicated for use in the treatment of acute postoperative pain.[11] The features and uses of the fentanyl ITS are substantially different from those of the conventional TTS formulation. The objectives of this article are to describe the method of transdermal iontophoretic medication administration and to review the literature pertaining to the fentanyl ITS. To help achieve these objectives, a literature search of the MEDLINE database was carried out using the search terms "iontophoresis," "transdermal," "patient-controlled analgesia," "opioid," and "fentanyl." References were restricted to English-language articles published within the past 20 years (January 1986 to August 2006). Additional relevant literature was procured after searching the reference citations of retrieved articles.

TRANSDERMAL DRUG DELIVERY AND IONTOPHORESIS

Transdermal drug delivery holds significant potential for the noninvasive administration of therapeutic agents. It avoids the problems of first-pass metabolism and chemical degradation in the gastrointestinal tract and provides a simple method of continuous administration of medication.[12] In addition, the skin provides a large, accessible surface area for drug delivery. However, the principal disadvantage is that the composition and architecture of the skin render it a formidable barrier to chemical permeation.[11,13-16] The major barrier to permeation is the uppermost of the five layers of the epidermis, the stratum corneum, which constitutes the rate-limiting layer for transdermal absorption of drugs.[15] The physicochemical constraints of the stratum corneum (i.e., multiple layers of corneocytes embedded in lipid bilayers) severely limit the number and type of molecules that can be considered as realistic candidates for passive delivery via this route of administration.[11,14,16]

In order for medications to penetrate the stratum corneum and reach the systemic circulation in clinically significant amounts, drugs need to be potent, have a low molecular weight (MW), and preferably be both lipophilic and ionized.[12-15] The physicochemical and pharmacological properties of opioid analgesics (e.g., capable of eliciting a pharmacological effect at relatively low systemic concentrations, typically in the ng/ml range; MW in the range of 300 to 500 Da; and usually positively charged at physiological conditions) make these molecules candidates for transdermal delivery.[14] However, the fundamental reason for there being so few transdermal opioids on the market is that the highly impermeable skin limits daily drug dosage, delivered from an acceptably sized patch, to about 10 mg.[13]

Fentanyl is a synthetic opioid that is widely used as both an analgesic and an anesthetic agent because of its rapid onset and short duration of action after parenteral administration.[17] Several of fentanyl's characteristics make it the ideal opioid for transdermal delivery. Fentanyl is a very potent analgesic (100 to 500 times the analgesic efficacy of morphine per dose) with high affinity for the μ opioid receptor.[14] Consequently, the dose needed to elicit a therapeutic response is on the order of magnitude of μg/kg (rather than mg/kg), and the therapeutic levels necessary to produce analgesia (0.6 to 3 ng/ml) are much lower than those for other opioids, particularly morphine.[14,18,19] Fentanyl has a low MW of 286 g/mol (morphine's MW is 337 g/mol)[4] and is highly lipophilic, whereas morphine is a hydrophilic molecule. Fentanyl's lipid-soluble nature allows it to diffuse through the stratum corneum via the intercellular lipid medium.[19] Fentanyl is positively charged at a physiological pH; 8.5 percent of fentanyl is un-ionized at a pH of 7.4, whereas morphine is 23 percent un-ionized at this pH level.[14,19] Furthermore, fentanyl is subject to a considerable hepatic first-pass effect and variable metabolism, which preclude oral administration of the drug.[19] Unlike morphine, however, fentanyl does not have active metabolites that can accumulate over time.[19] Thus, fentanyl is an ideal candidate for transdermal administration, and it was the first opioid analgesic commercially available for use via this route of administration.

A number of chemical and physical enhancement techniques have been developed in the hopes of increasing the range of medications available for transdermal delivery.[14] Iontophoresis is a method of enhancing the transdermal administration of drugs across the skin by using an external electrical field.[11,12,20] A number of comprehensive reviews have been written on this subject, and clinicians interested in this topic are encouraged to review these works.[14,15,21,22] Briefly, the iontophoretic system consists of a skin delivery electrode, a skin current-returning electrode, and an electric power source. Iontophoresis functions via two main mechanisms: 1) the electrical repulsion of ionized drug from the delivery electrode, and 2) the electro-osmosis of drug via solvent flow into the stratum corneum (Figure 1).[11,13,16,23] When an external electrical field is applied, the electrically charged components of the drug are propelled through the skin and into the systemic circulation.[19] While iontophoresis substantially increases the penetration capacity of agents that are positively charged, lipophilic, and small in size,[11] this process is also capable of enhancing the delivery of both hydrophilic molecules and un-ionized moieties, including those that are not ideal candidates for this route of administration.[14,15] For example, iontophoresis has been used to deliver clinically significant doses of morphine,[24] lidocaine,[25,26] and corticosteroids to achieve analgesia.[20,27]

For the advantages of iontophoresis to be realized in pain management, the delivery method must provide pain control that is comparable to that offered by current standard therapy.[8] The efficiency and safety of this technique depend on several factors, such as current-wave form and electrode design.[15,28] The factors affecting the delivery of fentanyl by iontophoresis have been investigated extensively, and it is recognized that delivery is affected by the physicochemical nature of the drug (e.g., molecular size) and its solution (e.g., pH, concentration) and the voltage, duration, and nature of the current.[17,28-32]

PHARMACOKINETICS OF TRANSDERMAL FENTANYL DELIVERY

The fentanyl ITS is differentiated from the TTS formulation by its pharmacokinetics. There have been several reports in the literature describing the transdermal delivery of fentanyl via iontophoresis both in vitro and in vivo.[17,29,33-39] Testing in healthy volunteers has indicated that the fentanyl ITS rapidly and consistently delivers calibrated, clinically significant doses of fentanyl into the systemic circulation.[17,35] Patient characteristics such as age, gender, ethnicity, or body weight have been shown to have no significant pharmacokinetic effect.[39] Studies

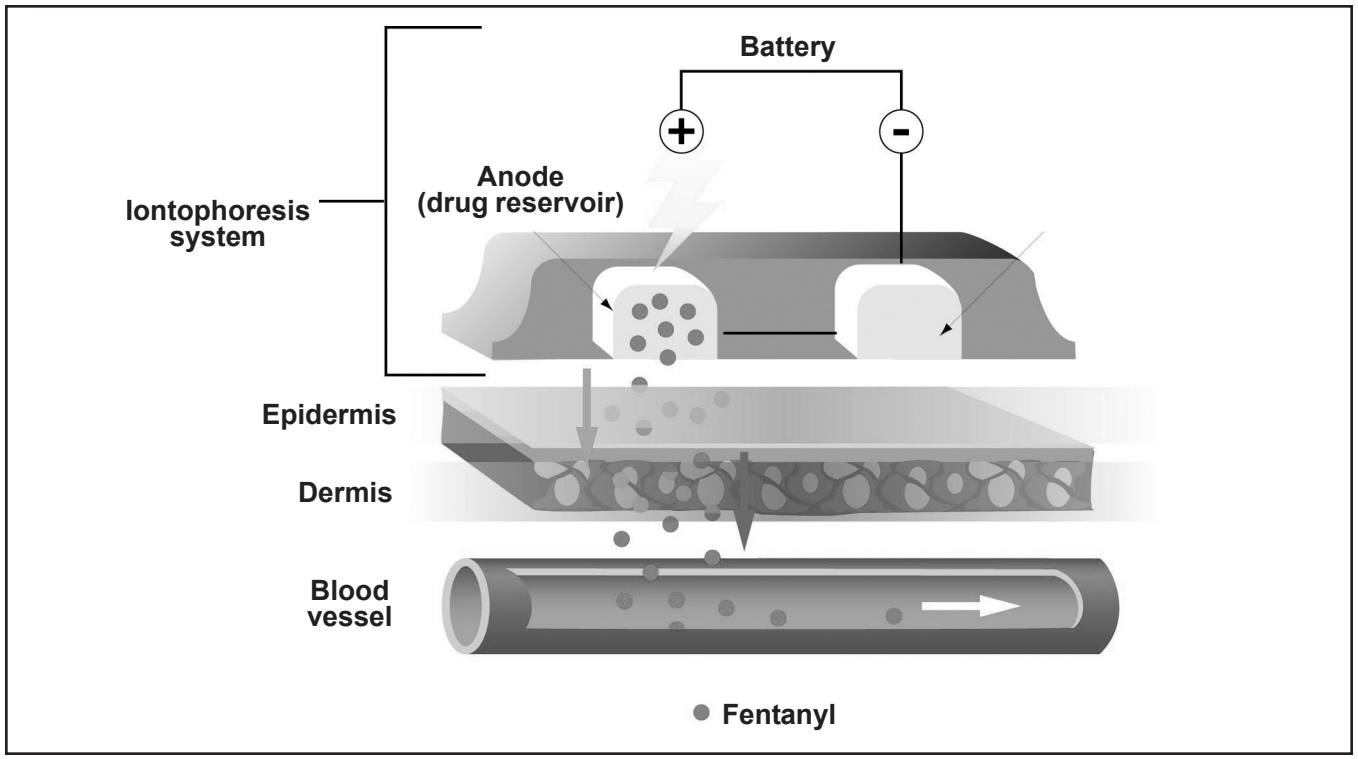

Figure 1. Schematic diagram of transdermal iontophoretic delivery of fentanyl. Reprinted with permission from Ortho-McNeil and Chelly JE.[23]

have also demonstrated that the pharmacokinetics of fentanyl delivered by the ITS remain consistent over multiple-day administration periods at the same level of opioid consumption (40 μg)[38] and that the amount of drug absorbed from the system is independent of dosing frequency.[37] However, the amount of drug absorbed from the fentanyl ITS is proportional to the magnitude of the current applied to the system,[17] with a 170 μA current/2.75 cm^2 delivering a nominal 40 μg dose of fentanyl.[38] It appears that a threshold current density (μA/cm^2) is required for a linear relation between current and amount absorbed. For fentanyl, this threshold current density seems to be about 75 μA/cm^2 or greater.[17] Thus, one may surmise that the dose of fentanyl administered by iontophoresis can be adjusted by changing the magnitude of the current. In fact, 24-hour continuous and on-demand drug delivery via iontophoresis is feasible.[17] This is in contrast with the conventional fentanyl TTS, which has the advantage of a stable pharmacokinetic profile that mimics a continuous parenteral infusion for periods of between 48 and 72 hours with repeated dosing; however, this passive transdermal formulation does not afford the same degree of dose adjustment flexibility.

The TTS formulation of fentanyl is designed to enable consistent, continuous, passive absorption of fentanyl for the duration of the patch's application. This formulation uses a rate-controlling membrane permeation model and the principle of a concentration gradient for passive diffusion of fentanyl across the skin. After application of the first TTS, the opioid is absorbed through the skin, and a depot of fentanyl concentrates in the upper skin layers. The skin depot needs to be reasonably filled before significant vascular absorption will occur.[19] Thereafter, fentanyl becomes available to the systemic circulation, and it takes several hours' latency before the clinical effects of fentanyl can be observed.[4] Specifically, fentanyl concentrations are not measurable until at least two hours after application of a 75 or 100 μg/h TTS[40,41]; plasma concentrations of fentanyl peak at an average of 24 hours (range: 14 to 28 hours) after the patch is applied[19] and approach steady state at approximately 72 hours postapplication.[42,43] Conversely, the ITS uses iontophoresis to drive fentanyl across intact skin. Passive absorption of fentanyl from the ITS is minimal; in trials serum fentanyl levels were undetectable in patients when the system was applied without the activation of electrical current.[35] The mean amount of time between the activation of the fentanyl ITS and maximum serum concentration has been shown to be slightly longer than that seen with IV fentanyl administration over the same duration; however, the increase in concentration after termination of the ITS dose is small.[11,38]

The presence of a fentanyl skin depot also has implications for the drug's duration of activity and elimination. Upon inactivation or removal of the fentanyl ITS, the rapid decline in serum fentanyl concentrations that occurs is similar to the decrease in serum fentanyl concentrations following the cessation of IV fentanyl treatment,[17,36] suggesting that a subcutaneous depot or "reservoir effect" with the fentanyl ITS is minimal. In contrast,

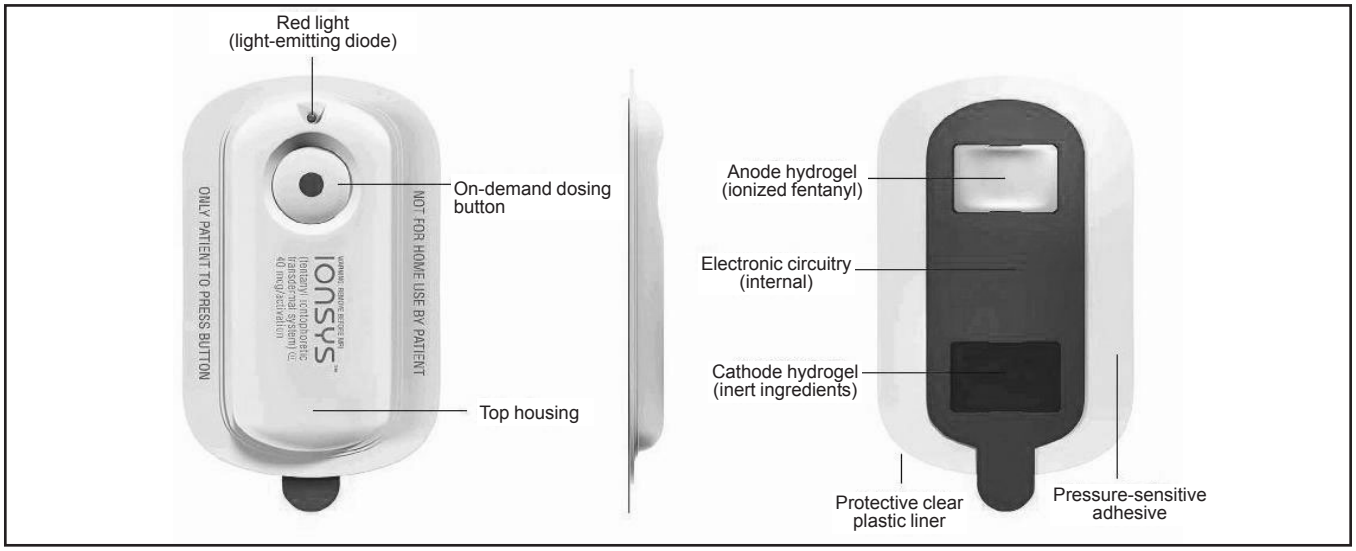

Figure 2. The fentanyl ITS (IONSYS™). The system is composed of a plastic top housing that contains a 3V lithium battery and electronics and a bottom housing containing two hydrogel reservoirs and a polyisobutylene skin adhesive. The anode hydrogel, which is located under the dosing button, contains fentanyl along with inactive ingredients; the cathode contains only inactive ingredients. The unit weighs 15 g and is 3.3 in long, 1.9 in wide, and 0.39 in high.[50] Reprinted with permission from Ortho-McNeil.

the prolonged terminal half-life of fentanyl after removal of the TTS is due to the slow, continued absorption of fentanyl from its cutaneous depot,[40,44] as the amount of fentanyl remaining within the skin depot after removal of the patch is substantial.[19] For example, at the end of a 24-hour period of use with the 100 µg/h TTS, 1.07 ± 0.43 mg of fentanyl, or approximately 30 percent of the total dose delivered, remains deposited in the skin.[19,44] These differences in fentanyl absorption and elimination make the ITS better suited for the control of acute pain, such as in the postoperative setting, and the TTS formulation of fentanyl more appropriate for use in patients with chronic pain, such as those suffering from cancer-related pain.[45] Collectively, these pharmacokinetic data suggest that iontophoresis may enable transdermal administration of fentanyl with a rapid achievement of steady state and the ability to vary delivery rate. This capability would potentially be beneficial for the management of acute pain and breakthrough pain.[12]

DOSING AND ADMINISTRATION

The safety and efficacy of IV fentanyl PCA has been demonstrated with doses ranging from 10 to 60 µg using lockout intervals ranging from one to 10 minutes.[46-49] The fentanyl ITS is preprogrammed to deliver a 40 µg dose over a 10-minute period.[50] The 40 µg dose was selected based on the results of the dose-finding study by Camu et al.,[51] in which use of a 40 µg on-demand dose yielded an optimal profile of pain relief and safety compared with a 20 or 60 µg on-demand dose of fentanyl. A key objective in the optimization of an iontophoretic system is to maximize delivery while minimizing the level of the current[14]; the density of the current (62 µA/cm^2) provided by the fentanyl ITS is generally imperceptible to the patient.[38,50]

In order for the electronic circuit for drug delivery to be complete, the system must be attached to the patient. The fentanyl ITS has an adhesive backing and is placed either on the outer upper arm or on the chest (Figure 2). The device should be applied to clean, dry, intact, nonirritated skin. Other application sites, such as the legs or abdomen, have not been studied; therefore, application to such sites is not recommended.[50] Drug delivery begins when the electrical field is activated by double-clicking the dose-activation button.[8] In other words, absorption of clinically significant levels of drug occurs only after the patient activates the system.[11] The fentanyl ITS provides an audible tone (beep) and visual alert (red light from a light-emitting diode [LED]) to indicate the start of delivery of each dose; the red LED remains on throughout the dosing period.[8] A system-initiated lockout prevents the patient from activating the system for additional drug during the 10-minute delivery period; this period is preprogrammed by the manufacturer, and fentanyl administration can not be interrupted, accelerated, or extended beyond this interval. Patients can initiate up to six doses an hour for up to 24 hours from the time the first dose was initiated or up to a maximum of 80 doses, whichever occurs first. If a treatment duration of longer than 24 hours (or 80 doses) is required, a new fentanyl ITS should be applied to a different application site.[50] After each dose is delivered, the LED turns off momentarily and then flashes to indicate the cumulative number of doses the patient has received, with each flash signifying delivery of a range of five doses (one flash = one to five doses delivered, two flashes = six to 10 doses, and so on, up to a maximum of 16 flashes [80 doses]).[8,50]

Table 1. Summary of clinical trials evaluating the efficacy of fentanyl ITS

Reference	Treatment group	Dose	n	Study duration (h)	Primary efficacy endpoint	p value	Secondary efficacy endpoints					
							Mean pain intensity*	p value	PGA†	p value	IGA†	p value
Chelly 2004[6]	Fentanyl ITS	40 µg	142	24	25.4 percent	0.049	30.9 ± 2.4	0.047	3.0	0.047	3.1	0.007
	Placebo	–	47		40.4 percent		40.8 ± 4.6		2.6		2.6	
Viscusi 2006[52]	Fentanyl ITS	40 µg	244	24	28.7 percent	< 0.0001	3.5 ± 0.16	< 0.0001	73.4 percent	< 0.0001	72.1 percent	< 0.0001
	Placebo	–	240		60.0 percent		5.4 ± 0.17		45.9 percent		46.6 percent	
Viscusi 2004[8]	Fentanyl ITS	40 µg	316	72	73.7 percent§	0.36	32.7‖	0.45	§		N/A	
	Morphine IV PCA	1 mg‡	320		76.9 percent§		31.1‖					

Abbreviations: IGA: investigator global assessment; ITS: iontophoretic transdermal system; IV: intravenous; N/A: not applicable; PCA: patient-controlled analgesia; PGA: patient global assessment. * Reported as mean last pain intensity recorded during the first 24 hours ± SEM. † In the study by Chelly et al.,[6] PGA and IGA were rated on an ordinal scale, whereas in the trials performed by Viscusi et al.[8,52] these measures were categorized on a nominal scale. The percentage of the latter reflects the proportion of patients and investigators, respectively, who considered the treatment a good or excellent method of pain control. ‡ The dose of morphine was a 1 mg bolus with a five-minute lockout interval. § Unlike in the placebo-controlled trials,[6,52] the primary efficacy endpoint in this study was the PGA of method of pain control during the first 24-hour treatment period (combined rating of good and excellent). ‖ Refers to the mean of the last recorded VAS within the first 24 hours (not 72 hours).

The audible and visual signals afforded by the fentanyl ITS provide information on system function and dosing similar to that of standard IV PCA,[8] with the exception of cumulative dose approximation. For example, each system can be tested to ensure that it is operational while still in the pouch by locating the on-demand button through the foil packaging and pressing it twice. An audible beep will indicate that the system has been activated, and it will be followed by a series of beeps indicating that no dose was delivered. Testing the system in this manner does not initiate the 24-hour, 80-dose active delivery period, since no dose was delivered. Pressing the on-demand button once during or prior to drug delivery displays the approximate number of doses administered.[50] Alerts for nonfunctioning conditions are a short series of beeps (indicating decreased fentanyl delivery [e.g., poor skin contact] and that the fentanyl ITS should be restarted) and continuous beeping (indicating the system has shut down [e.g., low battery] and should be removed).

EFFICACY AND SAFETY

There are few published data on the clinical use of opioids delivered via iontophoresis, but the delivery of fentanyl via this mechanism has been investigated more extensively than that of other opioids.[12] Fentanyl ITS has been evaluated for the management of postoperative analgesia after abdominal, orthopedic, and thoracic surgery.[6,8,52] The results of the studies investigating the efficacy and safety of the fentanyl ITS are summarized in Tables 1 and 2, respectively.

A multicenter, randomized, double-blind, placebo-controlled trial was conducted to assess the efficacy and safety of the fentanyl ITS for the management of the first 24 hours of postoperative pain.[6] The primary efficacy endpoint was the percentage of patients withdrawn from the study because of inadequate analgesia after completing at least three hours of treatment. Of the 189 patients considered evaluable for efficacy, 25 percent of patients in the fentanyl ITS 40 µg group withdrew because of inadequate analgesia, as compared with 40 percent of the placebo group (p = 0.049). Secondary efficacy endpoints included the last available mean pain intensity (measured using an ungraded visual analogue scale [VAS] that ranged from no pain [0 mm] to the worst possible pain [100 mm]) and patient and investigator global assessments (PGA and IGA, respectively) of the method of pain control at the end of the 24-hour study period or at the time of withdrawal (measured via a categorical scale with assigned values [1 = poor, 2 = fair, 3 = good, 4 = excellent]). The estimated number of treatment doses used by a patient, the number of patients requiring rescue medications during the first three hours, and the total amount of rescue medication administered were also recorded. Patients in the fentanyl group used a mean of 31 on-demand doses, whereas the placebo group used a mean of 27 doses (p value not reported). During the first three hours, 48 percent of the fentanyl group and 55 percent of the placebo group required rescue

medication (p = 0.377); the mean amount of IV fentanyl rescue medication given to each group was 99.6 μg and 95.4 μg, respectively (p value not reported). This study showed that the fentanyl ITS provided significantly better pain control than placebo for up to 24 hours after major surgery, as assessed by the primary efficacy endpoint of withdrawal secondary to inadequate analgesia; however, the difference between groups was marginal.

The findings by Chelly et al.[6] were not as robust as would be expected in a placebo-controlled efficacy trial of opioid therapy. Several limitations were present in this study, including the lack of control for pain intensity at study entry and the randomization scheme used. These issues most likely contributed to the disappointing results seen. More specifically, approximately 19 percent of patients in the fentanyl group entered the study with a VAS pain score of ≥ 75 mm (indicative of severe pain), and the 3:1 fentanyl-to-placebo assignment disproportionately enrolled more patients with high baseline pain scores in the active treatment group, potentially underestimating fentanyl's overall efficacy.[6] In order to address these limitations, Viscusi et al.[52] employed a similar study design to compare the safety and efficacy of the fentanyl ITS with placebo for the management of moderate to severe postoperative pain. The primary difference between the studies conducted by Chelly et al.[6] and Viscusi et al.[52] was that patients included in the latter study were initially titrated to comfort with IV opioids (VAS score of < 5 as measured on an 11-point VAS with 0 denoting no pain and 10 the worst possible pain) prior to the application of the fentanyl ITS; in addition, a 1:1 randomization scheme was used. As in the study by Chelly et al.,[6] the primary efficacy endpoint was the percentage of patients who discontinued participation in the study because of inadequate analgesia during the 24-hour treatment period. The investigators found that fewer patients using the fentanyl ITS discontinued therapy because of inadequate analgesia compared with the placebo group (29 percent versus 60 percent; p < 0.0001); also, a significantly larger proportion of patients receiving placebo discontinued the study for any reason (36.9 percent versus 68.3 percent; p < 0.001). Secondary efficacy endpoints included mean last pain intensity scores and PGA and IGA scores; global assessments of the method of pain control were categorically rated (poor, fair, good, or excellent). The estimated number of doses used by a patient and the proportion of patients requiring rescue medications during the first three hours were also recorded. At each measured time point, patients using the placebo system activated more doses per hour than patients receiving the active treatment (data not reported). A significantly larger percentage of patients receiving placebo required rescue medication in the first three hours of the study than patients receiving the active treatment (57.5 percent versus 45.5 percent, respectively; p = 0.008). These findings are more robust than the results from the earlier multicenter clinical trial by Chelly et al.[6]; a 31 percent treatment difference was observed between groups who withdrew because of inadequate analgesia in the Viscusi et al.[52] study, compared to the marginal 15 percent in the study by Chelly et al.[6]

In a multicenter, randomized, unblinded, active-control study, Viscusi et al.[8] established that the fentanyl ITS is equivalent to a standard morphine IV PCA regimen in postoperative pain management. The primary efficacy endpoint was PGA at 24 hours, which was measured as a categorical variable of the method of pain control (poor, fair, good, or excellent). Ratings of good or excellent (categorized as success) were given by 73.7 percent and 76.9 percent of patients in the treatment groups, respectively; treatment difference was -3.2 percent (95 percent confidence interval [CI]: -9.9 percent to 3.5 percent; p = 0.36). According to the investigators' definition of the primary endpoint, fentanyl ITS and morphine PCA were therapeutically equivalent (i.e., 95 percent CI of the difference in success rate fell within ± 10 percent, with α = 0.025). Additional efficacy measures were the proportion of patients discontinuing the study because of inadequate analgesia or for any reason, patient-reported pain intensity scores on a 100 mm ungraded VAS (no pain = 0 mm, worst possible pain = 100 mm), PGA at 48 and 72 hours, and the proportion of patients requiring rescue medications during the first three hours. Withdrawals secondary to inadequate analgesia were fewer but not statistically significant in the morphine PCA group (10.3 percent) compared with the fentanyl ITS group (15.2 percent; p = 0.07). There also was no difference in the number of withdrawals due to adverse events (5.9 percent versus 6.0 percent, respectively; p = 0.97). With continued treatment for up to 48 to 72 hours, more than 80 percent of patients in each treatment group rated the pain control as good or excellent. The proportion of patients who received supplemental IV opioids within the first three hours after treatment initiation was also similar for both treatment groups (fentanyl, 22.8 percent, versus morphine, 27.2 percent; p = 0.20).

Overall, patients included in these studies were predominantly female (69 to 74 percent), white (73 to 84 percent), and approximately 50 years of age, and the majority had an American Society of Anesthesiologists physical status of II (mild to moderate disturbance). Limitations of the studies with regard to assessment of the efficacy of this fentanyl ITS were related to the study design and the system itself. The first such limitation is attributable to the comparison with placebo[6,52] and disallowing patients to receive additional analgesics after a set period of time (e.g., three hours).[6,8,52] Current approaches for acute pain management use adjuvant analgesics such as regional blocks or systemic nonsteroidal anti-inflammatory drugs in combination with PCA[53]; such treatment modalities were not allowed in these studies. Therefore, the external validity of these studies is somewhat suspect, as these exclusions do not mirror the "real world" of acute pain management.[50] Future studies of the fentanyl ITS will need to address its use in a multimodal analgesic

Table 2. Most common treatment-related adverse events reported in clinical trials of fentanyl ITS (≥ 2 percent of patients)*

Adverse event	Treatment group I[6]		Treatment group II[52]		Treatment group III[8]	
	Fentanyl ITS (n = 154)	Placebo (n = 51)	Fentanyl ITS (n = 244)	Placebo (n = 240)	Fentanyl ITS (n = 316)	Morphine IV PCA (n = 320)
Nausea	48 (31.2)	13 (25.5)	65 (26.6)	35 (14.6)	129 (40.8)	147 (45.9)
Vomiting	11 (7.1)	0 (0)	10 (4.1)	10 (4.2)	31 (9.8)	27 (8.4)
Headache	10 (6.5)	4 (7.8)	10 (4.1)	8 (3.3)	36 (11.4)	24 (7.5)
Pruritus (general)	18 (11.7)	3 (5.9)	8 (3.3)	1 (0.4)	26 (8.2)	(0)
Application site reactions (pruritus, vesicles, other)	8 (5.2)	5 (9.9)	11 (4.5)	3 (1.3)	20 (6.3)	40 (12.5)
Constipation	NR	NR	NR	NR	12 (3.8)	7 (2.2)
Hypoxemia	2 (1.3)	0 (0)	NR	NR	12 (3.8)	7 (2.2)
Fever	NR	NR	6 (2.5)	4 (1.7)	11 (3.5)	13 (4.1)
Dizziness	1 (0.6)	1 (2.0)	6 (2.5)	2 (0.8)	6 (1.9)	12 (3.8)
Somnolence	NR	NR	NR	NR	6 (1.9)	7 (2.2)
Anxiety	NR	NR	NR	NR	4 (1.3)	9 (2.8)
Gastrointestinal disorder	2 (1.3)†	1 (2.0)†	2 (0.8)‡	0 (0)‡	3 (0.9)‡	2 (0.6)‡
Urinary retention	1 (0.6)	1 (2.0)	NR	NR	5 (1.6)	2 (0.6)
Hypertension	0 (0)	1 (2.0)	NR	NR	NR	NR
Bradycardia	0 (0)	1 (2.0)	NR	NR	NR	NR
Insomnia	NR	NR	6 (2.5)	8 (3.3)	NR	NR

Abbreviations: ITS: iontophoretic transdermal system; IV: intravenous; NR: not reported; PCA: patient-controlled analgesia.
* Values are given as n (percent). † Not specified. ‡ Ileus.

setting.[8] Because the fentanyl ITS is programmed to only indicate the approximate number of doses delivered, whereas PCA pumps indicate the precise number of doses delivered, the patient-administered dose is estimated. In all three of the efficacy trials, the total fentanyl dose administered via the ITS was estimated as five times the number of displayed light flashes minus two to obtain the midrange dose number; as mentioned, each flash represents the delivery of one to five doses, corresponding to the delivery of 40 to 200 μg/h of fentanyl. In practice, individual patients may require varying amounts of drug based on differences in their pain perception, opioid tolerance, or weight, and therapy is frequently adjusted based upon previous opioid dose. However, a fivefold difference in estimated dose may result in either under- or overestimation of true opioid requirements, potentially delaying subsequent achievement of adequate analgesia or resulting in overdose if supplemental or alternative opioid analgesics are used in conjunction with or to replace (respectively) the fentanyl ITS. Therefore, it is imperative that patients are titrated to an acceptable level of analgesia before initiating treatment with the fentanyl ITS. Patients should be evaluated frequently to ensure that they are receiving adequate analgesia, and subsequent adjustments in the patient's pain regimen should be made by medical personnel with expertise in pain management.

The most frequent treatment-related adverse events reported in clinical studies of the fentanyl ITS are summarized in Table 2. In general, most adverse events viewed as probably related to the fentanyl ITS were judged to be mild to moderate in severity and were either opioid-related (e.g., constipation, somnolence) or local effects (e.g., pruritus),[6,8,52] all of which are commonly experienced by patients receiving opioid analgesia and by those in the immediate postoperative period.[54] Nausea was the most commonly reported systemic adverse event associated with treatment, ranging in incidence from approximately 30 percent to 40 percent. The most commonly reported application site reaction was erythema, which was believed to be

related to the delivery mode itself and not to fentanyl. Scheduled skin evaluations after system removal revealed erythema in 54, 45, and 25 percent of patients receiving active treatment in trials performed by Viscusi et al.,[8] Chelly et al.,[6] and Viscusi et al.,[52] respectively, although, on the whole, application site reactions were reported in less than 10 percent of all patients. Most erythema was mild and self-limiting and resolved without treatment.[6,8,52] In all three clinical trials of the fentanyl ITS, respiratory function was the primary measure of systemic safety, and clinically relevant respiratory depression (CRRD) was defined as the simultaneous occurrence of bradypnea (respiratory rate < 8 breaths/min) and excessive sedation (patient not easily aroused).[6,8,52] Importantly, no patient who received this therapy experienced CRRD.

The biophysical effects of iontophoresis itself have been extensively reviewed by Jadoul et al.[55] and Curdy et al.[16] Briefly, skin appendages, which include sweat glands and hair follicles, are postulated to be major pathways of drug transport during iontophoresis.[15,56] There is concern about iontophoresis causing damage to growing hair and other possible irreversible changes to the skin at clinically acceptable current densities.[57] However, evidence from studies of iontophoretic delivery in both hairless mice and excised human skin suggests a much larger contribution by sweat glands and ducts, as opposed to hair follicles, in the pathway of electric current.[56-60] In fact, tap-water iontophoresis is one of the most popular treatments for hyperhydrosis (or hyperhidrosis), defined as excessive sweating of the hands and feet.[61,62] Overall, however, the evidence for the dominant current path via iontophoresis is conflicting.[63,64] To date, there have been no reports of hair loss or permanent skin damage in randomized, controlled trials of transdermal iontophoretic PCA with fentanyl.

THERAPEUTIC USES

Iontophoresis as a process of transdermal drug delivery has applications in pain management, allowing noninvasive administration of opioid analgesics.[14] As mentioned, the amount of drug delivered by the device to the patient is linearly related to the magnitude of the electric current applied to the system.[38] Therefore, appropriate modulation of the current's profile means that iontophoresis can be used to deliver analgesics via the transdermal route to provide relief in response to acute pain episodes as well as to alleviate chronic pain. Furthermore, in addition to providing a mechanism to deliver drugs to achieve systemic pain relief, iontophoresis can be used as an administration modality for local analgesics to provide local pain relief or local anesthesia prior to minor surgical procedures.[14]

The effectiveness of transdermal fentanyl administration was first demonstrated with acute postoperative pain. Peng and Sandler[19] extensively reviewed the literature related to the use of the fentanyl TTS as an analgesic in the postoperative period. The results of their review indicate that because of the slow attainment of an analgesic plasma concentration, the inability to rapidly adjust the dose, and the relatively short duration of postoperative pain, the fentanyl TTS formulation should not be used for management of acute pain. Furthermore, a high incidence of CRRD associated with the conventional TTS was also reported in this and other reviews of the literature[4,19,65]; such use is now contraindicated. On the other hand, clinical trials have shown the fentanyl ITS to be superior to placebo and comparable to morphine PCA in terms of both efficacy and safety for the treatment of acute postoperative pain. It is for this reason that the US Food and Drug Administration approved fentanyl ITS (May 22, 2006) for the short-term management of acute postoperative pain in adult patients requiring opioid analgesia during hospitalization; commercial availability is not expected until 2007.

It is possible that the fentanyl ITS may have therapeutic applications outside of postoperative pain management, such as for the management of breakthrough pain experienced by cancer patients. Those who have pain that requires the long-term administration of opioids (such as patients with cancer pain or chronic nonmalignant pain) benefit from constant, time-contingent (e.g., around-the-clock) opioid administration. In addition, these patients frequently require the rapid administration of potent immediate-release opioids for the management of breakthrough and incident pain. As stated, the fentanyl TTS is a noninvasive, passive delivery system for time-contingent analgesic therapy. Numerous studies have demonstrated the effectiveness of the fentanyl TTS in the treatment of chronic cancer and noncancer pain.[66-74] This formulation's prolonged 72-hour duration of therapy is ideal for chronic pain states in which the patient's pain is fairly stable but displays slow onset and offset not suitable for acute pain management.[75] Iontophoresis may allow rapid administration of additional amounts of fentanyl for the management of incident and breakthrough pain, and iontophoresis, as a mode of drug delivery, provides a level of flexibility in adjusting the amount of fentanyl delivered.[4,29] However, as previously mentioned, the fentanyl ITS is preprogrammed to deliver a 40 μg dose of fentanyl upon patient demand, and the dose delivered by the system can not be adjusted. The use of the fentanyl ITS for these and other related indications has yet to be investigated in controlled clinical trials, so use of the fentanyl ITS for any off-label indication is not recommended.

SUMMARY

In order for an iontophoretic product to find a place in a clinician's armamentarium, this technology must provide added value over existing administration methods.[14] Aside from the pharmacokinetic and pharmacodynamic benefits of fentanyl itself, there are several potential

advantages to the fentanyl ITS. The system provides pain control comparable to that offered by a standard regimen of morphine PCA, without the pump apparatus, IV lines, tubing, and other equipment required for PCA administration.[8] Because the fentanyl ITS is preprogrammed and relatively easy to operate, there is a low risk of dosing errors and potentially fewer administrative, technical, and clinical resources required to operate the system. Also, the self-contained transdermal drug delivery system is convenient and may aid patient mobility, especially after major surgery. Furthermore, in clinical trials most patients were very satisfied with the pain control provided by the fentanyl ITS, and most patients characterized the system as very convenient and very easy to use.[8,52]

Use of the fentanyl ITS also has a number of associated limitations. Appropriate selection of patients is necessary for safe and effective use of the system. Current practice dictates that patients using PCA should be awake, alert, and able to understand how to use the device; these same requirements apply in use of the fentanyl ITS.[50] Patients unable to operate the system because of deficiencies in upper extremity mobility or comprehension would not be appropriate candidates for either standard opioid PCA or the fentanyl ITS.[76] Although the process of iontophoresis affords the ability to titrate medication dosage, thus making continuous iontophoretic delivery of fentanyl feasible,[17] fentanyl ITS is not a continuous drug delivery system and therefore would not be appropriate as monotherapy for the management of chronic pain. The rationale for the development of the current, intermittent fentanyl ITS was that previous studies indicated that a continuous basal infusion does not enhance efficacy during acute use in the postoperative setting.[7,19] Moreover, this system is intentionally not designed to treat the intense levels of pain immediately following surgery; rather, it is meant to deliver small, frequent doses of fentanyl to maintain analgesia once initial pain control has been established, typically with parenteral opioids. This is consistent with the manner in which PCA is currently used in the clinical postoperative setting.[52] The fentanyl ITS may not be appropriate for opioid-tolerant patients, whose opioid dose requirement may be higher than that provided by the system.[8] Future research and development efforts may lead to the availability of varying dosage strengths that would allow for even more versatility for this product and potentially result in wider clinical application.[45]

Additional concerns regarding the fentanyl ITS involve the high incidence of application site reactions and the paucity of pharmacoeconomic data. The skin irritation associated with iontophoresis in general has been addressed by several studies, and it is an issue preventing wide application of this technology. However, the use of ITS in combination with other enhancement techniques (e.g., electroporation, sonophoresis) may result in lower current levels being able to deliver therapeutically effective amounts of medication, and this may dramatically reduce the skin irritation problem.[15] In terms of cost, there have been no studies to date evaluating the cost effectiveness of the fentanyl ITS. Evidence suggests that postoperative pain (in particular) continues to be treated inadequately and that this is one reason that many patients postpone elective surgery.[77-82] Inadequate pain control in the postoperative period not only contributes to patient discomfort but also may reduce patient satisfaction with hospital care, prolong and complicate a patient's recovery, and increase healthcare costs.[45,76,78,83,84] In contrast, effective pain management may lead to increased patient satisfaction, a less complicated postoperative course including earlier hospital discharge, decreased resource utilization, and lower direct and indirect costs.[85,86] Effective analgesia may also prevent the development of chronic pain syndromes, which are extremely expensive and difficult to manage.[77] A cost comparison between standard IV PCA and the fentanyl ITS is warranted.

In conclusion, the application of new knowledge and technology to existing opioids such as fentanyl provides physicians and healthcare teams with new treatment options in pain management. Iontophoresis is one method of enhancing transdermal drug delivery that shows considerable promise in pain medicine. The fentanyl ITS addresses some of the limitations of traditional PCA administration while still providing patients with personal control over their pain management. The on-demand dosing and pharmacokinetics of this system differentiate it from the fentanyl TTS, which was designed for the management of chronic pain. The fentanyl ITS has been demonstrated to be effective for the management of acute postoperative pain, but its use may not be limited to this area. Well-designed, randomized, controlled studies should examine the safety and efficacy of the fentanyl ITS for pain management in additional settings and indications; these include ambulatory surgery, labor and delivery, adjunct therapy for regional anesthesia, and moderate to severe cancer-related pain, among others. In addition, a comparative cost-benefit analysis incorporating the potential for improved safety and decreased demand for resources would provide further insights into the potential economic advantages of the iontophoretic fentanyl ITS.

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ORIGINAL ARTICLE

A randomized, open-label study of once-a-day AVINZA® (morphine sulfate extended-release capsules) versus twice-a-day OxyContin® (oxycodone hydrochloride controlled-release tablets) for chronic low back pain: The extension phase of the ACTION trial

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ABSTRACT

Study design and objective: *The ACTION® trial, an open-label, randomized, multicenter, two-part study, compared the efficacy and safety of two sustained-release opioids (SROs), AVINZA (A-MQD), morphine sulfate extended-release capsules given once a day, and OxyContin® (O-ER), oxycodone modified-release tablets given twice a day, in subjects with chronic, moderate to severe low back pain. The first part of the study, the evaluation phase, was followed by an optional four-month extension phase aimed at evaluating the long-term stability of pain control, SRO dose, and quality of sleep.*

Results: *Three hundred and ninety-two subjects were enrolled in the study; 220 completed the evaluation phase, and 174 entered the extension phase. During the latter phase, subjects in the A-MQD group (n = 79) continued to report lower pain scores, better quality of sleep, lower daily morphine-equivalent doses (means of 86 mg versus 119 mg), and a comparable usage of ibuprofen compared to subjects in the O-ER group (n = 95). The incidence and severity of elicited opioid side effects were similar between the two groups.*

Conclusions: *Both study drugs resulted in significant pain relief and improved sleep in SRO-naive patients with chronic low back pain, and this outcome was attained with a stable daily SRO dose. In patients who completed opioid dose titration, AVINZA performed significantly better than OxyContin in reducing pain scores and improving sleep—with a lower morphine-equivalent daily dose—during both the evaluation and extension phases.*

INTRODUCTION

The ACTION study was a randomized, parallel-group, open-label, multicenter trial comparing the efficacy and safety of once-a-day AVINZA (A-MQD) and twice-a-day OxyContin (O-ER) in patients with chronic, moderate to severe low back pain. The study consisted of a three-to-six-week opioid dose titration period followed by an eight-week in-depth evaluation phase and an optional four-month extension phase. The primary efficacy objective of the study was to compare pain scores, daily sustained-release opioid (SRO) dose, and rescue medication usage between the two groups. The results from the evaluation phase were recently reported in this journal (Volume 2, Number 3) and demonstrated that in patients who completed opioid dose titration, A-MQD was significantly better than O-ER at reducing pain and improving sleep, while requiring a lower morphine-equivalent daily dose.[1] The current report presents the final results of the extension phase of this trial.

METHODS

Detailed information about the ACTION study design was previously reported.[1] In brief, eligible subjects were randomized to receive either A-MQD once every 24 hours as a morning dose or O-ER dosed every 12 hours and were instructed to take their study medication at the same time each day, ± 30 minutes. Subjects who enrolled in the extension phase continued on the same study

Table 1. Reasons for treatment discontinuation			
	Total	**A-MQD**	**O-ER**
Titration and evaluation phases			
Number of discontinuations	172	93	79
Extension phase			
Number of discontinuations	42	24	18
Reason for discontinuation			
Subject withdrew consent	15 (35.7 percent)	10 (41.7 percent)	5 (27.8 percent)
Noncompliance	9 (21.4 percent)	5 (20.8 percent)	4 (22.2 percent)
Subject lost to follow-up	7 (16.7 percent)	4 (16.7 percent)	3 (16.7 percent)
Other	6 (14.3 percent)	3 (12.5 percent)	3 (16.7 percent)
Serious adverse event	3 (7.1 percent)	1 (4.2 percent)	2 (11.1 percent)
Lack of efficacy/persistent pain	1 (2.4 percent)	0 (0.0 percent)	1 (5.6 percent)
Investigator withdrew subject	1 (2.4 percent)	1 (4.2 percent)	0 (0.0 percent)

medication they had been taking, with doses adjusted at the discretion of the treating physician to maintain an optimal balance of pain control and tolerability. Ibuprofen (200 mg tablets, maximum of 2,400 mg/d) was the only rescue medication permitted for breakthrough pain throughout the study.

Objectives of the extension phase

The primary objective was to measure the daily SRO dose over time. Other objectives included comparing the safety and efficacy of A-MQD and O-ER by assessing pain scores, sleep measures, quality of life, and patient satisfaction.

Outcome assessments during the extension phase

Assessments were conducted monthly for four months. Subjects assessed their average pain intensity over the preceding month using a numerical rating scale in which 0 = "no pain" and 10 = "pain as bad as you can imagine." Subjects were also asked to report their highest dose of study medication in the preceding month and the number of instances ibuprofen was used for breakthrough pain during the two days prior to the clinic visit. At the final visit, subjects were asked to report their overall satisfaction with the study drug after being given five choices ranging from "extremely satisfied" to "extremely dissatisfied."

Statistical methods

Baseline demographics were compared between the two groups using the Wilcoxon two-sample test for continuous variables and the Pearson's χ^2 test for categorical variables. Efficacy variables were analyzed for predefined assessment time points and presented as absolute values or as absolute and relative changes from baseline values, where baseline values were those obtained upon enrollment in the study. Categorical efficacy variables were compared using the Cochran-Mantel-Haenszel test. All comparisons between groups were two-sided, and significance was assigned to p values < 0.05. No adjustments were made for multiple comparisons. Standard descriptive statistics were used to describe the incidence and severity of the elicited opioid-related side effects, and in the case of multiple occurrences of the same event for a single subject the event was only counted once, and the highest reported severity grade was used to rate the event. The final results of the extension phase of the ACTION study were previously presented in an abstract form.[2]

RESULTS

Subject disposition

A total of 392 subjects were randomized, with 203

Table 2. Patient demographics				
	All subjects enrolled		Extension phase	
	A-MQD (n = 203)	O-ER (n = 189)	A-MQD (n = 79)	O-ER (n = 95)
Gender				
Male	74 (36.5 percent)	79 (41.8 percent)	27 (34.2 percent)	42 (44.2 percent)
Female	129 (63.5 percent)	110 (58.2 percent)	52 (65.8 percent)	53 (55.8 percent)
Age (years)				
Mean	49.6	50.4	47.7	49.8
Median (range)	50 (28 to 70)	50 (29 to 73)	49 (28 to 63)	50 (30 to 73)
Race				
African American*	47 (23.2 percent)	32 (16.9 percent)	24 (30.4 percent)	14 (14.7 percent)
Caucasian	154 (75.9 percent)	156 (82.5 percent)	54 (68.4 percent)	80 (84.2 percent)
Other	2 (1.0 percent)	1 (0.5 percent)	1 (1.0 percent)	1 (1.1 percent)
Weight (kg)				
Median (range)	87 (47 to 211)	91 (43 to 166)	86 (47 to 159)	91 (47 to 146)
Height (cm)				
Median (range)	168 (147 to 193)	168 (144 to 196)	166 (147 to 192)	169 (145 to 193)
Back pain history				
Median (years)	7	6	9	7
Cause of back pain**				
Mechanical	155 (76.4 percent)	160 (84.7 percent)	61 (77.2 percent)	85 (89.5 percent)
Nonmechanical	48 (23.6 percent)	29 (15.3 percent)	18 (22.8 percent)	10 (10.5 percent)
Nerve involvement**				
Yes	75 (36.9 percent)	51 (27.0 percent)	34 (43.0 percent)	27 (28.4 percent)
No	128 (63.1 percent)	138 (73.0 percent)	45 (57.0 percent)	68 (71.6 percent)
* $p < 0.05$ for extension phase; ** $p < 0.05$ for all subjects enrolled.				

assigned to the A-MQD group and 198 to the O-ER group. Of those, 220 subjects (56 percent of all subjects enrolled) completed the evaluation phase (110 per group), and 174 continued on to the extension phase, with 79 in the A-MQD group and 95 in the O-ER group. Of the 174 subjects who entered the extension phase, 42 (24 percent) withdrew from the study before completing the four-month therapy protocol (24 in the A-MQD group and 18 in the O-ER group). Thus, 132 of the initial 392 subjects (34 percent) completed the entire seven-month study (55 in the A-MQD group and 77 in the O-ER group). The reasons for discontinuation during the extension phase are shown in Table 1.

Baseline characteristics

Subject demographics and baseline characteristics are shown in Table 2. The demographics of subjects who entered the extension phase were comparable between the two groups, and they did not differ from those of the 392 subjects who enrolled in the study.

Exposure to study drug

There were no differences in the number of days of opioid use between the two treatment groups. The mean total daily opioid dose was 86 mg of morphine in

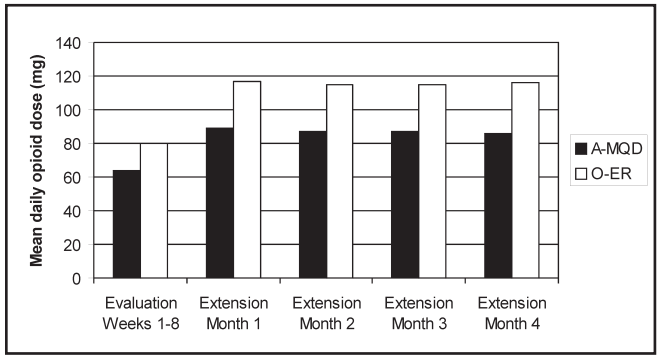

Figure 1. Mean morphine-equivalent daily dose.

the A-MQD group (range: 30 to 480 mg) and 79.5 mg of oxycodone in the O-ER group (range: 20 to 320 mg). After converting the O-ER dose into morphine equivalents using the ratio of 1:1.5 (1 mg oxycodone equivalent to 1.5 mg morphine), the mean daily morphine-equivalent dose in the O-ER group was found to be significantly higher than the mean daily morphine dose in the A-MDQ group (119.2 mg versus 86 mg; p = 0.0004). The mean daily ibuprofen dose was comparable between the two groups for each month from Month 1 to Month 4 and for the four months combined. Figure 1 shows the mean daily morphine-equivalent doses used on a monthly basis, and Table 3 summarizes study medication and ibuprofen use in the extension phase.

Pain assessments

The mean pain scores at baseline were comparable between the two groups (6.5 in the A-MQD group and 6.6 in the O-ER group). Pain scores had decreased to ≤ 4 in all subjects who entered the evaluation phase as required by study design, and they remained at ≤ 4 throughout the evaluation phase of the study. During the four-month extension phase, the monthly average pain scores remained at ≤ 4 in both groups, with mean monthly scores consistently lower in the A-MQD group than in the O-ER group (Figure 2). The mean absolute change in pain scores from baseline for each of the four monthly evaluations was consistently larger in the A-MQD group (Figure 3), and the differences were significant at Month 2 (p = 0.029) and Month 3 (p = 0.023).

Sleep and other efficacy assessments

Both treatments resulted in improved Pittsburgh Sleep Quality Index (PSQI) scores compared to baseline. The relative changes in PSQI scores from baseline were consistently better in the A-MQD group at each of the four monthly assessments (Figure 4), with a significant difference noted at Month 1 (p = 0.004). At the time of exit from study, subjects were asked, "Please rate your satisfaction with the study medication you have received during your participation in this clinical trial." In the A-MQD group, 68 percent reported being "extremely satisfied"

Table 3. Exposure to study medication

	A-MQD (n = 79)	O-ER (n = 95)
Days on study medication		
Mean	103.9	107.1
Median (range)	114 (11 to 149)	113 (14 to 143)
Total daily opioid dose (mg)		
Mean	86.0	79.5
Median (range)	90 (30 to 480)	80 (20 to 320)
Total daily morphine-equivalent dose (mg)		
Mean	86.0	119.2
Median (range)	90 (30 to 480)	120 (30 to 480)
Total ibuprofen dose in past two days (mg)		
Mean	621.6	626.1
Median (range)	500 (0 to 2,200)	425 (0 to 4,800)

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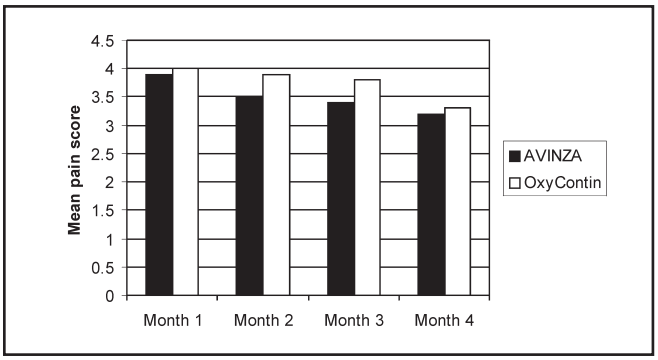

Figure 2. Mean monthly pain scores.

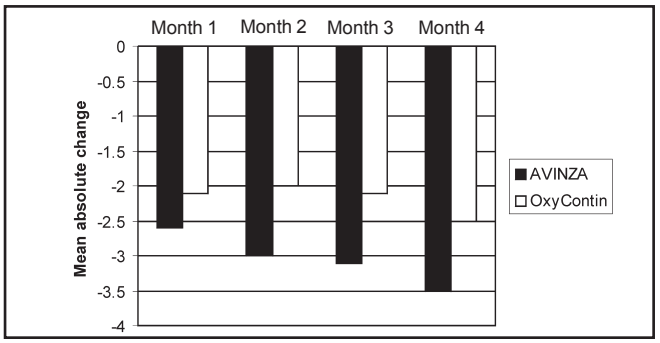

Figure 3. Mean absolute changes from baseline in monthly pain scores.

and 32 percent said they were "satisfied"; in the O-ER group, 57 percent reported being "extremely satisfied," 35 percent reported being "satisfied," and 8 percent said they were "neither satisfied nor dissatisfied."

Safety assessments

The incidence and severity of elicited opioid side effects were comparable between the two groups (Table 4) and were generally lower than those reported during the evaluation phase of the study.[1]

DISCUSSION

The ACTION study was conducted to compare the efficacy, safety, and daily SRO dose over time of A-MQD and O-ER in patients with chronic, moderate to severe low back pain. The evaluation phase of the study showed that in patients who completed opioid dose titration, A-MQD resulted in significantly better changes in pain scores from baseline, better sleep parameters, and a lower daily opioid dose (when converted into morphine equivalents) than O-ER, as well as a comparable safety profile.[1] The extension part of the study shows that A-MQD continued to perform better than O-ER on all these efficacy parameters and that the opioid daily dose remained stable over time in both groups.

In 2003, the American Pain Society issued guidelines indicating a preference for long-acting opioids over

Table 4. Incidence and severity score of elicited opioid side effects during the extension phase

	Incidence (percentage)		Mean severity*	
	A-MQD (n = 46)	O-ER (n = 40)	A-MQD (n = 46)	O-ER (n = 40)
Constipation	65	67	2.4	1.9
Dizziness	33	35	0.7	0.4
Drowsiness	54	60	1.3	1.0
Dry mouth	56	52	1.7	1.1
Itchiness	39	45	0.7	0.9
Nausea	24	22	0.5	0.2
Vomiting	9	12	0.2	0.1

* Using a scale from 0 to 10 where 0 = "not at all" and 10 = "an awful lot."

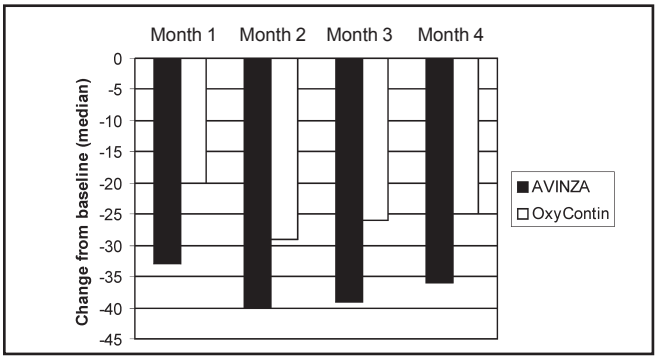

Figure 4. Median relative changes in PSQI scores from baseline.

short-acting opioids based on the belief that they may lessen the incidence and severity of end-of-dose pain.[3] Despite these recommendations, many patients with chronic, moderate to severe low back pain continue to be managed with short-acting opioids over the long term. Until this trial, there have been few reported studies on the long-term use of SROs, and these have been limited to smaller clinical trials which were not evaluated in a randomized setting.[4,5] To our knowledge, the ACTION trial is the first randomized study to evaluate the long-term use of SROs in patients with chronic low back pain. Together, the titration, evaluation, and extension phases correspond to a treatment period of approximately seven to eight months, during which comprehensive data on opioid dose, rescue medication use, pain scores, enhancement of sleep and quality of life, and safety were collected.

About two-thirds of the patients who enrolled in the study did not complete all phases of the trial. This rate of patient withdrawal is not unique to this trial and is comparable with rates reported in other randomized and single-arm studies of various SROs.[6-9] Withdrawal from the study was due to several factors, including intolerance to opioid side effects, persistent pain, and unwillingness to continue participating in a trial. The rate of withdrawal decreased at each phase of the study, with 35 percent of patients withdrawing during the three-to-six-week titration, 17 percent during the eight-week evaluation, and 18 percent during the four-month extension, corresponding to average monthly withdrawal rates of 23 percent, 9 percent, and 5 percent, respectively. The reason for withdrawal changed over time, with adverse reactions cited in 38 percent of the withdrawals during the titration and evaluation phases but in only 7 percent of the withdrawals during the extension phase. In contrast, withdrawal of consent was the most frequent cause during the extension phase, cited in 36 percent of the cases, compared to 22 percent of the cases during the titration and evaluation phases. Lack of efficacy was cited in only 2.4 percent of withdrawals during the extension phase.

In the extension phase of the study, the mean daily opioid dose remained constant at each monthly assessment in both groups. The low incidence of withdrawals due to lack of efficacy or toxicity during the extension phase and the stable opioid dose over time suggest that patients with low back pain whose SRO dose can be properly titrated may achieve pain relief over the long term with limited toxicity. Furthermore, the stable opioid dose observed over a period of four months suggests the slowing down, or maybe the abrogation, of the development of tolerance to opioids in patients whose pain is reliably well controlled. Additional clinical benefits observed in the study were improvement of sleep and limited use of rescue medication for breakthrough pain. These results support the recommendations of the American Pain Society for prescribing sustained-release rather than short-acting opioids when opioids are expected to be needed for the long term.

The ACTION trial showed that for patients who remained in the study, A-MQD was superior to O-ER in terms of improving pain scores from baseline, improving sleep scores, and allowing for lower morphine-equivalent daily doses and use of rescue medications. These differences were statistically significant during the evaluation phase and continued to be seen during the extension phase. Except for the opioid daily dose, which remained significantly lower in the A-MQD group for each of the four months of the extension phase, the other differences were not always statistically significantly different, most likely because the small number of patients continuing in the extension phase didn't offer an opportunity to detect significant differences. As in the evaluation phase, the incidence and severity of elicited opioid side effects during the extension phase were comparable between the two groups.

In conclusion, the two parts of the ACTION study demonstrate that for patients who completed opioid dose titration, once-daily A-MQD allowed for better pain scores and quality of sleep, with a lower daily morphine-equivalent dose and fewer uses of rescue medication than twice-daily O-ER. The study also documented that SROs are useful agents for the symptomatic management of patients with chronic low back pain and that pain was well controlled with stable doses of the SRO over a four-month period of time.

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ORIGINAL ARTICLE

Determinants of variation in analgesic and opioid prescribing practice in an emergency department

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ABSTRACT

Objective: *Adequate treatment of patients' pain is a top priority for the World Health Organization (WHO), American Medical Association (AMA), and American College of Emergency Physicians (ACEP), but "adequate" is not clearly defined. Most previous studies of emergency department (ED) pain treatments have centered on musculoskeletal pain in terms of rates of analgesia and disparities in treatment based on race and age. This study will examine complaints of pain other than musculoskeletal and will focus on treatment disparities that may result from differences in patient and physician characteristics.*

Methods: *This retrospective study is of ED patients 18 years and older with nonmusculoskeletal pain who were seen by ED faculty over a period of eight weeks. Logistic regression and χ^2 tests were performed to quantify effects of doctor, patient, and clinical characteristics on rates of ED analgesia, ED opioids, and analgesic prescriptions at discharge.*

Results: *A total of 1,360 patients were included. There was wide variation in the type and frequency of ED analgesia depending on the attending doctor. For example, patients seen by one specific ED doctor were less than half as likely to receive any analgesia and seven times less likely to receive an opioid than those seen by another doctor. Age, race, doctor's training and experience, and whether the patient had chronic pain were important predictors of ED analgesia. There were similar findings for ED opioids and discharge analgesics.*

Conclusion: *Pain practices in EDs are highly variable and seem inadequate when measured against the goals of WHO, AMA, and ACEP. Patient age, race, and type of pain and the physician's identity, training, and experience all contribute to practice variation. Further research is needed to identify the causes of these variations, and there is a need to develop interventions to standardize and improve pain assessment and treatment.*

Key words: emergency department, pain, pain management, analgesics, opioids

INTRODUCTION

Pain is the most common complaint in general medical practice and is especially common in emergency departments (EDs). Pain management is an increasingly important issue. The World Health Organization (WHO) cosponsored the first Global Day Against Pain to increase recognition of the fact that pain relief is an integral factor in attaining the highest level of physical and mental health.[1] The American Medical Association (AMA) recently distributed a comprehensive policy statement on pain management involving opioid analgesics. The AMA linked its findings to the Federation of State Medical Boards' *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain* and to a joint statement from 21 health organizations and the Drug Enforcement Administration titled *Promoting Pain Relief and Preventing Abuse of Pain Medications: A Critical Balancing Act*.[2] The American College of Emergency Physicians' (ACEP) board of directors approved a strongly worded policy statement in March 2004 advocating safe, rapid, and adequate pain treatment for ED patients and further research into ED pain management.[3] Unfortunately, none of these organizations defined adequate pain treatment or established standards for ED pain care.

A number of studies of ED management of specific pain complaints, primarily musculoskeletal, have been published. All report on the quantity of pain treatment but not on quality as judged against an objective standard.[4-14] Most assume that pain should be treated and that low rates of ED analgesia represent inadequate care, but

they offer no guidance on what is adequate. Several studies have explored the effects of patient characteristics such as age, race, and gender on ED analgesia practice, with equivocal results.[5-14] Selbst and Clark[5] studied pain from burns, sickle cell disease, and lower-extremity fractures. Brown et al.[6] studied pain from fractures using the National Hospital Ambulatory Medical Care Survey (NHAMCS), a national weighted sample of ED encounters. Both found that children were less likely to receive ED analgesia and discharge analgesic prescriptions than adults.

Raftery et al.[7] found that patient perception of pain was the greatest predictor of the number and strength of analgesics given in the ED and that patient gender was not a predictor of ED analgesic use for patients with headache or back and neck pain. Several studies have attempted to find race-based disparities, with some finding blacks and Hispanics receiving less ED analgesia and others finding no difference, primarily for patients with long-bone fracture.[8-10] Singer and Thode[12] studied burn patients using NHAMCS and found low rates of analgesia but no disparities based on gender, age, race, ethnicity, or financial status. Tamayo-Sarver et al.[11] also studied NHAMCS looking for racial and ethnic disparities in care provided for migraines, back pain, and long-bone fractures. They found no disparities in ED analgesic use except that blacks were less likely than whites to be prescribed opioids for back pain and migraines.

We found very little research examining the effect of provider characteristics on ED pain practice. Tamayo-Sarver et al.[13] examined pain practice by emergency physicians (EPs) using written case vignettes. They found wide variation in analgesic practice but could not identify any provider characteristics that explained the variations. Todd et al.[9] studied racial disparities in the care of long-bone fractures and statistically controlled for provider differences in their analysis.

Our research group[14] completed a companion study to the one presented here in which we investigated variations in treatment of musculoskeletal pain in the ED. We found that different physician characteristics and wide variation in practice were the only sources of disparities in the prescription of analgesics in the ED. However, the study found patient characteristics including race, age, chronic pain, and trauma influenced prescription for the subgroups receiving opioids in the ED and discharge analgesic prescriptions. No gender or financial status disparities were found. Fewer opioids and discharge analgesics were prescribed for black patients than for whites. Younger patients and those with trauma or chronic pain received more opioids and discharge analgesics than others. Doctors who completed emergency medicine (EM) residencies and those with less than three years of experience prescribed more analgesics in the ED than non-EM-trained physicians and those with more experience.

In summary, current knowledge about ED pain treatment is limited, and there are no valid standards for evaluating the adequacy of treatment. Some patient and doctor characteristics have been identified that predict ED analgesic use, primarily for musculoskeletal pain, but not all relevant contributors to ED pain treatment have been identified.

We sought to describe ED analgesic prescribing practice for painful conditions other than musculoskeletal pain and to investigate whether patient or doctor characteristics would predict variations in ED pain management.

METHODS

Study design and participant selection

After institutional review board approval and waiver of the Informed Consent requirement, we collected chart review data from complete records on all patients 18 years and older with documented pain other than musculoskeletal pain who were seen by our 10 core faculty members and discharged from our ED over an eight-week period in 2004. Our ED is part of an urban, academic medical center with Level 1 trauma designation and an annual census of about 30,000. A pain complaint was defined as any pain or discomfort described with words like ache, sore, tight, hurt, etc. at triage or during physical evaluation or a nonzero pain score on a verbal 0 to 10 scale.

Methods of measurement

Data were collected following the guidelines of Gilbert et al.[15] Chart abstractors were trained on the structure of charts, definitions of study variables, inclusion and exclusion criteria, the printed abstraction tool, and data entry procedures. Frequent discussion among investigators and abstractors via e-mail and in person helped resolve all uncertainties. In addition, random reabstraction of 10 percent of the charts was performed to assess inter-rater reliability by the κ statistic. Abstractors could not be blinded to all study hypotheses.

Patient variables abstracted included age (divided into "under 50" and "50 or older"), sex, race, insurance status (divided into self-pay or insured), location of pain, traumatic mechanism, presence of chronic pain, analgesic given in ED, opioid given in ED, and both analgesic and opioid prescribed at discharge. Because review of ED census data before the study revealed only a small population of patients 65 and older, patients 50 and older were assigned to the "older" group to provide adequate comparative samples based on age. The name of the attending was obtained from the chart. Data on physician gender, type of training, and time in practice were collected by interview.

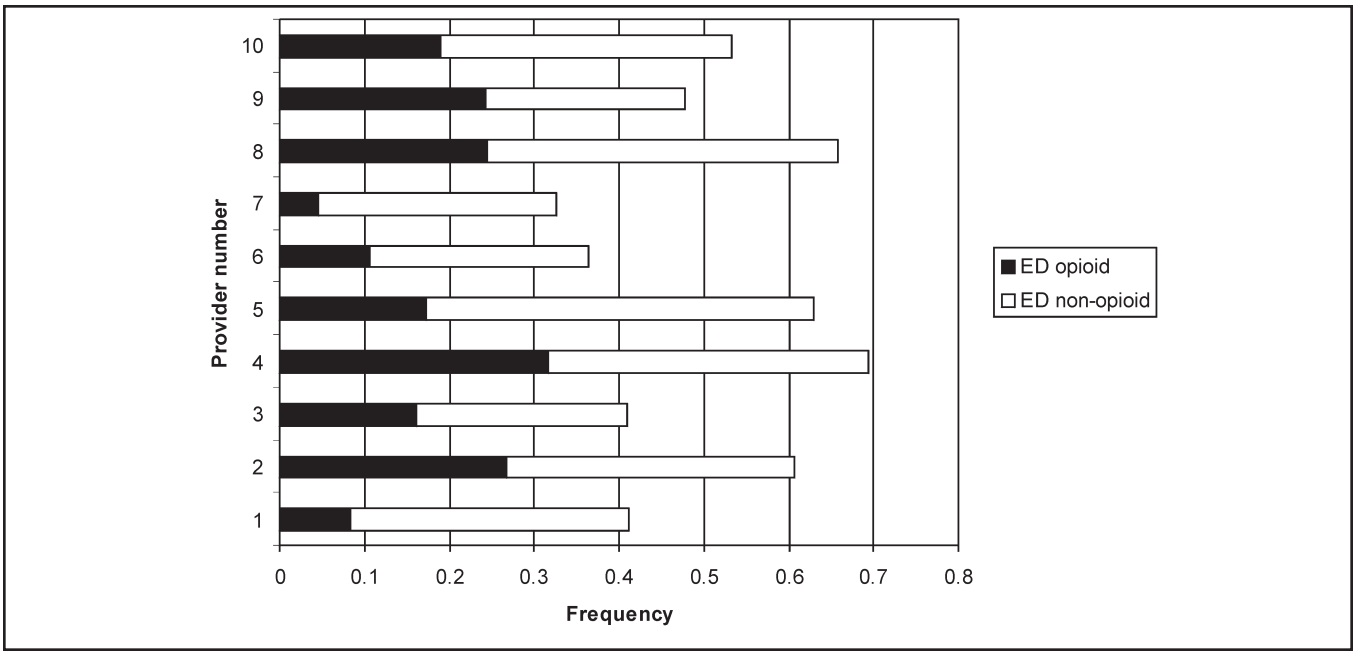

Figure 1.

Pains were described as headache, chest pain, abdominal pain, neuropathic pain, and other. The "other" category included primarily skin and skin structure pain from infection or superficial injury and dental, throat, and ear pain. (As noted earlier, patients with musculoskeletal pain were excluded from this study.)

For patients with multiple painful complaints, the patient's most important single site was recorded. Traumatic mechanism was coded if injury occurred within one week of presentation and no other healthcare had been sought previously for the injury.

No validated definition of chronic pain in EM was found through our literature search. Therefore, we allowed consensus of the investigators to define chronic pain as pain occurring for more than one month and treated with an analgesic on a regular basis before the ED visit.

Definitions of analgesics were broad and specific to pain location. We evaluated only pharmaceutical agents and did not code for analgesia if the only interventions were nonpharmacologic, e.g., ice, elevation, and splinting. Medications treating underlying conditions that might cause pain were not considered analgesics (e.g., antibiotics for a urinary tract infection causing suprapubic pain or for pneumonia causing chest pain, hypoglycemics given to a patient with diabetic neuropathic pain).

Acetaminophen, NSAIDs, and opioids were considered analgesics for all pain sites. For headaches, oxygen was considered an analgesic for cluster headache. Migraine-specific drugs such as prochlorperazine, droperidol, and sumatriptan were coded as analgesics. Tricyclic antidepressants, topical and injected anesthetics, and anticonvulsants such as gabapentin were considered analgesics for neuropathic pain. Nitroglycerin was counted as an analgesic for chest pain. Aspirin was not considered analgesic for chest pain as it was for all other pain because its use in chest pain is to treat suspected platelet aggregation, an underlying condition causing pain. Antacids, acid suppressors, and antispasmodics were analgesics for abdominal pain. Local anesthesia and procedural sedation for injuries and painful treatments were considered analgesics.

Outcome measures

Primary outcome was analgesic treatment in the ED. Secondary outcomes included ED opioid treatment and discharge opioid and nonopioid analgesic prescriptions.

Primary analysis

We described the range of practice in our group by using frequencies and percentages. We also used SAS 9.1 to perform χ^2 and binary logistic regression analysis to determine the significance of variations in analgesic treatment due to patient demographic and clinical characteristics and doctor identity, training, and experience in pain treatment, while controlling for other variables.

RESULTS

A total of 1,360 patients met inclusion criteria and were included in the analysis. Female patients made up 52.6 percent of the study group, blacks 69.8 percent, and uninsured patients 63.5 percent. The majority of patients (82.1 percent) were < 50 years of age. Other pain and abdominal pain were the most common complaints at

Table 1. Logistic regression results for each outcome		
	Odds ratio interval	**95 percent confidence interval**
ED analgesia		
> 50 vs. < 50 years	0.49	0.37-0.66
White vs. black	1.42	1.12-1.81
Chronic vs. not	2.36	1.50-3.71
EM-trained vs. not	1.28	1.02-1.61
> three years' experience vs. less	0.66	0.52-0.84
ED opioid		
White vs. black	2.27	1.64-3.16
Chronic vs. not	1.79	1.07-3.01
EM-trained vs. not	1.46	1.08-2.04
Discharge prescription		
> 50 vs. < 50 years	0.54	0.40-0.73
White vs. black	1.47	1.16-1.86
Chronic vs. not	2.12	1.38-3.23
Discharge opioid		
White vs. black	2.10	1.46-3.02
Trauma vs. not	1.66	1.05-2.62

39.7 percent and 31.3 percent, respectively. Chest pain accounted for 15.6 percent and headache 12.1 percent of patient pain complaints. In testing for inter-rater reliability of data abstraction, all variables had moderate to near-perfect correlation, with all κ values greater than 0.6.

The faculty included five EM-residency-trained physicians and five trained in other specialties but practicing EM full time. Five EPs had less than three years of attending experience, and five had more than three years. In both groups, the number included one female and four male doctors.

Just over half of the patients with pain (51.5 percent) received analgesia in the ED. Of the 700 patients who received ED analgesia, 36.0 percent received opioids. Of the 585 patients who received a discharge prescription, 57.6 percent were prescribed opioids.

Rates of ED analgesia by prescribing doctor are shown in Figure 1 and are primarily remarkable for the wide variation in practice. One specific doctor was less than half as likely to prescribe any ED analgesic and seven times less likely to give ED opioids than the doctor with the highest treatment rates.

An in-depth review of four individual cases of lower molar pain without signs of abscess was performed to illustrate the inconsistency of pain treatment in our ED. All patients reported severe pain (10 out of 10 on a verbal scale). Each was seen by a different doctor. Three patients were black and one white. Two were female, and one was over 50 years old. All were referred to a dentist upon discharge. Patient 1 received nothing in the ED and was given no discharge analgesic recommendation or prescription. Patient 2 received nothing in the ED and was told to take over-the-counter acetaminophen or ibuprofen for pain at discharge. Patient 3 received oral ibuprofen 800 mg in the ED and received a discharge prescription for hydrocodone/acetaminophen 5 mg/500 mg, 10 tablets, with instructions to take one by mouth every six hours as needed for pain. Patient 4 received hydrocodone/acetaminophen 5 mg/500 mg two tablets by mouth in the ED, and the emergency physician performed an inferior alveolar block with bupivacaine 0.5 percent with epinephrine. This last patient also received a prescription for hydrocodone/acetaminophen 7.5 mg/500 mg, 15 tablets, with instructions to take one tablet every four to six hours as needed for pain. No discharge

pain assessments were made, so no inference about adequacy of treatment was available.

The rate of analgesic use varied greatly according to pain location. ED patients with headache received analgesics 63.5 percent of the time, compared to 51.6 percent for abdominal pain, 51.9 percent for chest pain, and 48.0 percent for other pain. Headache and chest pain patients were less likely to receive opioids. Only 18.3 percent of headache and 20.0 percent of chest pain patients received opioids, compared to 49.1 percent of abdominal pain and 38.6 percent of other pain patients.

Logistic regression analysis of the primary and three secondary outcomes demonstrated significant predictors for each outcome (Table 1). For ED analgesia, age, race, chronic pain, and physician characteristics predicted use. Older people were half as likely to receive analgesia as younger patients. The undertreatment of older people continued with regard to discharge analgesics. Whites were 42.0 percent more likely to receive an ED analgesic.

Patients with chronic pain received analgesics, opioids, and discharge prescriptions twice as often as patients without chronic pain. EM-trained physicians were more likely to give analgesics and opioids in the ED than non-EM-trained providers. Physicians with less than three years of experience were more likely to prescribe analgesics in the ED. Blacks were only half as likely to receive ED opioids as whites.

DISCUSSION

Our study is consistent with other studies that have shown low rates of pain treatment in EDs and treatment disparities based on age and race.[4-6,8,9,11-14] Nearly half of our patients, with their varied pain complaints, received no analgesia in the ED. Patients 50 or older were less likely to receive analgesia both in the ED and at discharge. Blacks received less pain treatment than whites for all tested outcomes. These findings are statistically, and maybe clinically, significant, but we found that the most important factor determining rates of pain treatment was the identity of the doctor.

The reasons for the wide variation in pain practice by doctors in our ED are not clear and were not within the scope of this study. However, some possibilities could be suggested from our results and from anecdotal evidence from discussions with faculty after the study was completed. For instance, bias related to patient age and race likely plays some role. Fear, on the parts of patients and physicians, of opioid side effects, drug diversion, and addiction promotion also likely contribute to practice variation.

Understanding the factors associated with prescribing behavior and patient analgesic use is a key to providing better pain management in the ED. Our group is currently investigating which knowledge and attitudes of healthcare providers may determine pain management practice. Studies of patient factors that influence analgesic-taking behavior and desire for pain relief are also needed. Finally, development of systematic interventions to standardize pain practice may reduce inconsistencies in practice and improve satisfaction with care.

Tamayo-Sarver et al.[11,13] identified wide variation in pain practice by EPs based on written case vignettes but could not find any predictors of that variation, despite their investigation of many doctor characteristics. We found that type of residency training and length of experience significantly influenced rates of ED analgesia but did not influence discharge prescriptions. That EM-trained physicians and recent graduates give more analgesia in the ED makes some intuitive sense, considering the recent emphasis on pain management in the EM literature and by the largest EM professional organization.[3,4] In addition, our findings are consistent with a recent systematic review of the effect of years of experience on quality-of-care outcomes which demonstrated that increasing experience resulted in worse quality of care.[16]

If the finding of lower prescription rates of analgesia by more experienced practitioners is validated in a much larger sample of EPs, peer feedback, continuing education, or other intervention will be needed to overcome this deficiency.

Limitations

Due to the retrospective design, we are limited in our ability to draw firm conclusions about the causes of our findings, despite conscientious efforts to use rigorous chart-review methods to maximize the validity of our results. At best, we can generate useful hypotheses for future study.

Obviously, our EP group and patient list represent a tiny part of EM in the United States, so our findings must be generalized very cautiously. Since we are affiliated with a separate children's hospital, our patients are almost all adults, so we limited the study to those 18 years and older. Therefore, this study can not infer any conclusions about pain management in children. Also, this study includes no data on follow-up pain assessments or patient satisfaction with treatment, so we can not assess adequacy of treatment. Finally, our definitions of chronic pain and traumatic mechanism were arbitrary, so findings of influence on rates of analgesia require validation in other settings.

CONCLUSION

This study demonstrates that ED pain practices are highly variable and seem inadequate when measured against the goals of the WHO, AMA, and ACEP.[1-3] Patient age, race, and type of pain and physician identity, characteristics of training, and experience influence pain

treatment. Further research to identify causes of this variation is needed, and there is a need to develop interventions to standardize and improve pain assessment and treatment.

DISCLOSURE STATEMENT

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Results of a companion study to the one presented here were recently published.[14] Study cohorts were mutually exclusive, so no data from any patient were duplicated.

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ORIGINAL ARTICLE

Linkage to methadone treatment from acute opiate detoxification treatment

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ABSTRACT

Methadone maintenance treatment (MMT) is a safe pharmacological treatment strategy for addiction to heroin and other opiates; however, linking individuals to MMT is often challenging. We present results from a pilot project (Project VISTA) funded by the Center for Substance Abuse Treatment that helps heroin-dependent injection drug users (IDUs) transition from acute heroin detoxification to MMT. Participants are referred to Project VISTA by the state detoxification center, and Project VISTA facilitates entry into an MMT program, providing full financial support for up to 24 weeks. In addition, Project VISTA provides case management and referral to ancillary services such as housing, other medical care, and mental health treatment. From May 2005 to May 2006, 60 individuals were enrolled in Project VISTA. A total of 41 participants (69.5 percent) remained in treatment for at least 24 weeks, with a mean number of weeks in treatment of 31. A Kaplan-Meier analysis was performed on all participants, and the incidence of individuals being discharged from treatment was 2 percent per week. Project VISTA, in cooperation with the state detoxification center and a Providence-based MMT program, has created a model that provides continuity of treatment services to high-risk, HIV-negative IDUs. Our model demonstrates that through facilitating the transition from an opiate detoxification program into an MMT program, individuals with chronic heroin addiction can successfully access and engage in treatment.

Key words: methadone maintenance treatment, injection drug users, detox, HIV prevention

INTRODUCTION

Methadone maintenance treatment (MMT) is the most widely available opioid replacement therapy for addiction to heroin and other opiates.[1] Methadone prescription is a safe pharmacological treatment strategy and has been used to treat chronic opiate addiction for over 35 years. Many studies have demonstrated the effectiveness of MMT in reducing opiate use among injection drug users (IDUs) in various settings.[2-6] Furthermore, MMT is more effective than detoxification in retaining clients in drug treatment, aiding cessation of opiate use, and reducing drug-related HIV risk behaviors.[7]

There is substantial evidence confirming that consistent MMT reduces the risk of HIV infection among IDUs.[1] Several studies have demonstrated that MMT significantly reduces the frequency of injection and needle sharing.[8-13] For example, Kwiatkowski et al.[11] found that street-recruited injectors who received 90 days of free MMT reported considerably greater reductions in drug use (injections of all drugs, including heroin) compared to a control group who did not receive MMT. Even when controlling for confounding factors such as education level, incarceration, and duration of opiate dependency, MMT clients reported fewer drug-related risk-taking behaviors and, as a result, had a reduced likelihood of HIV seroconversion.[14-16]

Sexual risk behaviors are also reduced by participation in MMT; reduction in opiate use and injection in turn lead to a reduction in secondary risk behaviors such as trading sex for drugs or money or engaging in sex with high-risk partners. In addition, risky sex that is the result of impaired judgment is significantly reduced.[17] Reductions in unsafe sexual behaviors generally accompany injection cessation,[18] and MMT patients report fewer sexual encounters with high-risk partners than persons not in treatment. MMT also lowers crime and recidivism rates and is an important point of contact with service providers, including healthcare providers.[19] Overall, MMT is strongly related to lower levels of mortality from both overdose and natural causes.[5]

Compared to other forms of treatment, MMT has the most impressive record for retaining clients in drug treatment.[20] Many MMT clients will remain in treatment for as long as it is available and accessible. Even those who initiate MMT and subsequently discontinue treatment are arguably one step closer to recovery; the National Institute on Drug Abuse (NIDA) recognizes that multiple treatment episodes are often necessary when moving toward the ultimate goal of complete cessation of drug use.[21]

Project VISTA, funded by the Center for Substance Abuse Treatment (CSAT), utilizes multidisciplinary collaborations to link high-risk, HIV-negative IDUs to mental health and substance use treatment services. In May 2005, Project VISTA entered into a novel collaboration with Stanley Street Treatment and Resources (SSTAR) detoxification center and CODAC Behavioral Healthcare methadone clinic to provide continuity of care to IDUs in the Greater Providence (Rhode Island) area. The idea for this pilot project came out of the observation that many IDUs admitted to SSTAR detoxification have high recidivism rates and often do not access long-term treatment. Thus, these individuals are not receiving appropriate care for their addictions. The results of the first year of this collaboration are presented here.

METHODS

Individuals with high recidivism rates for heroin detoxification were assessed by the detoxification center's clinicians to evaluate the appropriateness of MMT. Individuals who were deemed appropriate for MMT (at least six acute detoxification admissions within the past year, which, based on the detoxification center's institutional guidelines, represents a high degree of recidivism and therefore warrants referral to alternative forms of treatment) were referred to the methadone program to begin treatment. Upon intake at the methadone program, individuals were eligible to enroll in Project VISTA. Eligibility requirements for Project VISTA are the following: 1) substance use within the past 30 days, 2) at least 18 years old, and 3) engagement in high-risk behaviors for HIV infection, e.g., any occasion of sharing needles and/or injection equipment, insufficient cleaning of works, and/or unprotected sex (vaginal and/or anal). For the purposes of this study, only individuals who had injected heroin within the past 30 days were included.

Through Project VISTA, participants receive full financial support for up to 24 weeks of MMT. In addition, participants are linked to other treatment services, including outpatient counseling and mental illness treatment. Linkage to treatment services is based on evaluation by a master's level clinical psychologist with experience in assessment and evaluation of addiction disorders and mental illness. The evaluation uses American Society of Addiction Medicine criteria as well as the participant's patient history and symptom self-report and is completed at the time of enrollment in the project. Project VISTA also provides supportive services such as transitional housing, transportation assistance, and case management services. Referral for these services is based on participant self-report of need.

Due to limited resources, Project VISTA is only able to reserve six slots for detoxification center referrals each month and can only provide financial support for up to 24 weeks, even though a participant's enrollment in the project is for a full year. At the time of a client's referral, the detoxification center assigns him or her a referral number. This number is then given to the methadone program and indicates that detoxification center clinicians have performed a Project VISTA eligibility assessment. Once a client completes the intake procedure for the methadone program and begins MMT, he or she is encouraged to contact Project VISTA in order to complete the enrollment procedures, either by phone or at one of the project's two drop-in support centers. If an eligible participant is unable to attend either drop-in center, he or she can make arrangements with Project VISTA staff to complete the enrollment process at the methadone program.

Table 1. Selected demographic characteristics (N = 60)

Demographic characteristic	Number (percent)
Gender	
Male	42 (70)
Female	18 (30)
Age	
20 to 29	11 (18.3)
30 to 39	30 (50)
40 to 49	16 (26.7)
> 49	3 (5)
Race/ethnicity	
White, non-Hispanic	43 (71.7)
African American	2 (3.3)
Puerto Rican	13 (21.7)
Other	2 (3.3)

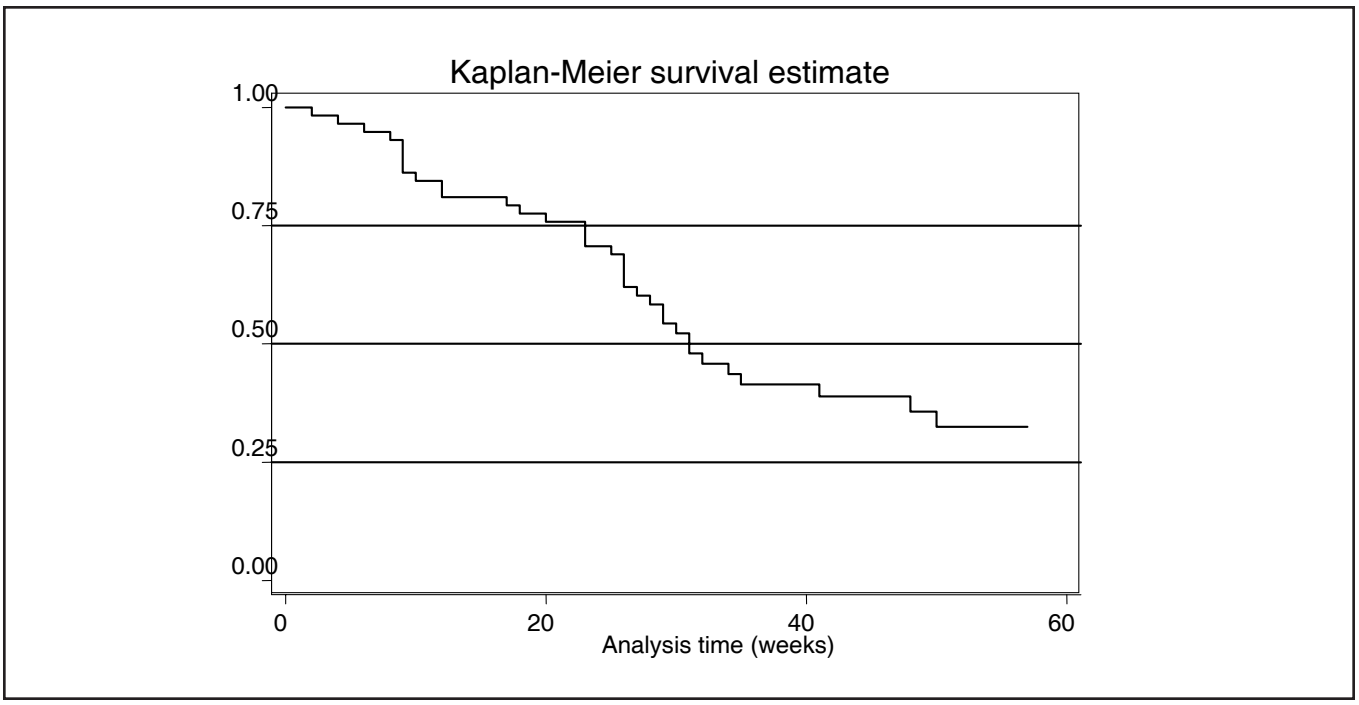

Figure 1. Kaplan Meier survival estimate of MMT retention among VISTA clients.

Although Project VISTA only has resources to provide financial assistance for 24 weeks, participation in the project lasts for one year, during which time individuals can access project staff and get additional referrals for substance use, mental health treatment, and social services. One of the primary aims of Project VISTA is to provide initial financial support and referral to ancillary services in order to stabilize individuals and help them progress toward self-sufficiency in their recovery. Approval for Project VISTA was obtained through The Miriam Hospital Institutional Review Board.

RESULTS

Demographics and referral services

From May 1, 2005, through May 1, 2006, a total of 65 individuals were referred to Project VISTA through CODAC Behavioral Services. Five individuals who were referred to Project VISTA did not complete the enrollment process, resulting in a total enrollment rate of 92.3 percent. Selected demographics are shown in Table 1. The majority of participants were white, non-Hispanic (71.7 percent), and male (70 percent). Table 2 lists ancillary services for which project participants were referred. Data regarding follow-up services were incomplete when this manuscript was written. Overall, the most common referrals among Project VISTA participants at CODAC were for medical services, housing, and transportation assistance. Many participants were referred for multiple services.

Outcomes

Table 3 gives the total number of weeks participants accessed MMT during their enrollment in Project VISTA. Project VISTA provides financial support for up to 24 weeks of MMT. A total of 41 participants (69.5 percent) remained in treatment for at least 24 weeks. Participants with less than 24 weeks of treatment and who were not incarcerated were administratively discharged, i.e., the participant either left the clinic against medical advice or missed seven or more doses within a 30-day period. At the time of the current analysis, 10 participants had been financially discharged and 24 participants (40.7 percent) were still active in treatment. Of the total number of participants referred for treatment, six experienced an interruption in their treatment due to incarceration (Table 3).

A Kaplan-Meier analysis was performed on all participants in treatment at CODAC during this period. Results of this analysis are shown in Figure 1. Overall, a total of 1,767 person weeks was analyzed. The mean duration of treatment was 31 weeks (95 percent CI 26 to 41 weeks; data not shown). The incidence of individuals being discharged from treatment was 2 percent per week (95 percent CI 1.4 percent to 2.8 percent; data not shown).

DISCUSSION

Project VISTA, in partnership with SSTAR detoxification center and CODAC methadone clinic, has created a model that provides continuity of treatment services to

Table 2. Ancillary services	
Type of service	**Number (percent)***
Medical	25 (41.7)
Housing (sober housing, transitional housing, shelters, etc.)	29 (48.3)
Employment (local employment agencies)	17 (28.3)
Benefits (SSI/SSDI, Medicaid, etc.)	13 (21.7)
Transportation assistance	21 (35)
Mental health treatment services	19 (31.7)
Legal services	2 (3.3)
No services	14 (23.3)
* Numbers and percentages do not add up to the total number of participants, as some participants were referred for multiple services.	

high-risk, HIV-negative IDUs. By facilitating entry into an MMT program through an opiate detoxification program, individuals with chronic heroin addiction can successfully access and engage in treatment. In addition, providing referrals for ancillary services may contribute to higher patient retention.

Detoxification protocols for opiate dependence are often unsuccessful.[22,23] Although opiate replacement can be used to detoxify opiate-dependent individuals, many of these individuals will relapse into opiate use after completion of the protocol. In actuality, most dependent persons who undergo detoxification ultimately return to heroin use.[7] It is not surprising that many opiate-addicted individuals who do not access long-term treatment cycle through many detoxification admissions without effectively dealing with their addictions. Case management has been shown to be an effective strategy in decreasing the number of detoxification admissions and in facilitating entry into long-term treatment programs.[24] Project VISTA utilizes a comprehensive case management approach to link IDUs to MMT after they are released from detoxification. Clients enrolled in Project VISTA underwent an average of 31 weeks of MMT. Although this amount of time is less than the recommended minimum of 12 months for achieving clinical benefits from MMT,[25] it still represents a longer duration of treatment than most clients had during the previous year, as all of the individuals referred to Project VISTA had been cycling in and out of detoxification during the past year.

Barriers to MMT

IDUs encounter numerous barriers to MMT. Despite the benefits of MMT programs, many IDUs do not access treatment. Misconceptions about methadone and ambivalence toward MMT have been well documented.[26,27] Patients hold a variety of inaccurate views, such as that methadone is harmful to teeth and bones, is more

Table 3. MMT duration				
Number of weeks on methadone	**Active (percent)**	**Discharged* (percent)**	**Incarcerated (percent)**	**Total (percent)**
0 to 10	0 (0)	8 (80)	2 (20)	10 (16.9)
11 to 20	0 (0)	4 (80)	1 (20)	5 (8.5)
21 to 30	7 (36.8)	9 (47.4)	3 (33.2)	19 (32.2)
31 to 40	4 (44.4)	5 (55.6)	0 (0)	9 (15.3)
41 to 50	3 (50)	3 (50)	0 (0)	6 (10.2)
> 50	10 (100)	0 (0)	0 (0)	10 (16.9)
* Individuals discharged prior to 24 weeks were administratively discharged.				

damaging to one's health than heroin, and is nearly impossible to withdraw from. Negative attitudes regarding methadone result in many patients leaving MMT programs prematurely, which may facilitate relapse into old patterns of risky behaviors.[28] Aversion to MMT has been implicated as a primary barrier to treatment among IDUs who would consider some form of treatment for their addiction.

Once a patient is admitted into treatment, there can still be obstacles to achieving a full recovery. Polysubstance abuse and mental illness are associated with a greater likelihood of being discharged.[29] There is well-documented evidence of associations between opiate addiction and specific psychiatric illnesses, most notably major depressive disorder. Among opioid users, lifetime rates of psychiatric disorders are greater than 40 percent.[30] Many opioid users frequently use other drugs as well, and their psychiatric illnesses are often exacerbated through addiction to multiple substances. In many cases, psychiatric disorders precede drug dependence.[31] Among IDUs both in and out of treatment, there are significant unmet needs, including social services such as housing, mental health treatment, financial support, and other medical services[32]; the majority of Project VISTA participants indicated that housing was a primary concern.

Limitations

Our results should be interpreted with certain limitations in mind. This is an evaluation of a specific intervention facilitating access to MMT within the context of a treatment service grant. Therefore, there was no specific experimental design employed to collect data for the purposes of qualitatively evaluating outcome indicators. The information presented in this manuscript is the result of a small pilot project enrolling a sample of only 60 IDUs, and selection bias likely influenced this sample; individuals were referred from SSTAR based on eligibility and willingness to enter into an MMT program. However, our aim was to conduct a demonstration pilot project in order to assess the feasibility of referring high-risk, HIV-negative IDUs from detoxification directly to MMT.

Although Project VISTA was able to successfully engage and retain IDUs in MMT, it is difficult to differentiate which aspects of the project are most closely associated with patient retention and risk reduction. For example, case management alone likely does not explain why many individuals were able to access treatment. Project VISTA provides financial support for up to 24 weeks of MMT for IDUs referred directly from SSTAR. Without such financial support, most of these individuals would likely not be able to access care due to their inability to pay for treatment. However, while the ability to pay for treatment is likely highly correlated with initial access to treatment, it may not be as strongly correlated with retention in treatment. For example, Deck and Carlson[33] studied MMT retention rates in publicly funded MMT programs in Washington and Oregon and found that inadequate financing of MMT can influence patient retention, but the retention rates observed were modest. The authors noted that there is limited research on the association of cost and MMT retention.

CONCLUSION

IDUs represent a subset of illicit substance users who are difficult to engage in treatment. Project VISTA links IDUs to MMT and provides linkages to ancillary services including housing, medical care, and social services through provision of case management and outreach. On-site service delivery and case management services have been shown to be successful in linking treatment clients to ancillary services, which are important for retention in addiction treatment.[20] In this pilot study, Project VISTA has demonstrated the feasibility of engaging IDUs in MMT at the time of their discharge from detoxification. Future directions will include expanding on the pilot project in order to include more participants, refer more individuals to ancillary services, and develop a better system for following up on referrals to determine the proportion of referred IDUs who are actually receiving services.

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ORIGINAL ARTICLE

Breakthrough pain in opioid-treated patients with neuropathic pain

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ABSTRACT

Objective: *This report aims to describe the prevalence and characteristics of breakthrough pain in patients with neuropathic pain.*

Methods: *The study represents data from a subset of patients from a larger survey of 228 patients with chronic noncancer pain. Patients were identified from nine pain programs and were administered a telephone questionnaire. The study population comprised 45 chronic noncancer pain patients with primary neuropathic pain diagnoses who were being treated with opioids.*

Results: *Pain had been present for a median of six years. Medications used for pain in addition to opioids included nonsteroidal anti-inflammatory agents (29 percent), antidepressants (60 percent), and anticonvulsants (53 percent). Thirty-five of the patients (78 percent) described a total of 42 distinct types of breakthrough pain. The median number of episodes per day was two; the median time to maximum intensity was 10 minutes, and the median duration of pain was 60 minutes. Patients could identify a precipitant for 62 percent of the pains, and 88 percent of the precipitants were activity related. The onset of breakthrough pain could not be predicted for 48 percent of the pains and could only sometimes be predicted for 29 percent of the pains.*

Conclusion: *Breakthrough pain is common in opioid-treated patients with chronic neuropathic pain. Such pain often has a rapid onset and a relatively short duration, and it is frequently difficult to predict, similar to breakthrough pain in cancer patients.*

Key words: breakthrough pain, chronic pain, neuropathic pain, survey

INTRODUCTION

Neuropathic pain, defined as any pain initiated or caused by a primary lesion or dysfunction of the nervous system,[1] encompasses many heterogeneous conditions that can not be explained by a single etiology or a specific anatomical lesion.[2] Among the most common causes of neuropathic pain are painful diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, and degenerative spinal disease. Persistent neuropathic pain can impair a patient's quality of life by interfering with mood, sleep, mobility, work, social relations, leisure activities, emotional well-being, and enjoyment of life.[3,4]

Over the past 20 years there has been a greater effort on the part of the medical community to actively identify patients with painful conditions and provide them with adequate analgesia. Though considerable advances have been made in the field of pain management, neuropathic pain continues to present a clinical challenge because of the heterogeneity of diseases associated with neuropathic pain and the complexity of the nervous system. Indeed, pharmacotherapy for neuropathic pain has been reported to result in effective analgesia in less than half of patients.[2] Therefore, in order to identify specific therapies directed at neuropathic pain, there must be a clear understanding of the phenomena and clinical circumstances surrounding this type of chronic pain.

Chronic pain is typically characterized by persistent pain requiring around-the-clock analgesics. Chronic pain patients commonly experience transient exacerbations of pain, or breakthrough pain. The prevalence of breakthrough pain in patients with chronic pain (both cancer-related and noncancer pain) has been estimated at 50 to 90 percent, and it has been shown to be associated with functional impairment and psychological distress.[5-9] A survey of the prevalence and characteristics of breakthrough pain in 228 patients with chronic noncancer pain was recently completed.[7] The results of the survey indicated that the prevalence (74 percent) and characteristics of breakthrough pain in patients with chronic noncancer

Table 1. Patient demographics (N = 45 patients)			
	Patients with breakthrough pain (n = 35)	**Patients without breakthrough pain (n = 10)**	**Total (N = 45)**
Median (range) age, years	45 (21 to 74)	43.5 (34 to 59)	45 (21 to 74)
n (percent) female	21 (60 percent)	6 (60 percent)	27 (60 percent)
Median (range) years since diagnosis	7 (0.08 to 55)	4.25 (1 to 11)	6 (0.08 to 55)
Diagnosis, n (percent)			
Central pain	2 (6 percent)	0 (0 percent)	2 (4 percent)
Complex regional pain syndrome	14 (40 percent)	2 (20 percent)	16 (36 percent)
Postherpetic neuralgia	2 (6 percent)	0 (0 percent)	2 (4 percent)
Diabetic neuropathy	1 (3 percent)	0 (0 percent)	1 (2 percent)
Peripheral neuropathy	4 (11 percent)	0 (0 percent)	4 (9 percent)
Other neuropathy	12 (34 percent)	8 (80 percent)	20 (44 percent)
Severity of baseline pain, n (percent)			
Mild	6 (17 percent)	1 (10 percent)	7 (16 percent)
Moderate	29 (83 percent)	9 (90 percent)	38 (84 percent)

pain are similar to those in patients with cancer-related pain. To date, the prevalence and characteristics of breakthrough pain specifically in patients with neuropathic pain have not been described. This report is a subgroup analysis and describes breakthrough pain and its treatment in patients with neuropathic pain.

METHODS

This paper presents a subgroup analysis based on a survey of breakthrough pain in opioid-treated patients with chronic noncancer pain.[7] The survey was conducted at nine pain treatment centers in the United States. Patients were recruited for participation in the study at the pain clinics and were subsequently interviewed via telephone regarding their pain experience. An Institutional Review Board approved the study protocol, and all subjects provided written informed consent. This report comprises data only from patients who had a pain diagnosis known to cause neuropathic pain.[10]

Patient selection and procedures

Investigators screened patients at the clinic for study eligibility. Eligible patients were between 18 and 75 years of age, had been experiencing pain for six months or longer, and had controlled baseline pain. Patients were considered to have controlled baseline pain if they provided an affirmative response to the following question: "Does your pain currently have a component you would describe as 'constant' or 'almost constant' or that would be constant or almost constant if not for the treatment you are receiving?" They also had to be following an opioid regimen that either 1) provided treatment for at least 12 hours per day and yielded a baseline pain that was, on average during the past week, absent, mild, or moderate, or 2) provided treatment for less than 12 hours per day

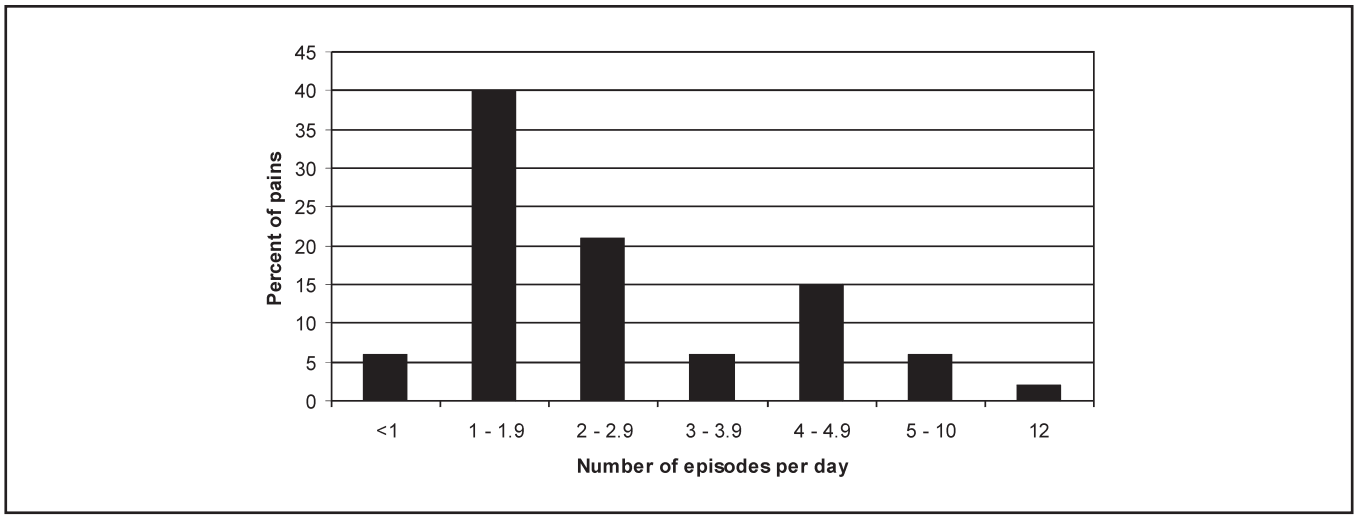

Figure 1. Breakthrough pain frequency (N = 42 pains).

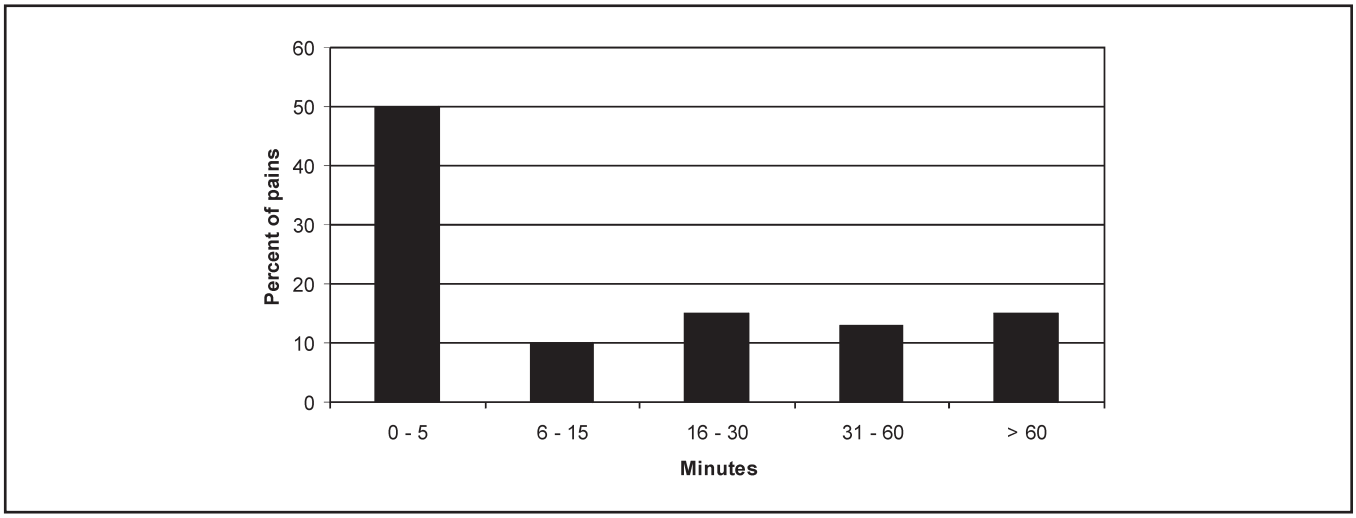

Figure 2. Time from first perception of pain to maximal intensity (N = 42 pains).

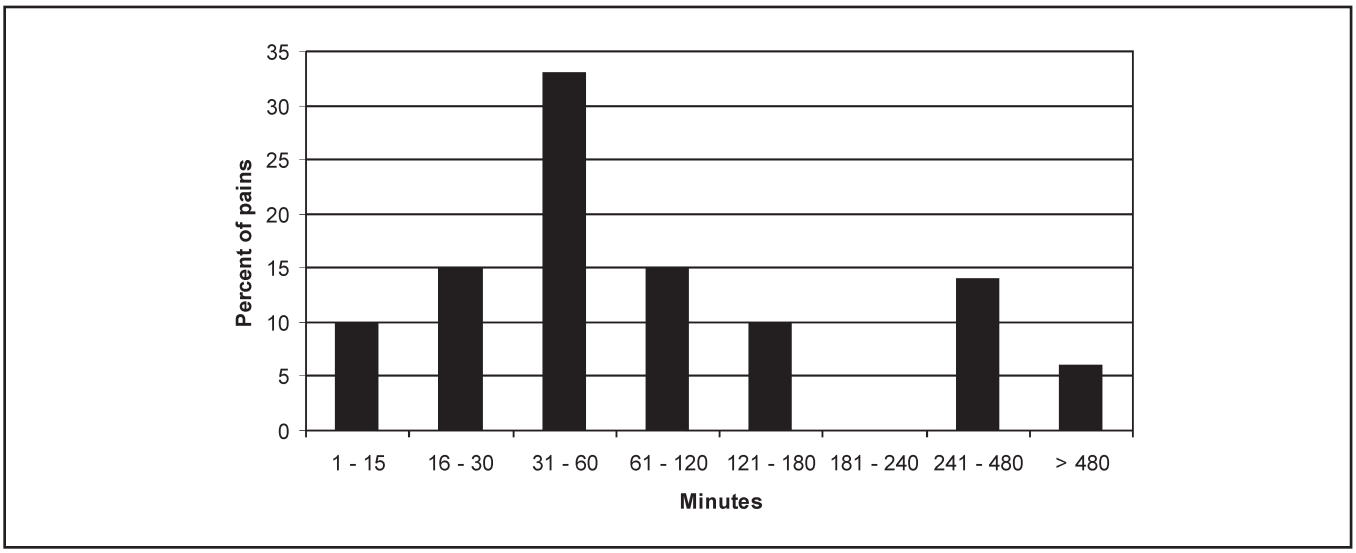

Figure 3. Duration of breakthrough pain (N = 41 pains; duration information was missing for one pain).

Table 2. Analgesics and co-analgesic medications of patients with and without breakthrough pain		
Medication	**Patients with breakthrough pain (n = 35)**	**Patients without breakthrough pain (n = 10)**
Opioid analgesics	35 (100 percent)	10 (100 percent)
Oral sustained-release	16 (46 percent)	2 (20 percent)
Transdermal	6 (17 percent)	0 (0 percent)
Methadone	5 (14 percent)	2 (20 percent)
Intrathecal	3 (9 percent)	0 (0 percent)
Short-acting opioids[a]	31 (89 percent)	7 (70 percent)
Others		
NSAIDs[b]	10 (29 percent)	3 (30 percent)
Antidepressants	21 (60 percent)	6 (60 percent)
Anticonvulsants	18 (51 percent)	6 (60 percent)

[a] Includes oral normal-release opioids (combined with acetaminophen or a nonsteroidal anti-inflammatory drug [NSAID] or not combined) and oral transmucosal fentanyl citrate. [b] Includes COX-2 selective and nonselective NSAIDs.

and yielded a baseline pain that was, on average during the past week, mild or moderate. Patients with cancer-related pain or who had recently (i.e., within the previous month) been hospitalized for uncontrolled pain were excluded. Patients were included in this analysis if they had a primary pain diagnosis indicative of the presence of neuropathic pain. At the clinic, demographic information was recorded and the telephone interview was scheduled. Within approximately one week of the clinic visit, a trained interviewer administered the survey to the patient. Data collection occurred from February through April of 2004.

Data collection

The survey instrument was adapted from a pain assessment algorithm used previously with cancer patients.[5,6] Information gathered regarding baseline pain included location, time since onset, and characteristics. To determine whether breakthrough pain was present, patients were asked if they experienced temporary flares (i.e., duration of ≤ 12 hours) of severe or excruciating pain in addition to their baseline pain. Only patients with breakthrough pain continued the interview. Information collected to characterize breakthrough pain included frequency, onset (time from first perception to maximal intensity), duration, severity (severe or excruciating), predictability, precipitants, and pain therapies and their success at alleviating the pain. If patients reported experiencing more than one type of breakthrough pain, they were asked to report first on the worst flare-up they had experienced within the previous 24-hour period and then on the remaining types separately.

RESULTS

Forty-five subjects with neuropathic pain were included in this subgroup analysis. The most common pain diagnoses were nondiabetic neuropathy (44 percent) and complex regional pain syndrome (36 percent). The median age of subjects was 45 years (range of 21 to 74 years). More than half (60 percent) of the subjects were female, and the median duration of pain was six years (Table 1). Of the 45 subjects, 35 (78 percent) reported flares of breakthrough pain. Several experienced more than one type of breakthrough pain, with a total of 42 distinct types of breakthrough pain identified by the 35 subjects.

The median frequency of breakthrough pain episodes was two per day and ranged from one per week to 12 per day (Figure 1). The median time to maximum intensity was 7.5 minutes and ranged from 0.2 to 180 minutes. Half of the pains reached maximum intensity within five minutes

(Figure 2). The median duration of pain was 60 minutes and ranged from five to 720 minutes (Figure 3). A precipitant could be identified for most of the pains (62 percent), with the most common precipitant being activity (88 percent). Forty-eight percent of the pains could never be predicted, and 29 percent could only sometimes be predicted. Most pains (93 percent) could be at least partially lessened by one or more of the following approaches: medication (81 percent); rest, lying down, or sitting (55 percent); heat (26 percent); cold (12 percent); movement, stretching, or physical therapy (5 percent); sleep (2 percent); massage (2 percent); spinal cord stimulation (2 percent); and distraction (2 percent). However, these interventions were reported to be consistently effective for only 28 percent of the pains.

All subjects were using opioids for their pain, as required for inclusion in the study (Table 2). Most subjects were using shorter-acting opioids for their pain (89 percent of subjects with breakthrough pain and 70 percent of subjects without breakthrough pain). Antidepressants and anticonvulsants were also used to manage pain in more than half of subjects.

DISCUSSION

Chronic neuropathic pain is a serious medical condition that affects more than 2 million Americans.[11] Neuropathic pain often proves difficult to relieve, and unfortunately it is not yet treated effectively in most patients.[2] Undertreated neuropathic pain can result in severe limitations for patients and can have profound negative effects on their quality of life.[12] To improve the likelihood of an effective treatment outcome for patients, a clear understanding of the nature of the pain must be achieved. The results of this study indicate that patients with neuropathic pain experience breakthrough pain in a similar proportion and with similar characteristics as patients with chronic pain of a non-neuropathic origin.[5,7,9] Such pain often has a rapid onset and a relatively short duration, and it is frequently difficult to predict. Although the phenomenon of breakthrough pain has been demonstrated to be a pervasive and debilitating condition, studies to evaluate the treatment options in this population are limited.

Current treatment options for relieving chronic neuropathic pain include tricyclics, selective serotonin reuptake inhibitors, anticonvulsants, capsaicin, levodopa, ion channel blockers, and opioids.[2,13-16] In patients for whom treatment with nonsteroidal anti-inflammatory drugs and acetaminophen no longer provides adequate pain control, opioids are the therapy of choice.[14,17] The use of opioids for chronic neuropathic pain, however, remains controversial due to experimental studies and some studies in humans that suggest that this type of pain is less responsive to opioid therapy.[18-20] Clinicians who are already reluctant to prescribe opioids to patients with noncancer pain because of concerns about opioid abuse may be even more reluctant to prescribe opioids to patients with neuropathic pain due to added concerns about the responsiveness of such pain to opioid treatment.[21] However, over the past few years several controlled studies have demonstrated the efficacy of opioids in relieving pain associated with diabetic neuropathy[22,23] and postherpetic neuralgia.[24] A recent review of randomized, controlled studies on the safety and efficacy of opioid agonists in combating neuropathic pain of noncancer origin concluded that short-term studies yielded mixed results with respect to the analgesic efficacy of opioids, while intermediate-term trials showed consistent opioid analgesic efficacy.[25] To date, the body of support for the use of opioids for neuropathic pain is continuing to grow.[11]

Our study suffers from some important limitations. First, we are reporting on a small sample of patients who were being treated at pain clinics and receiving opioids for their pain. Patients whose neuropathic pain is being managed outside of a pain clinic may have a different experience with their pain. Second, this survey depended on self-report of patients, and although the questionnaire has been used in previous studies,[5,6] it has not yet been validated. Despite these limitations, this study adds to the expanding literature of the characteristics and management of neuropathic pain, a prerequisite for finding effective treatments for this difficult pain condition.

The results show that breakthrough pain is highly prevalent in patients with chronic neuropathic pain, and the characteristics suggest the need for therapies that provide effective pain relief involving analgesics with rapid onset and a relatively short duration.

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Perioperative management of opioid-tolerant chronic pain patients

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ABSTRACT

Opioids occupy a position of unsurpassed clinical utility in the treatment of many types of painful conditions. In recent years there has been a noticeable shift regarding the use of opioids for the treatment of both benign and malignancy-related pain. As acceptance of the prescribing of opioids for chronically painful conditions has grown, many more opioid-tolerant patients are presenting for surgical procedures. It is therefore imperative that practicing anesthesiologists become familiar with currently available opioid formulations, including data regarding drug interactions and side effects, in order to better plan for patients' perioperative anesthetic needs and management. Unfortunately, there is a lack of scientifically rigorous studies in this important area, and most information must be derived from anecdotal reports and the personal experience of anesthesiologists working in this field. In this review, we shall discuss current chronic pain management and the impact of opioid use and tolerance on perioperative anesthetic management.

Key words: opioids, opioid tolerance, chronic pain, perioperative, anesthesia

INTRODUCTION

Pain represents one of the most common reasons that people seek medical care.[1] In the past, most physicians were reluctant to prescribe strong opioid analgesics for chronic nonmalignant pain, and the use of opioids in such patients was considered controversial by many clinicians well into the 1990s.[2] This controversy persisted despite numerous published studies that documented the safety and efficacy of opioids in the management of a wide variety of chronic nonmalignant pain states, including those of neuropathic, myofascial, and arthritic origin.[3,4] However, following a joint consensus statement published by the American Academy of Pain Medicine and the American Pain Society[5] in 1997, *The Use of Opioids for the Treatment of Chronic Pain*, noticeable shifts in physician attitudes toward the rational use of these drugs occurred. Primary care physicians and pain specialists are prescribing opioids to a great number of patients with nonmalignant pain, in doses appropriate to their needs.[6] For example, Clark,[7] in a recent review of 300 randomly selected patient charts from a population of patients at the Veterans Affairs Palo Alto Health Care System, found that 50 percent of the patients selected suffered from at least one form of chronic pain. Of those patients with chronic pain, 75 percent were prescribed at least one analgesic drug, and most received two or more. In the group of patients who received analgesic medication, 44 percent were prescribed an opioid. It is not surprising that as a consequence of exposure to long-term opioid therapy, chronic pain patients become opioid tolerant. In this review, we shall discuss the clinical aspects of opioid use and tolerance, including the impact they may have on perioperative anesthetic management.

PREOPERATIVE CONCERNS WITH THE OPIOID–TOLERANT PATIENT

The ultimate goal of the preoperative medical assessment of a patient is to reduce the morbidity and mortality of surgery. In addition, in today's cost-conscious hospital environment there is an emphasis on reducing the cost of perioperative care and returning the patient to full functioning as quickly as possible. To achieve these ends, the anesthesiologist must perform a preoperative assessment of the patient. This traditionally includes a preoperative history, physical examination, laboratory evaluation, and risk classification of the patient. Armed with the resulting information, the anesthesiologist then formulates an individually tailored plan of care for the anesthetic management of the patient. Multiple guidelines have been published to help facilitate thorough evaluations of high-risk patients. Unfortunately, there are no specific guidelines to help anesthesiologists evaluate the unique requirements of the chronic pain patient. There are, though, several general principles

Table 1. Commonly used single opioid preparations			
Opioid name	**Preparation**	**Dosage forms**	**Comments**
Morphine			
MS Contin	Sustained-release oral tablet/capsule	15, 30, 60, 100, 200 mg	Q12 h dosing; tablets or capsules must not be broken, chewed, crushed, or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of morphine
Kadian		20, 30, 50, 60, 100 mg	
Avinza		30, 60, 90, 120 mg	
Oramorph ST	Oral liquid	10 mg/5 ml, 10 mg/2.5 ml, 20 mg/5 ml, 20 mg/ml, 100 mg/5 ml	
Roxinol		10 mg/2.5 ml, 20 mg/ml, 100 mg/5 ml	
Actiq	Transoral delivery system	200, 400, 600, 800, 1200, 1600 μg	Only indicated for the management of breakthrough pain in patients who are already receiving and who are tolerant to opioid therapy
Oralet		100, 200, 300, 400 μg	
Oxycodone			
Oxycontin	Sustained-release tablets	10, 20, 40, 80, 160 mg	Q12 h dosing; tablets or capsules must not be broken, chewed, crushed, or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of oxycodone
OxyIR	Immediate-release tablets	5 mg	
OxyFast	Oral liquid	20 mg/ml	
Hydromorphone			
Dilaudid	Tablet	8 mg	Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people
Dilaudid liquid	Oral liquid	5 mg	
Methadone			
Dolphine	Tablet	5, 10 mg	Dose-dependent prolongation of the QT interval
Fentanyl			
Duragesic	Transdermal delivery system	25, 50, 75, 100 μg/hr	Apply every three days; fentanyl delivery may be altered by application of heat

that can help to guide the anesthesiologist in perioperative management of the opioid-tolerant patient.

During the initial patient assessment, the anesthesiologist should determine whether the patient is a chronic opioid user, while being careful to recognize that the terms "opioid user" or "abuser" may be considered derogatory labels by the patient. Patients are keenly aware of the significant social stigma surrounding opioid use and are entitled to privacy and the right to confidentiality. It is imperative to take a detailed history from these patients and to establish a good rapport through nonjudgmental communication. In some cases, patients may not be taking their medication as directed. A minority of these patients may be selling or trading their pain medicines. If there is concern regarding the validity of a patient's stated drug requirement, the medicine can be portioned out over a longer period of time, instead of giving a large and potentially dangerous single dose. Physicians should communicate to their patients that an improper dose of opiates can potentially result in either a life-threatening overdose or withdrawal phenomena associated with inadequate analgesia. Good rapport with the patients and a clear description of the expectations of the patients by hospital staff may help to promote an honest dialogue about drug history and medications.[8]

A preoperative medication history should include the dose, frequency of ingestion, and time of last dose. All regular medications, including opioids and adjuvants, should be reviewed with the patient. Physicians should be well versed in the commonly used opioid preparations. Opioids are available in both sustained- and immediate-release forms, and they can be administered by a number of routes, including oral, parenteral, rectal, sublingual, transdermal, and transmucosal. The prototype opioid, morphine, represents the most commonly used type of opioid. Morphine and other opioids with short half-lives require frequent administration to maintain analgesia. Immediate-release morphine products provide about four hours of pain relief and need to be dosed accordingly. Controlled-release formulations such as MS Contin provide alternatives to frequent opioid administration. Medications with longer half-lives (e.g., methadone and levorphanol) yield analgesia for six to 12 hours. Some of the more common commercially available opioids are listed in Table 1.

Tolerance to opioids is characterized by shortened duration and decreased intensity of analgesia, euphoria, sedation, and other effects caused by depression of the central nervous system. Opioid tolerance is a predictable pharmacologic adaptation. Chronic opioid exposure results in a rightward shift in the dose-response curve, and patients require increasing amounts of a drug to maintain the same pharmacologic effects. In general, the higher the daily dose requirement, the greater the degree of tolerance development. Although there are no clear gradation guidelines, individuals requiring the equivalent of 1 mg or more of intravenous (IV) morphine or 3 mg or more of oral morphine per hour for a period of longer than one month may be considered to have high-grade opioid tolerance.[9,10]

Various studies and anecdotal clinical experience suggest that tolerance to various opioid side effects develops at different rates; this is termed "selective tolerance."[11] The initial effects associated with opioid administration include analgesia, sedation, nausea and vomiting, respiratory depression, pupillary constriction, constipation, and euphoria or dysphoria. Tolerance to nausea and vomiting, sedation, euphoria, and respiratory depression occurs rapidly, while tolerance to constipation and miosis is minimal over any length of time.[12,13]

Preoperative management of the opioid-tolerant patient begins with administration of the daily maintenance or baseline opioid dose, before induction of general, spinal, or regional anesthesia. Patients should be instructed to take the usual dose of oral opioid on the morning of surgery and, if applicable, to maintain any transdermal fentanyl patches. Because most sustained-release opioids provide 12 hours or more of analgesic effect, baseline requirements will generally be maintained during preoperative and intraoperative periods. However, with shorter-acting opioids or patients who have missed a dose prior to surgery, an "opioid debt" may develop preoperatively. Opioid debt has been defined as the daily amount of opioid medication required by an opioid-dependent patient to maintain his or her usual, prehospitalization opioid level. Discontinuation of opioids in a patient who is opioid-dependent will result in a lowering of the opioid plasma level to a point below the patient's "comfort zone," leading into either early (subjective) or late (objective) withdrawal. In addition, hyperalgesia has been observed in association with opioid tolerance.[14]

A patient-controlled analgesia (PCA) pump can be used but is limited in that it is designed primarily to maintain analgesia, not to establish analgesia or overcome an opioid debt.[15] In opioid-tolerant patients, if the opioid debt is not covered, the repeated bolus doses from a PCA pump are unlikely to achieve an analgesia effect. A background infusion should be considered in opioid-tolerant patients currently on high-dose opioid therapy. One anesthesia group advocates loading the opioid-tolerant patient with opioids in the operating room as the patient is waking from surgery. Opioid-tolerant patients who undergo major surgery can receive a low dose of intraoperative ketamine (0.25 mg/kg IV, up to 20 mg) for potential reduction in opioid tolerance and improved postoperative pain control.[16,17] Unless contraindicated, patients should also be instructed to take their morning dose of cyclooxygenase-2 inhibitor to reduce inflammatory responses to surgery and to augment opioid-mediated analgesia.

Epidural and intrathecal opioid infusions delivered by internally implanted devices are generally maintained throughout the perioperative period and are used to maintain baseline pain control. The only exception to this rule applies to patients receiving intrathecal infusions of the nonopioid relaxant baclofen. It may be advisable to discontinue or reduce the intrathecal infusion rate of baclofen during the immediate perioperative period, because the central nervous system effects and peripheral skeletal muscle relaxing effects of this medication may enhance neuromuscular blockade and increase the incidence of hypotension and excessive sedation.[18]

In addition, two areas of concern in the opioid-tolerant patient that can be investigated during the preoperative interview are the risk of gastric aspiration and cardiac arrhythmias. Perioperative aspiration of gastric contents is a potentially fatal complication of anesthesia. The classic example is the patient in acute pain and with a full stomach who must have emergency surgery. Patients who are pregnant, obese, or diabetic; those with gastroesophageal reflux; or those with a hiatal hernia all may be at risk for aspiration of gastric contents and subsequent chemical pneumonitis.

Delay in gastric emptying may be caused by decreased gastric motility and gastric tone or increased pyloric tone. The tone of the pyloric sphincter regulates the outflow to the duodenum. The pylorus has a rich enkephalinergic innervation, and several studies have demonstrated that opioid administration delays gastric emptying, presumably by increasing pyloric-sphincter tone.[19] Although the exact mechanism of inhibition of gastric emptying by opioids is unclear, both central and peripheral mechanisms have been implicated.[20-22] Unfortunately, there are no studies that assess the risk of aspiration in the opioid-maintained chronic pain patient. Nevertheless, it would seem prudent to consider all chronic pain patients who have been maintained on opioids for any length of time as being at high risk for gastric aspiration, and appropriate precautions should be taken. Particular attention should be paid in those cases where the dose or formulation has recently been changed.

Recent reports have also raised concern that methadone, a commonly used medication for the treatment of chronic pain, may prolong the QT interval (QTc when corrected for heart rate). Although reviews of the literature do not provide clear evidence of the arrhythmia-inducing effects of methadone, there are a number of authors who argue that their findings suggest an effect.[14,23-28] The QT interval on electrocardiogram (EKG) has gained clinical importance, primarily because prolongation of this interval can predispose patients to potentially fatal ventricular arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Multiple factors have been implicated in QT prolongation and torsades de pointes, including older age, gender, reduced left ventricular ejection fraction, left ventricular hypertrophy, ischemia, slow heart rate, and electrolyte abnormalities including hypokalemia and hypomagnesemia.[29-34] However, the studies that have examined this risk in chronic methadone patients are limited, and major references differ on whether methadone should be considered a risk factor for torsades de pointes.[28,35,36] Reviews of the literature do not provide clear evidence of the arrhythmic effects of methadone, and certain sources argue that it is improbable that methadone is a cause of QT prolongation. In a mixed sample of 104 methadone-treated patients, 32 percent had QTc prolongation, but none had a QTc duration beyond the value considered a definite risk for torsades de pointes (500 msec).[36-38] Although a large percentage of patients presented with QTc prolongation, the lack of serious prolongation in a sample of patients taking as much as 1200 mg of methadone daily is reassuring and suggests that the general risk of seriously prolonged QTc and torsades de pointes may be low in these patients. In addition, there are data suggesting that a relationship between dose and cardiac effects may be complex and related to gender and duration of treatment. The data indicate that the risk of methadone-induced QTc prolongation may be greater for males, especially soon after treatment is initiated. The lack of dose-dependent cardiac effects for male patients on methadone for 12 months or more suggests that tolerance to any possible cardiac effects of methadone in males may develop over time.[39]

Further studies are needed to define the prevalence and severity of QTc prolongation and to identify predisposing factors, but at least two previous studies reported methadone-induced QTc prolongation. A widely cited retrospective case series by Krantz et al.[40] documented 17 cases of torsades de pointes in methadone-treated patients. In this review, the mean daily methadone dose was 397 mg/day, with a range of 65 to 1000 mg/day. Overall, 14 of 17 patients had at least one risk factor for arrhythmia in addition to methadone as a potential causative factor for ventricular arrhythmias. Seven patients had hypokalemia, and one patient had hypomagnesemia on initial presentation. Nine patients were receiving a potentially QT-prolonging drug (gabapentin), and one patient was taking a medication known to inhibit the metabolism of methadone (nelfinavir). Only three patients were found to have structural heart disease. The design of this study does not allow for determination of either the prevalence of QTc prolongation in patients taking methadone or the possible causal role of methadone. Moreover, seven of the patients in the study were hypokalemic, and this may have been the actual predisposing factor in these patients, rather than methadone.

Another study looked retrospectively at 190 patients treated with IV methadone and 301 treated with IV morphine over the course of 20 months. The risk appears

greatest in the following situations: oral administration of doses greater than 200 mg/day, IV administration of methadone, and medical conditions or medications that predispose patients to QTc-interval prolongation. In the 47 methadone patients who underwent at least one EKG while receiving methadone, mean QTc duration increased significantly (by 42 msec) when compared to EKGs done while the patients were off methadone. In contrast, the QTc duration increased by only 9 msec for the 35 patients treated with morphine who also had at least one EKG.[25] Some of the currently used medications known to cause QT prolongation, and which may interact with methadone, are listed in Table 2.

A recent paper by Cruciani et al.[39] examines the measurement of QTc in patients receiving chronic methadone therapy. In this study, the overall mean QTc increased significantly, from 418 to 428 msec, but there were no instances of torsades de pointes in patients receiving up to 150 mg/day of methadone. There were no significant gender-related differences, although males' QTc increased by 13 msec while females' increased by 6 msec. These results suggest the absence of serious QTc prolongation, as well as the possibility of a dose-dependent effect in male patients on methadone for less than one year. The question of whether QTc prolongation lasted substantially beyond the two-month follow-up of the methadone-maintenance patients remains. Given the limited and exploratory nature of this study, no conclusions can be drawn about the risk of prolongation related to other variables, such as structural heart disease or the dose or duration of use of medications known to prolong QTc duration or increase serum methadone levels. Further studies are needed to address these potential risk factors, as well as to confirm the importance of gender and treatment duration on the cardiac effects of methadone. Although absence of QTc prolongation above 500 msec is reassuring, the data suggest that methadone may prolong QTc in males within one year of the start of treatment.

INTRAOPERATIVE CONCERNS IN THE OPIOID–TOLERANT PATIENT

The management of anesthesia in the opioid-tolerant chronic pain patient is usually determined by the potential interactions between medications, the nature and severity of the patient's underlying disease process, and the planned surgical procedure itself. Although there may not be an ideal anesthetic technique, several areas of concern deserve special attention in this patient population.

Thermal regulation in patients using a fentanyl patch

In an effort to reduce the hypothermic effects associated with general anesthesia, it is common practice for anesthesiologists to apply forced-air warming blankets to patients about to undergo surgical procedures, and these blankets are known to be capable of generating skin temperatures up to 43°C. While there are no current studies of the effects that warming blankets may have on transdermal fentanyl patches, anecdotal case reports suggest that this practice may lead to potentially dangerous complications. In addition, recent reports have suggested that temperature and anesthetic agents may alter the pharmacokinetics of the transdermal fentanyl system.

Transdermal fentanyl patches are manufactured so that the amount of the drug released into systemic circulation is proportional to the surface area of the patch. The system comprises a drug reservoir and a rate-limiting membrane with an impermeable backing that is applied to the skin via an adhesive coating. Pharmacokinetic studies indicate that after the first application, a depot of fentanyl is present in the upper layers of the skin. From this depot, fentanyl is released into circulation, resulting in a delayed onset of clinical effect, the length of which is highly variable (1.2 to 40 hours).[41] The time necessary to achieve a steady-state concentration of the drug may not be reached until 48 to 72 hours post-application, but once reached the concentration can be maintained as long as the patches are replaced regularly. Fentanyl continues to be absorbed into the systemic circulation following removal of the patch, with a terminal half-life of 13 to 25 hours.[42]

Although fentanyl patches have proved relatively reliable in administering controlled amounts of the drug over long periods of time, recent case reports and small studies suggest that the amount of fentanyl delivered to the patient may be significantly altered in certain clinical situations.[43-48] Several factors that have been shown to influence serum fentanyl concentrations obtained from a transdermal delivery system in the perioperative period are body temperature,[46,48] anesthetic,[45] and direct or indirect warming of the transdermal delivery system itself.[43,47,48] Changes in body temperature alter skin perfusion and permeability, release of fentanyl from the drug reservoir, and total body clearance of fentanyl.[49] Because fentanyl is largely cleared by the liver, isoflurane and halothane, for example, may have different effects on the elimination of transdermally administered fentanyl due to their different effects upon hepatic function,[50] hepatic-artery blood flow,[51] and hepatic sinusoidal blood flow.[52] The vascular uptake of fentanyl from dermal depots may also vary with the choice of anesthetic inhalant agents because of the variable peripheral vasodilation induced by different volatile gases.[53] An experimental animal study by Pettifer and Hosgood[45] compared the effects of halothane versus isoflurane on the serum concentration of transdermally applied fentanyl in both normothermic and hypothermic (35°C) conditions. Results of that study

Table 2. Medications suspected to cause QT prolongation*		
Class	**Very probable**	**Probable**
Antiarrhythmics	Amiodarone, Disopyramide, Dofetilide, Ibutilide, Procainamide, Quinidine, Sotalol	
Antipsychotics	Thioridazine	Pimozide, Ziprasidone, Chlorpromazine, Haloperidol, Olanzapine, Risperidone
Anti-infectives	Clarithromycin, Erythromycin, Gatifloxacin, Pentamidine, Sparfloxacin	Fluconazole, Levofloxicin, Trimethoprin-sulfamethoxazole
Antidepressants		Amitriptyline, Desipramine, Imipramine, Sertraline, Venlafaxine
Others	Droperidol, grapefruit, grapefruit juice	Gabapentin

*Modified version based upon Al-Khatib SM et al.: What clinicians should know about the QT interval. *JAMA*. 2003; 289(16): 2120-2127.

indicated that significant decreases in serum fentanyl concentration occurred in the isoflurane group in both the normothermic and hypothermic conditions as compared to halothane. It was postulated that isoflurane produced a greater reduction in cutaneous blood flow, which resulted in reduced vascular uptake of the dermal fentanyl depot.

The effects of applied heat on transdermal fentanyl delivery have also been studied recently.[44-48] In an effort to speed up the transdermal absorption of fentanyl, Shomaker et al.[47] studied the effects of applying a heat pack to the transdermal fentanyl patch in six healthy, adult volunteers in an open, two-period, randomized, crossover study. In this study, a 25 µg/hr fentanyl patch was applied to each volunteer for a total of 240 minutes, both with and without the application of heat. The heat source used was a Controlled Heat Aided Drug Delivery (CHADD) patch (ZARS, Inc., Salt Lake City, UT), which was specifically designed to pass heat through the fentanyl patch, increasing skin temperature to 41°C, ± 1°C. Data analysis was conducted to examine the plasma concentration of fentanyl over a four-hour period in the heat versus no-heat groups. The results of this study showed that there was a four-fold difference in plasma concentrations of fentanyl between the heat group (0.39 ng/ml) and the no-heat group (0.11 ng/ml). They postulated that the use of heat drives the drug from the patch, through the subcutaneous skin depot known to be present in transdermal drug delivery, and into the systemic circulation.

Case reports now suggest that the accidental presence of a heat source near the application site of a fentanyl patch has led to adverse outcomes.[48] Frolich et al.[43] recently published a case report on how the effects of warming blankets on transdermal fentanyl patches can lead to dangerous complications. In this case, a 57-year-old woman with a past medical history of reflex sympathetic dystrophy was receiving multiple analgesic medications, including transdermal fentanyl 75 µg/hr, gabapentin 600 mg/day, baclofen 5 mg TID, sertraline 50 mg/day, and acetaminophen/oxycodone 325 mg/5 mg for breakthrough pain. She underwent an open reduction and internal fixation of a right tibial stress fracture. The patient had a lumbar epidural catheter placed at the L3-L4 interspace for intra- and postoperative analgesia. The catheter was tested with 3 ml of 1.5 percent lidocaine with epinephrine, but it was not used during the procedure. General anesthesia was induced and maintained with IV propofol, and a laryngeal-mask airway was inserted to facilitate spontaneous ventilation with a 50 percent air-oxygen mixture. The patient was noted to have a three-day-old transdermal fentanyl patch on the left side of her chest. The patch was left in place during the procedure, and an upper-body warming blanket was then placed over the patient, covering the site of the patch. Her respiratory rate at the beginning of the procedure was noted to be 16 breaths/min, with a tidal volume of 300 ml. No changes were made in the anesthetic, but over the next hour a steady decrease in respiratory rate was noted. The rate fell to three breaths/min, with a tidal volume of 800 ml, and her pupils were noted to be pinpoint bilaterally. Fortunately, following multiple doses of naloxone and close postoperative observation, the patient made an uneventful recovery. It was also interesting to note in this case that the patient's recorded core temperature had decreased to 34.9°C, with the associated exposed-skin temperature probably being lower. The authors speculated that following the application of the warming blanket significant increases in skin temperature and perfusion occurred, which were likely responsible for increased transdermal delivery of fentanyl into the systemic circulation.

This case illustrates a potentially serious adverse event that can occur with the transdermal fentanyl delivery system. While product labeling of the fentanyl patch includes a warning advising patients to avoid exposing the application site to direct heat sources, no specific recommendations or precautions are provided for the intraoperative use of fentanyl patches. Anesthesiologists need to be aware of the potential variations in systemic absorption that can occur when the fentanyl patch is exposed to a heat source.

Intraoperative analgesic requirements

The intraoperative and postoperative analgesic requirements of opioid-naïve patients, as well as those with a history of chronic opioid use and tolerance, may vary widely in terms of the dosage of opioid necessary to produce effective analgesia.[54-56] There are few published reports that can guide the anesthesiologist in determining the intraoperative opioid requirements in this population of patients. In a retrospective study, Weintraub et al.[57] contrasted the opioid requirements of 37 patients who underwent liver transplantation surgery and who were on chronic methadone maintenance therapy with a case-matched sample of 19 liver transplant recipients not receiving methadone maintenance therapy and not opioid tolerant. Intraoperative opioid requirements were determined from a review of operating room records and were analyzed by comparing mean doses of IV fentanyl. The authors found that the mean fentanyl dose in the opioid-tolerant group was significantly higher (3,175 μg) than in the opioid-naïve group (1,324 μg). In addition, they reviewed the postoperative analgesic requirements of these patients and found similar results. The mean daily postoperative analgesia requirements were significantly higher in the opioid-tolerant group (67.86 mg/day of morphine) when compared to the opioid-naïve group (12.17 mg/day of morphine). Unfortunately, the authors do not indicate how they made these intraoperative or postoperative determinations. While these findings are not surprising, they provide little guidance for determining the intraoperative analgesic requirements for individual opioid-tolerant patients.

Perhaps a more rational and quantifiable approach to the determination of individual opioid requirements in the chronic pain patient is one based upon existing data suggesting that the minimum effective plasma concentration of fentanyl necessary to provide adequate analgesia is approximately 25 to 30 percent of the concentration associated with significant respiratory depression.[58,59] A group from the University of Utah Medical Center has recently published a case report on the use of a novel technique to determine individual opioid requirements in the opioid-tolerant patient.[60] In this report, a 47-year-old female presented to the operating room for a repeat tricuspid valve replacement. The patient had a history of chronic pain and was receiving multiple analgesic medications, including sustained-release morphine 400 mg/day, two 100 μg/h transdermal fentanyl patches, and oxycodone 120 mg every eight hours. To assess the patient's response to opioids, the authors used a large-dose fentanyl infusion immediately before anesthetic induction. The goal was to determine the amount of fentanyl required to achieve clinically relevant endpoints, including apnea and/or unresponsiveness. In the operating room, standard monitors were applied and a radial artery catheter was inserted. An IV infusion of fentanyl was started at a rate of 2 μg/kg/min, based upon an ideal body weight of 69 kg. No other adjunctive anesthetics were administered during the fentanyl infusion. The infusion rate was increased incrementally until a final rate of 40 μg/kg/min had been reached and the patient was noted to be unresponsive. The total dose of fentanyl administered at the time of unresponsiveness was 24 mg (340 μg/kg). The patient was then induced with etomidate and rocuronium to facilitate endotracheal intubation. A continuous infusion of fentanyl was then started at a rate of 2 μg/kg/h and maintained throughout the surgical procedure.

The same authors then attempted to determine the opioid requirement necessary to provide subsequent analgesia. Using pharmacokinetic simulation software, the authors determined the effect-site concentration of fentanyl achieved at the time of unresponsiveness was 293 ng/ml, and to maintain a plasma level of fentanyl corresponding to 25 percent of that value an infusion rate of 33 μg/kg/min would be required. A PCA pump was programmed to allow a total hourly dose of 33 μg/kg/h by delivering fentanyl at a basal rate of 16.5 μg/kg/h with a lockout interval of 15 min and a demand dose of 250 μg. One hour after arrival in the ICU, the patient was easily awakened and able to follow commands. The patient, according to the authors, reported being satisfied with her quality of analgesia and denied any recall or pain associated with the operative procedure. She specifically commented that her experience during this perioperative course was markedly improved compared with prior surgeries. Four days after the surgery, the transition to oral and transdermal opioids was begun. By the fifth postoperative day, the patient's pain was successfully managed without IV medications, and the remainder of her postoperative course was noted to be uneventful.

Clearly, opioid-tolerant patients have analgesic requirements that are significantly higher than those of opioid-naïve patients. While the large-dose fentanyl infusion technique is a useful tool that makes it possible to accurately define the limits of a patient's opioid tolerance, it is not practical for the majority of patients encountered by anesthesiologists. Because there may be significant interpatient

variability in opioid-dose requirements, intraoperative vital signs, including heart rate, respiratory rate, and degree of pupil dilation, should be closely monitored. The amount of opioids necessary to ensure adequate analgesia in any given patient can generally be assumed to be 50 to 300 percent in excess of the opioid dose given to the naïve patient.[61] One technique that may help to gauge the adequacy of intraoperative opioid dosing is to reverse neuromuscular blockade and allow patients to breathe spontaneously at the later stages of general anesthesia. Patients with respiratory rates greater than 20 breaths/min and exhibiting slight to markedly dilated pupils generally require additional opioid dosing. IV boluses of morphine, fentanyl, or hydromorphone are titrated as needed to achieve a rate of 12-14 breaths/min and a slightly miotic pupil. The optimal intraoperative dose avoids undermedication and overmedication, both associated with adverse perioperative outcomes.[62,63]

POSTOPERATIVE CONCERNS IN THE OPIOID–TOLERANT PATIENT

Expert opinion suggests that, whenever possible, opioid-tolerant patients should be offered regional anesthesia or analgesia, particularly for surgical procedures performed on the extremities.[64,65] Techniques that may be considered include tissue infiltration and nerve and plexus blockade. Patients may be discharged with indwelling brachial plexus catheters, and local anesthetic can be infused for up to 48 hours via disposable pumps. Other interventions may include injection of local anesthetics and opioids into disc spaces or the iliac crest for spinal surgery. The goal is to minimize pain perception and reduce, but not completely eliminate, the use of oral or parenteral opioids for baseline requirements in opioid-tolerant patients.

In patients who have undergone general anesthesia with surgical procedures not amenable to regional anesthesia or analgesia, a continuous parenteral opioid infusion or IV PCA provides useful options for effective postsurgical analgesia. Initiation of IV PCA in the recovery room minimizes the risk of undermedication and breakthrough pain that may occur during patient transport to the surgical care unit. A basal infusion equivalent either to the patient's hourly oral dose requirement or one to two PCA boluses/h may be added to maintain baseline opioid requirements. Basal infusions may not be necessary in patients receiving baseline analgesia via transdermal fentanyl patches or by implanted epidural or intrathecal devices.

The importance of providing adequate analgesics in the postoperative period and understanding the physiologic adaptation that can occur with opioid administration has been underscored by a recent case report by Higa et al.[66] at the Bariatric Surgery Center in Fresno, California. They describe the case of a 27-year-old woman with a medical history significant for mild depression, for which she was treated with sertraline, who underwent uncomplicated laparoscopic Roux-en-Y gastric bypass surgery. The patient subsequently developed a chronic and unremitting course of nausea, vomiting, abdominal distention, and pain that resulted in seven readmissions to the hospital, numerous and extensive diagnostic evaluations, and five surgical procedures, all of which failed to relieve her symptoms. It was only in retrospect that the physicians involved in this case realized that the patient had become opioid tolerant during her multiple hospitalizations and that her symptoms were the result of opioid withdrawal. Following a trial of methadone 20 mg/day, her symptoms completely resolved. After that the patient did not require any hospital readmissions and her symptoms of depression were alleviated, and she has continued to do well. The physicians in this case underestimated the patient's physiological response to perioperative opioid analgesia and the level of dependence that developed during the course of her hospitalization.

DISCUSSION

Safe and effective care of the opioid-tolerant patient requires that the anesthesiologist correctly assess the patient's degree of tolerance and modify perioperative procedure accordingly. Unfortunately, scientifically rigorous studies in this important area are lacking, and most information must be derived from anecdotal reports and the personal experience of anesthesiologists. Furthermore, chronically administered opioids are often mismanaged in the perioperative setting because of unrecognized patient usage, fear of overdose, or temporary unavailability of the oral route of administration. Significant reductions in opioid dosage from preprocedural levels may lead to hyperalgesia in the perioperative period. Potentially adding to this problem is the presence of pain caused by the surgical procedure itself.

The studies and case reports described above were designed to explore the influence of chronic opioid administration on perioperative anesthetic management. Awareness of the special concerns of this patient population and administration of appropriate doses of analgesics, as well as continuous clinical monitoring, remain the keys to successful perioperative anesthetic management. The anesthesiologist plays the key role in developing and implementing a safe and effective perioperative management strategy for the opioid-tolerant patient. We have included some basic guidelines in Table 3 to aid in the formulation of an effective management plan.

Table 3. Perioperative anesthetic management guidelines for opioid-tolerant patients
Preoperative
1. Preoperative evaluation should include early recognition of possible opioid tolerance. Determine that patient received usual baseline opioid medications. Determine total opioid-dose requirement.
2. Review baseline EKG for signs of possible QT prolongation; generally 440 msec is considered the upper limit of normal. Dangerous arrhythmias have been shown to occur if the heart rate is slow (< 60) and the QT is > 600 msec. Obtain cardiology consultation if QT is prolonged.
3. Reassure the patient regarding possible fears of pain control, intraoperative awareness, etc.
4. If the patient has an implanted infusion device, continue usual dosage of opioid, but consider reducing intrathecal dose of baclofen.
5. Consider all opioid-tolerant patients as possibly having full stomachs and take usual precautions.
Intraoperative
1. Maintain all baseline opioids, including transdermal, IV, and intrathecal forms (except baclofen).
2. Avoid placing warming blankets or other warming devices over or near transdermal fentanyl patches.
3. Avoid administering any medication known or suspected to interact with patient's current analgesic and adjuvant regimen.
4. Anticipate that intraoperative analgesic requirements may be 50 to 300 percent greater than in the opioid-naïve patient. Closely monitor vital signs for indication of under- or overmedication.
5. Consider early reversal of the patient to allow for spontaneous breathing, and titrate opioid dose to achieve a respiratory rate of 12 to 14 breaths/min and a slightly miotic pupil.
Postoperative
1. Plan preoperatively for postoperative analgesia; formulate primary strategy as well as suitable alternatives.
2. Maintain baseline opioids, unless the surgical procedure is reasonably expected to reduce the patient's preoperative pain level, in which case opioid administration should be reduced by 25 to 50 percent.
3. PCA: Use as primary therapy or as supplementation for epidural or regional techniques.
4. If surgery provides complete pain relief, consult with pain service to slowly begin opioid taper; do not abruptly discontinue medications.
5. Arrange for a timely outpatient pain clinic follow-up visit.

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CASE STUDY

Safety and tolerability of high doses of intrathecal fentanyl for the treatment of chronic pain

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ABSTRACT

Fentanyl is commonly used systemically or neuraxially for the management of chronic pain. It can be administered intrathecally via implanted pump, but it is generally considered only after trials of intrathecal (IT) morphine and hydromorphone have proven ineffective. Published experience with IT fentanyl is limited, and long-term therapy at relatively high doses has not been described previously. We describe four patients who were treated with IT fentanyl after other analgesic approaches had failed and who gradually underwent dose escalation to levels as high as 20 times those previously reported. Safety and tolerability were maintained during dose titration. Our experience highlights an expanding scope of practice in the use of IT opioids in general and fentanyl specifically and suggests that high-dose fentanyl can be used safely in highly selected patients.

Key words: fentanyl, intrathecal, dose escalation, chronic pain

INTRODUCTION

Fentanyl is a potent μ agonist opioid widely used in anesthesia and pain management. It is commercially available for systemic administration as a solution and in formulations that deliver the drug transdermally or transmucosally. Neuraxial administration may be accomplished via epidural or intrathecal (IT) delivery systems. Although supporting data are limited, long-term IT infusion through an implanted pump is an accepted approach for carefully selected patients with chronic pain, typically those who have not responded satisfactorily to IT morphine and/or hydromorphone.[1-3]

The literature describing the long-term use of fentanyl delivered by IT infusion is limited to case series. IT doses up to 300 μg/d have been reported.[3] Although higher doses are used clinically and the potential outcomes associated with this approach are assumed to be comparable to those observed during neuraxial infusion with other opioids, there are no published observations. We describe four patients with chronic pain whose doses of IT fentanyl were gradually titrated to levels as high as 20 times those previously reported. These cases are relevant to an understanding of both safety and tolerability of IT fentanyl during long-term therapy.

CASE REPORTS

Case 1

A 58-year-old diabetic man was experiencing severe chronic pain from multiple sources. He reported persistent lower back pain and L4-5 radicular pain which began after laminectomy to correct L4-5 stenosis in 1989. Years later, he required a below-the-knee amputation for complications of diabetes and subsequently developed phantom limb pain. He reported constant moderate pain which became severe with activity. There were no other medical or psychiatric comorbidities, and his functioning was markedly impaired by the pain. Examination was consistent with lumbar spinal stenosis.

During this patient's years of pain he underwent multiple trials of opioid and adjuvant analgesics. Trials of oral methadone and hydromorphone, transdermal fentanyl, and injectable meperidine had all yielded opioid-related side effects and minimal pain relief. A trial of IT therapy was recommended, and the patient initially responded well to IT morphine. Gradual dose escalation was needed to maintain adequate pain control, however, and as the dose of IT morphine was increased, he developed multiple medical problems, which were interpreted as

the results of a combination of opioid-related toxicity and his baseline diabetes. These included severe constipation complicated by impaction (and an episode of bowel perforation), mental clouding, somnolence, weight gain, and decreased libido.

Approximately three years ago, the patient was admitted to the hospital to facilitate a switch to an alternative IT infusion. The IT morphine was discontinued and the patient was started on intravenous (IV) fentanyl at a dose of 200 μg/hr, plus 50 μg every 10 minutes as needed. The IV infusion was adjusted to optimize benefit, at which point the infusion was stopped and IT fentanyl was administered using an IV:IT ratio of 1:1. During the next week, the IT fentanyl was rapidly increased to 14,000 μg/d and bupivacaine was added at a dose of 3.52 mg/d. The patient was discharged with good pain control and tolerable side effects.

Over the next three years, the IT fentanyl dose was slowly titrated at an average increment of 20 percent every two months. The patient is currently treated with IT fentanyl at a dose of 24,000 μg/d and bupivacaine at a dose of 7.69 mg/d. Various systemic drug trials have been undertaken in the interim, and, over time, the most helpful supplemental therapy has been a combination of diazepam 20 mg every four hours as needed and meperidine injection 200 mg every four hours as needed. On this regimen of two IT drugs and two supplemental drugs as needed, the patient reports satisfactory pain relief and no side effects, and his ability to function has not declined over the years.

Case 2

A 56-year-old woman reported intense pain and disability related to a 30-year history of low back pain and a nine-year history of pudendal neuralgia. She experienced moderate, constant, burning pain in the lumbar region and buttocks that flared with any activity and prolonged sitting. She could walk 15 feet without stopping and usually used a wheelchair. The examination revealed allodynia in the painful region.

She had received multiple trials of opioids and adjuvant analgesics over the years. Opioid trials included oral methadone and hydromorphone and transdermal fentanyl, all of which provided little benefit. She underwent coccygectomy in 2000 but showed no improvement, and during the succeeding years she had S5 dorsal root ganglion block followed by bilateral S5 dorsal root ganglionectomy, epidural injections, and a trial of spinal cord stimulation. None of these interventions was helpful.

A trial of IT morphine and bupivacaine yielded moderate pain control, and a pump was implanted. Escalation of the morphine dose to 34 mg/d yielded worsening side effects, and in 2004 the IT infusion was switched to fentanyl and bupivacaine, initially at doses of 750 μg/d and 9 mg/d, respectively. There was initial improvement, but this was transitory, and the patient was referred to us for further intervention.

The IT fentanyl was gradually titrated to 4,000 μg/d, at which point the patient reported benefit. This improvement lasted two months, after which the pain again worsened. The IT fentanyl dose was slowly titrated to 7,000 μg/d, and pain control improved. When pain again increased, oral methadone was added, with good effect. For the past year, the patient has been receiving IT fentanyl and bupivacaine, methadone 10 mg five times a day, and gabapentin 300 mg three times daily, a dose that could not be increased due to side effects. Pain control is adequate, she reports no significant side effects, and function has improved—she no longer uses a wheelchair.

Case 3

A 55-year-old woman had an episode of viral (Epstein-Barr) transverse myelitis at C5 in 1981. She recovered to a level of mild quadriparesis, atrophy of the distal muscles of the left upper extremity, and persistent incontinence. Slowly progressive pain became the major problem and was severe below the knees and in her left arm and left abdomen. The pain awakened her from sleep and was exacerbated by standing, walking, and prolonged sitting. Intermittent severe flares of pain occurred spontaneously and resulted in frequent hospitalizations.

Prior therapeutic trials had included opioids and adjuvant analgesic drugs, physical therapy, and acupuncture. None of these therapies yielded substantial pain relief. In 1999, she underwent a successful IT morphine/clonidine trial and a pump was implanted. For five years, she reported acceptable pain control and tolerable side effects while receiving this IT infusion combined with oral methadone at a dose of 20 mg three times daily, nortriptyline 50 mg three times daily, tizanidine 4 mg three times daily, and access to supplemental oral transmucosal fentanyl citrate 1,200 μg as needed up to three times daily. In 2004, pain flared and she required hospitalization. The IT morphine was switched to IT fentanyl; an infusion was initiated at 40 μg/d, and the patient reported that this dose provided good pain control without side effects. Several months later, pain again flared. Bupivacaine and clonidine were added to the IT infusion and the oral medications were adjusted. Pain control remained inadequate and she was referred to us for further interventions.

Given the lack of side effects from the IT infusion, the IT fentanyl was initially titrated. Pain control improved at a dose of 2,000 μg/d. There were still no significant side effects. Several months later pain worsened, and the dose of IT fentanyl was slowly titrated to 5,967 μg/d. Pain control was satisfactory for about one year. Recently, the patient experienced a severe pain flare, and the IT fentanyl was replaced by an IT trial of ziconotide (5,400

μg/d) combined with transdermal fentanyl patches (300 μg/hr patches changed every three days), oral transmucosal fentanyl citrate (1,600 μg, usually once daily), and duloxetine (40 mg daily). The pain improved, but due to changes in mental status the dose was reduced to 4,800 μg/d.

Case 4

A 58-year-old man had been experiencing slowly progressive pain since becoming paraplegic after traumatic spinal cord injury at the T7 level almost 30 years ago. At the time of his first visit, he was wheelchair bound and reported excruciating back pain radiating to the abdomen and pelvis. The pain awakened him from sleep and interfered with all activities. There were no significant medical or psychiatric comorbidities. Physical examination was significant for muscle atrophy and spastic paralysis of the lower extremities.

Prior treatments for the pain had included systemic opioid analgesics, including morphine, oxycodone, methadone, and transmucosal fentanyl, and trials of adjuvant analgesics. The patient reported inadequate analgesia and intolerable side effects from many medications. Prior trials of spinal injections and physical therapy had also yielded no benefit. In 1999, a trial with IT baclofen was effective for spasticity, and a pump was implanted. The pain continued to worsen, and approximately one year later morphine was added to the pump. Over the subsequent year, the dose of IT morphine was gradually increased to 10 mg/d. The patient developed drowsiness and progressive constipation, and the morphine was switched to fentanyl.

The IT fentanyl was initiated at a dose of 600 μg/d. The IT morphine was stopped and oral morphine was given to supplement the IT fentanyl. The fentanyl dose was increased gradually, and as pain control improved the oral morphine dose was reduced. After approximately one month, the dose of IT fentanyl had reached 6,000 μg/d and the patient reported good pain control. Although he denied typical opioid side effects, spasticity increased substantially, and he requested a switch back to IT morphine. This was accomplished, and efforts at pain control via combined IT infusion and systemic analgesics continued. Currently, the patient is reporting incomplete pain control while receiving IT morphine at a dose of 7 mg/d and oral transmucosal fentanyl citrate at a dose of 1,600 μg six times daily.

DISCUSSION

These cases exemplify a small subset of patients with severe and intractable chronic pain. Numerous analgesic interventions had been tried over a period of years in each case before the decision was made to implement neuraxial infusion. IT morphine or morphine combined with other drugs was ineffective, and the conventional practice of opioid rotation was undertaken in the hope of identifying a drug with a more favorable balance between analgesia and side effects.[1,2] Fentanyl is often empirically selected for a trial in such circumstances, despite limited published data documenting outcomes during long-term IT fentanyl infusion.

Published descriptions of IT fentanyl have included patients receiving a maximum dose of approximately 300 μg/d.[3] The present cases substantially expand on published experience, demonstrating the potential for safe and effective therapy at doses up to 20 times higher. Neither early side effects due to the presumed systemic redistribution of the IT drug nor any evidence of fentanyl-induced chest wall rigidity were observed in any of these cases. With the exception of one patient with spinal cord injury, whose baseline spasticity worsened with high-dose IT fentanyl, side effects were those anticipated for opioids.

After IT administration, fentanyl rapidly equilibrates in the general circulation, resulting in significant plasma levels. Indeed, one study demonstrated that plasma fentanyl concentrations were similar two hours after equal doses of IV and IT fentanyl.[4] Hence, rapid clearance into the systemic circulation may result in lower-than-expected concentrations at the level of the posterior spinal horn when single doses of fentanyl are administered. Nonetheless, the analgesia produced by fentanyl can be more efficacious with the IT route than the IV, even with equal doses.[5] The reasons for this are not entirely clear, but it could potentially be related to differences in drug concentrations reaching active sites in the spinal cord and brain.[6] Studies that measure pain while concurrently assessing fentanyl concentrations systemically and at several neuraxial sites during steady-state infusion would be needed to better understand these differences.

Patients who undergo pump trials have to be evaluated for psychiatric disorders, including depression and drug abuse. Patients with depression, a common comorbidity in patients with chronic pain, may develop psychotic features or anxiety and may not tolerate the pump.[7] A recommended practice is to order an evaluation by an experienced pain psychologist to address these specific issues before the trial is started. In the four cases that we are presenting, there was no history of significant depression or drug abuse in any patient. Patients were monitored for the possibility of misuse and diversion of medications at every visit. There was no evidence of multiple prescriptions, early calls for refills of medications, or any other abuse-related issues in any of the four patients.

Although this case series illustrates that high doses of IT fentanyl can be used safely for the treatment of chronic pain in patients who have not responded satisfactorily to conventional treatment, a survey shows that it is the

drug of preference of only 1 percent of the physicians who responded.[2] Larger studies are needed to confirm our observations.

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