Journal of Opioid Management™

A medical journal for proper and adequate use

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Editorial Policy

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

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The Legal Perspective Series
Taking back your turf: Understanding the role of law in medical decision making in opioid management
by Jennifer Bolen, JD
Will return in the next issue of *Journal of Opioid Management.*

EUROPEAN AUTHORITIES RECOMMEND APPROVAL FOR IONSYS

IONSYS, a transdermal fentanyl delivery system produced by the ALZA Corporation (Mountain View, CA), has been recommended for approval in Europe. The system is approximately the size of a credit card, and can be attached to a patient's upper arm or chest. Patients can push a button to receive a small dose of fentanyl, a short-acting prescription opioid analgesic.

The manufacturer of IONSYS claims that through the use of the E-TRANS drug delivery system (also found in ALZA's Duragesic transdermal fentanyl patches), the drug is transported through intact skin via low-level electrical energy, providing a rapid onset of action and sustained effect comparable to that seen with intravenous dosing. In addition, IONSYS dosing can be easily adjusted incrementally to suit patient-specific needs.

Once formal approval has been received, Janssen-Cilag will market the system throughout Europe. In the United States, IONSYS is currently under review by the Food and Drug Administration. Ortho-McNeil will market the product if approval is received. (Source: Drug Policy Central Web site, October 17, 2005.)

OPIOID USE AND NSAIDS IN MIGRAINES

A recent study headed by Dr. Rami Burstein, an Associate Professor at Harvard Medical School and Vice Chairman of Research of the Department of Anesthesia and Critical Care at Beth Israel Deaconess Medical Center, found that patients with a history of opioid use received no benefit from intravenous nonsteroidal anti-inflammatory drugs (NSAIDs) during treatment for migraine headaches. The study consisted of 32 participants with advanced migraines whom had developed allodynia (skin hypersensitivity).

One-half of the study participants received the NSAID ketorolac (Toradol, Roche Laboratories, Inc., Nutley, NJ) delivered intravenously beginning four hours after the start of a migraine. The other participants received an injection of one of the triptans (sumatriptan) four hours after the migraine began, followed by ketorolac two hours later, if the pain had not subsided. With the ketorolac infusion, 64 percent of the patients were pain-free one hour after, with skin sensitivity returning to normal. However, 32 percent received no benefit at all, and it was noted that these individuals all had a previous history of using opioids.

According to Dr. Burstein, NSAIDs were chosen for this study because previous research had shown that inflammatory molecules play a role in chronic pain, including frequent migraines. These inflammatory molecules are found in the periphery of the body and also the central nervous system. Whereas NSAIDs in pill form block inflammation only in the periphery, they can reach high enough concentrations to block inflammatory production in the central nervous system in intravenous form.

Previous research has indicated that once allodynia occurs, triptans—drugs commonly used to treat migraines—no longer work. Once this occurs, migraine patients visiting the emergency room often are given an infusion of opioids (51 percent, according to one 1998 survey). With the results of this new study, Dr. Burstein recommends that physicians revisit the prescription of opioids for migraine patients and consider intravenous NSAIDs as a viable, nonhabit-forming alternative. (Source: *Times Herald-Record* Web site, October 19, 2005.)

PHASE II TRIAL FOR ABUSE-RESISTANT EXTENDED-RELEASE OPIOID

Alpharma, Inc. has received clearance from the US Food and Drug Administration to begin a Phase II trial of an abuse-resistant extended-release opioid. Target audiences for the product include individuals with chronic moderate to severe cancer- and noncancer-related pain. Alpharma also currently produces Kadian, a sustained-release morphine product.

The new product features a combination of an extended-release opioid with an antagonist in a single tablet. Tampering with the dose (e.g., crushing, chewing, or dissolving the tablet) will cause the antagonist to be released, thereby suppressing the opioid's effects. Alpharma hopes that this product will help improve the treatment of patients with chronic pain and also reduce the potential for abuse of opioid medications by eliminating the ability of patients to use the medication in any way other than that intended by the prescribing physician. (Source: Alpharma, Inc. press release, October 10, 2005.)

μ-OPIOID THERAPY AND CHRONIC ARTHRITIS PAIN

Led by Dr. Jason McDougall, researchers at the University of Calgary recently conducted an experiment on the effectiveness of endomorphin 1, a natural morphinelike

compound, in lieu of morphine in knee joint pain. Male rats with induced acute and chronic arthritis were used in the study, in which endomorphin 1 was injected into affected knee joints. The effectiveness was measured by joint edema formation and sensory nerve activity associated with pain.

The rats with acute arthritis showed a reduction in joint nerve hypersensitivity of up to 75 percent. However, the rats with chronic arthritis showed no observable effect on the telltale triggers of pain. From these results, Dr. McDougall and colleagues concluded that chronic inflammation negates the pain-relieving benefits of the body's μ-opioid receptors, and that the endogenous opioid system may be inadequate in alleviating chronic arthritis pain.

Details of the study appear in the October 2005 issue of *Arthritis & Rheumatism*, which is available online at *http://interscience.wiley.com/journal/arthritis*. (Source: Medical News Today, October 1, 2005.)

REDUCED OPIOID AVAILABILITY IN MINORITY AREAS

Pharmacies in minority neighborhoods are much less likely to carry sufficient supplies of frequently prescribed opioid medications than those in white neighborhoods, as reported in a study led by Dr. Carmen R. Green of the University of Michigan Medical School. In this study, it was found that pharmacies in wealthy black neighborhoods were no more likely to carry opioids than those in poorer black neighborhoods; however, pharmacies in wealthy white neighborhoods were far more likely to carry opioids than those in poorer white neighborhoods. In addition, 91 percent of independent pharmacists were found to have adequate stock, whereas only 59 percent of chain stores met the criteria.

The study surveyed 188 Michigan pharmacies. Of those pharmacies, 87 percent within predominantly white Zip codes were found to have sufficient supplies of opioids, compared to only 54 percent in predominantly minority Zip codes. Dr. Green and other researchers noted that their study is consistent with earlier ones that showed doctor reluctance in prescribing opioids to minority patients.

One possible nonclinical explanation for lower availability offered by the authors is concern over potential illicit use and ensuing consequences for the dispenser. Several of the surveyed pharmacists echoed that concern, as did Susan Winkler, the Vice President for Policy of the American Pharmaceutical Association. Winkler also noted that pharmacists carry the burden of determining whether prescriptions are actually valid and/or clinically appropriate, with heavy fines as a consequence and limiting factor in the decision to stock medications with high potential for abuse.

In response to the study results concerning chain stores, Valerie Stork, spokeswoman for the National Association of Chain Drug Stores, stated that although the Drug Enforcement Administration tracks and monitors the sale of controlled drugs, there is no direct mandate on how much of a medication each pharmacy must carry.

The study appears in the October 2005 issue of the *Journal of Pain*. (Source: *The Washington Post* Web site, October 15, 2005.)

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GUEST EDITORIAL

What can we learn from baseball's steroid scandal?

Gary M. Reisfield, MD
George R. Wilson, MD

Pain journals and professional organizations have devoted much attention recently to the increasing intrusion of the Drug Enforcement Administration (DEA) into the practice of pain medicine.[1] Little attention, however, has been given to the role of clinicians—as the sole licit source of opioid analgesics—in inviting this intrusion. As we watched Major League Baseball (MLB) come under intense congressional and media scrutiny this year for its handling of the steroid abuse problem, it prompted us to look at medicine's issues with chronic opioid therapy in a somewhat different light. This editorial contains a few of our observations.

Self-reports of drug use, no matter how convincing and who they're from, are of limited value. Baltimore Orioles superstar Rafael Palmeiro testified this past spring before the US House Committee on Government Reform, convened to investigate steroid misuse in baseball. Under oath, Palmeiro jabbed his finger at the panel, swearing, "Let me start by telling you this: I have never used steroids. Period. I don't know how to say it any more clearly than that. Never." So convinced was the committee of Palmeiro's verity that they appointed him to spearhead Zero Tolerance, an outreach program designed to keep our nation's children off steroids. The children would have been especially receptive to this squeaky clean superstar, because over the summer, Palmeiro became only the fourth player in baseball history to collect 3,000 hits and 500 home runs. The plan was quickly scuttled, however, when Palmeiro was suspended and fined for a random drug screen that demonstrated the presence of an anabolic steroid, stanozolol, in his urine. Despite incontrovertible evidence to the contrary, Palmeiro, like virtually all players who fail drug tests, maintained his innocence.

Similarly, self-reports of opioid and other drug abuse are unreliable in our patient population.[2] Yet, in managing patients on chronic opioid therapy, physicians depend almost entirely on patient self-reports. Patients who display aberrant behaviors are easy to identify, but many patients who abuse or divert their opioids—the "professionals"—are able to get their act together for the 10 minutes every month (or every few months) that they spend in our offices, and are adept at being seen as "model" patients.

There is indeed a problem, the magnitude of which remains to be determined, but is probably bigger than previously thought. Until recently, and despite occasional player reports to the contrary, MLB maintained that it had no drug problem, merely a few bad apples. In 2003, after congressional threats, MLB and the Players Association amended their collective bargaining agreement to include anonymous survey testing. Knowing that testing would be conducted, and with methods unable to detect the new designer steroids and other performance-enhancing substances, 5 to 7 percent of players tested positive for steroids, automatically triggering a new disciplinary testing policy for the 2004 season.

The lifetime prevalence of substance use disorders in this country is estimated to be 15 percent.[3] A reasonable inference would be that the prevalence of substance use disorders in the population of patients on chronic opioid therapy is at least as high, and the available literature indicates that this might be the case.[4,5] A related issue is that for each of several popular prescription opioids—morphine, oxycodone, fentanyl, hydrocodone, and hydromorphone—the number of prescriptions written increased every year from 1994 to 2001, and in most cases, so did the ratio of illicit to licit use.[6] While there are many sources for illicitly obtained prescription opioids, we must consider the likelihood that a significant, although indeterminate, percentage originates from our prescription pads.

There is no profile for drug abusers. Drug testing in baseball has revealed some unexpected findings. Long thought to be manna only for the gargantuan home-run hitters like Mark McGwire and Barry Bonds, we now know that steroid abusers fit no profile. This season has seen steroid-related suspensions of pitchers, base-stealers, superstars, and even benchwarmers—all looking to get an edge.

Likewise, opioid and other drug abuse in society and in our practices is nondiscriminatory, blind to social, racial, educational, economic, and gender lines. Physicians cannot make assumptions about substance abuse based on demographic factors.

Testing is essential. It is inconceivable that the drug problem in MLB could have been fully understood or seriously addressed without drug testing. A few vocal players have been complaining for years about the prevalence of steroid abuse in the locker room, to no avail. This year, Jose Canseco's book, *Juiced: Wild Times, Rampant 'Roids, Smash Hits, and How Baseball Got Big* (which, incidentally, identified Palmeiro as a steroid abuser), was dismissed as the ranting of a publicity hound. Only with the establishment of drug testing has the problem begun to be seen as credible. Clearly, the proof is in the urine—yet, physicians do not test. Recent data indicate that less than 10 percent of primary care physicians who prescribe chronic opioid therapy for their pain patients use urine-based drug testing (UDT).[7]

Failure to address drug abuse results in government involvement. MLB, unlike most other sports, has long been viewed as not taking its drug problem seriously. Their testing program has been seen as weak, and their penalties even weaker. Unlike track and field, for example, in which a positive UDT results in a two-year ban from international competition, MLB's "five strikes and maybe you're out"-type policy has been seen as a wink and a nod to the players who fill the stands (and the owners' pockets), resulting in congressional scrutiny and threats of legislative action.

Likewise, physicians have not faced up to the breadth of drug abuse in our chronic opioid population. Drug testing, when done at all, is generally used in the face of aberrant behavior to weed out and banish problem patients from our practices. With our busy schedules and our sensitivity about giving offense, patients who cause no problems tend to be the beneficiaries of a laissez-faire policy (i.e., absence of aberrant behaviors means absence of testing). Yet, there is evidence that the absence of aberrant behaviors is not a reliable indicator of absence of substance abuse.[8] And, like that of the MLB, our problem has piqued the interest of government agencies. Unfortunately, however, the attention has not come from Congress, but rather from law enforcement. The attention is also directed at physicians, not just the patients, or "players." It is more than just a threat—the DEA is bypassing medical societies and bringing physicians directly into the criminal justice system.

There is a growing list of what we need to do. MLB now mandates one unannounced UDT of each player during the baseball season, with further testing of select players. Physicians managing patients with chronic opioid therapy should do the same. This and other monitoring should be part of our own collective bargaining agreement and promulgated in our individual physician-patient opioid agreements. This will enable us to test all of our patients on chronic opioid therapy without feeling uneasy and without making them feel stigmatized—it will be just another part of the deal. Of course, UDT is not a panacea and lacks perfect sensitivity and specificity. It is imperative that we understand their capabilities and their limitations. We suggest that all physicians prescribing chronic opioid therapy should have a working knowledge of UDT, particularly the specific tests used by their labs.

An important caveat is that neither screening tests (usually immunoassays) nor confirmatory tests (e.g., gas chromatography-mass spectrometry) are immune to false positives or false negatives, both of which could result in patients being (wrongly) labeled as drug abusers or diverters and deprived of appropriate therapies. In addition to demonstrating the presence (or absence) of prescribed opioids, UDT is also valuable for what else it can detect in urine—illicit drugs and nonprescribed or unauthorized licit drugs that raise red flags for substance use disorders. The importance of this sensitivity lies in the improbability of successfully treating pain while concurrent substance use disorders remain unaddressed.

We are not suggesting that UDT be the only monitoring tool used. There is no substitute for spending time with patients, regularly reassessing their pain and the effects of pain—and its treatment—on their lives. We also need to use other tools in conjunction with UDT, such as the following:

- Intervisit pill counts. Having patients come to the office (on, for example, 24 hours notice) with their opioid medication can be helpful in detecting abuse and diversion and can help make sense of (false) negative drug screens.

- Selective witnessed administration of opioids, with continual observation through the period of peak opioid effect (and with naloxone on hand!), particularly for those on higher-dose opioid therapy, may result in somnolence or respiratory depression in those who are diverting their opioids.

- Interviews with significant others (with patient permission).

Some might object that this is an unfair burden on our already time-strapped schedules, or that we are physicians, not police officers (and are treating patients, not criminals). We would counter by suggesting that the responsible management of pain with chronic opioid therapy is not as simple as writing a prescription and hoping for the best. Indeed, writing the prescription is merely the simplest part of a process that begins with meticulous assessment, and continues with ongoing reassessment for level of pain relief, functional level, adverse drug effects, and aberrant behaviors, and may occasionally progress to referral to specialists in addiction medicine/psychiatry. We also cannot ignore the fact that

opioids are the prescription drugs with the greatest potential for abuse and diversion,[6] and that we sometimes play an unwitting role in enabling these behaviors. This places us at risk for censure (or worse), and places our present and future patients at risk for being deprived of appropriate treatment for legitimate pain issues. UDT, as one component of a comprehensive treatment and monitoring program, is a reliable and time- and cost-effective method for detecting drug abuse. If it is deemed essential for the integrity of professional sports, we believe it should likewise be viewed as essential to the integrity and continued viability of our endeavor.

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CASE REPORT

Dextropropoxyphene and the cardiovascular system: About two cases of acute poisoning with cardiac conduction abnormalities

Frédérik Staikowsky, MD, PhD
Sébastien Candella, MD
Maurice Raphael, MD

INTRODUCTION

Dextropropoxyphene (DP) is a mildly analgesic synthetic opiate structurally related to methadone. Peak plasma concentrations are reached 2.0 to 2.5 hours after oral administration. N-demethylation is the major biotransformation pathway of DP to norpropoxyphene (NP). The manifestations of acute overdose with DP are similar to those of narcotic overdose. DP poisoning may also result in cardiac failure and arrhythmias. These cardiac side effects are the result of a local anesthetic effect.

The effectiveness of naloxone to reverse all opiate features in DP poisoning is well established. However, data from animal and human reports suggest that naloxone fails to reverse DP cardiotoxicity. Positive inotropic drugs are usually used to treat cardiac failure. In uncommon cases, lidocaine and sodium bicarbonate have been successfully used in the management of cardiac conduction abnormalities.

Acute intoxication by ingestion of DP is considered to be easily treatable with low mortality rate at hospital. However, legal medicine institutes in the United States, the United Kingdom, and the Nordic countries have reported a pronounced proportion of prehospital deaths.[1-3] The majority of these deaths are attributed to cardiovascular complications and opioid effects.[3] Restriction of availability and even total withdrawal of DP from the market are currently being debated in some countries. Observation of the following two cases has led to discussion of the links between the cardiovascular system and DP.

CASE REPORTS

Case 1

A 29-year-old man was admitted for acute self-ingestion of flunitrazepam, bromazepam, paracetamol, and DP (1.3 g); the patient was a former heroin addict who took benzodiazepine and DP (650 to 1,300 mg per day) as a substitute. On admission, he was conscious but restless. He suddenly presented a generalized convulsive crisis and, after resolution, the neurological examination was normal apart from altered consciousness and constricted pupils. Seizures were recurrent. The blood pressure was low (70/40 mmHg) and the heart rate 55 beats per min. The patient was also cyanosed and bradypneic, with the following arterial blood gases in ambient air: pH 7.09, HCO_3^- 20 mmol per L, $PaCO_2$ 9.80 kPa, PaO_2 6.10 kPa, SaO_2 65 percent (normal ranges: pH 7.38 to 7.42, HCO_3^- 22 to 25 mmol per L, $PaCO_2$ 4.9 to 5.6 kPa, PaO_2 12 to 14 kPa, SaO_2 > 95 percent). The venous lactates were 12.2 mmol per L (normal range, 0.6 to 2.4 mmol per L). After diazepam and sodium valproate infusions, the seizures stopped; PaO_2, blood pressure, and pulse normalized after endotracheal intubation, mechanical ventilation, and hydroxyethylamidon infusion. Many tablets were evacuated by gastric lavage, and activated charcoal was administered.

The serum electrolytes and liver function tests were normal. Glycemia was 7.7 mmol per L (normal range, 4.2 to 5.8 mmol per L). Serum creatinine was increased to 132 µmol per L (normal range, 40 to 100 µmol per L), with normal blood urea nitrogen. The complete blood cell count showed hyperleucocytosis to 16.6 x 10^3 µ per L (normal range, 3.6 to 10.0 10^3 µ per L) without anemia or thrombopenia. A rhabdomyolysis was found (serum creatinine kinase 1,401 U per L; normal < 195 U per L) and serum troponin was negative. The arterial blood gases improved after one hour of mechanical ventilation (pH 7.34, HCO_3^- 25.5 mmol per L, $PaCO_2$ 6.5 kPa, PaO_2 26 kPa with FiO_2 to 60 percent), and the venous lactates were restored to normal (2 mmol per L). Tests to detect antidepressants in the blood and cocaine in the urine were negative, and weakly positive for benzodiazepines and paracetamol (respectively, 98 g per L and 6.3 mg per L). The blood alcohol level test was also negative.

On admission, the electrocardiogram (ECG) showed a regular junctional rhythm (55 beats per min), an absence of P waves, and broad QRS complexes (0.16 mm per sec) with an aspect of right bundle-branch block (Figure 1).

After airway management and arterial pressure improvement, a second ECG, done 11 minutes after the first, revealed a regular sinusal rhythm (90 beats per min) with the persistence of wide QRS complexes (0.16 mm per sec) and right bundle-branch block. Four hours after the initial ECG, the cardiac rhythm was sinusal, the QRS complexes were normal (0.10 mm per sec), and the right bundle-branch block had disappeared.

The patient was quickly weaned from mechanical ventilation and extubated. He was discharged home on the fourth day of his hospitalization without complications.

Case 2

A 21-year-old drug-addicted woman was admitted for acute self-ingestion of medicines. On admission, she showed a regular respiratory rate of 12 breaths per min without pause, a blood pressure of 120/90 mmHg, and a heart rate of 84 beats per min. The patient was conscious and answered appropriately. Her pupils were slightly constricted. She acknowledged having ingested two packs of flunitrazepam, and was treated by activated charcoal. Thirty minutes after her admission, the patient was deeply asleep with no verbal response but did respond to nociceptive stimuli, and her respiratory rate remained regular (12 breaths per min). Twenty minutes later, the decrease in consciousness had advanced, and the patient was bradypneic with a respiratory rate of six breaths per min. A short-duration awakening was obtained after an intravenous injection of 0.3 mg flumazenil. Qualitative tests to detect toxic substances in the blood showed 301 mg per L of benzodiazepine and the absence of imipraminic antidepressant or neuroleptic agents.

Eight hours later the patient was sleepy, but able to be aroused; hemodynamic and respiratory indices were normal, and the pupils were constricted. Intravenous injection of 0.8 mg naloxone resulted in complete awakening and disappearance of the myosis. The patient confessed the ingestion of DP associated with flunitrazepam and also a snort of heroin: she was trying to come off heroin with these medicines. In the urine, the opiates were greater than 1,000 mg per L and there was no trace of cocaine. The presence of DP and one of its metabolites was confirmed in mass spectrometry. The initial ECG showed a first-degree auriculoventricular block (PR interval, 0.24 mm per sec) that persisted after naloxone injection. The PR interval was 0.18, then 0.16 mm per sec, respectively, 16 and 20 hours after admission. The patient was discharged home without ECG abnormality.

DISCUSSION

DP is a weak opioid analgesic that is commonly combined with other nonopioid analgesics such as paracetamol. Analgesic drugs and DP are respectively implicated in 7 percent and 4 percent of all acute self-drug poisonings in French emergency departments.[4] Fatal DP poisonings seem uncommon in France, while they are frequent in the United Kingdom and Nordic countries.[1-3] A UK study designed to assess the suicide rate due to DP-acetaminophen compound (co-proxamol) versus acetaminophen alone and tricyclic antidepressants, reported that the odds of dying after overdose with co-proxamol was 2.3 times that for tricyclic antidepressants and 28.1 times that for acetaminophen.[1] Legislation limiting the pack sizes of analgesics in the United Kingdom has been beneficial for reducing paracetamol poisoning, and the restriction of DP-paracetamol availability has also been recommended.[1,5] Moreover, it has been suggested that suicide reports where DP is in question may in fact be better categorized as accidental poisonings.[2] The Britain Committee on Safety of Medicines announced in 2005 that co-proxamol will be gradually withdrawn from the market.[6]

DP is mainly metabolized through N-demethylation into NP, a weak opioid analgesic with a significant local anesthetic effect. After repeated administration of DP, this metabolite is present in plasma in higher quantity and with a three-times-longer half-life than the parent molecule. In case of the use of great quantities of DP, as a substitute by heroin addicts or during acute intoxication, the contribution of NP to toxic effects is significant, and its long half-life can explain a prolonged action. In our observations, the addicted individuals substituted heroin for DP. It is likely that NP, because of its pharmacokinetics, has played a particular and additive role on the acute DP cardiotoxicity.[5]

Acute poisoning is characterized by a short period between the ingestion and the onset of symptoms. Toxic effects include coma, respiratory depression, myosis, and convulsions[7]; pulmonary edema, cardiogenic shock, or cardiac arrest can also occur. In a study including 222 consecutive patients hospitalized in the intensive care unit for serious acute DP intoxication over a six-year period, one-half of the patients suffered from circulatory failure at their admission, and 10 out of 17 deaths were attributed to a cardiac insufficiency[3]; ECG abnormalities were present in 41 percent of patients with widening of the QRS complex (43 patients), first-degree auriculoventricular block (1 patient), or varied ventricular arrhythmias (19 patients). Other ECG particularities have been described, such as typical bundle-branch block, widening of the QT interval, and nonspecific modifications of the T wave and ST segment. These ECG abnormalities are considered independent of all ischemic modifications secondary to respiratory failure.

Most of the toxic DP effects are linked to its opioid activities and can be reversed by opiate antagonists; the cardiac effects are apparently without link to analgesic activity. Naloxone has shown its incapacity to reverse DP cardiotoxicity[7] in vitro and in some clinical observations.[8] On isolated Purkinje fibers, DP and NP have produced a dose-dependent inhibition of V_{max}, a shortening of the action potential duration (APD), and a decrease of the effective refractory

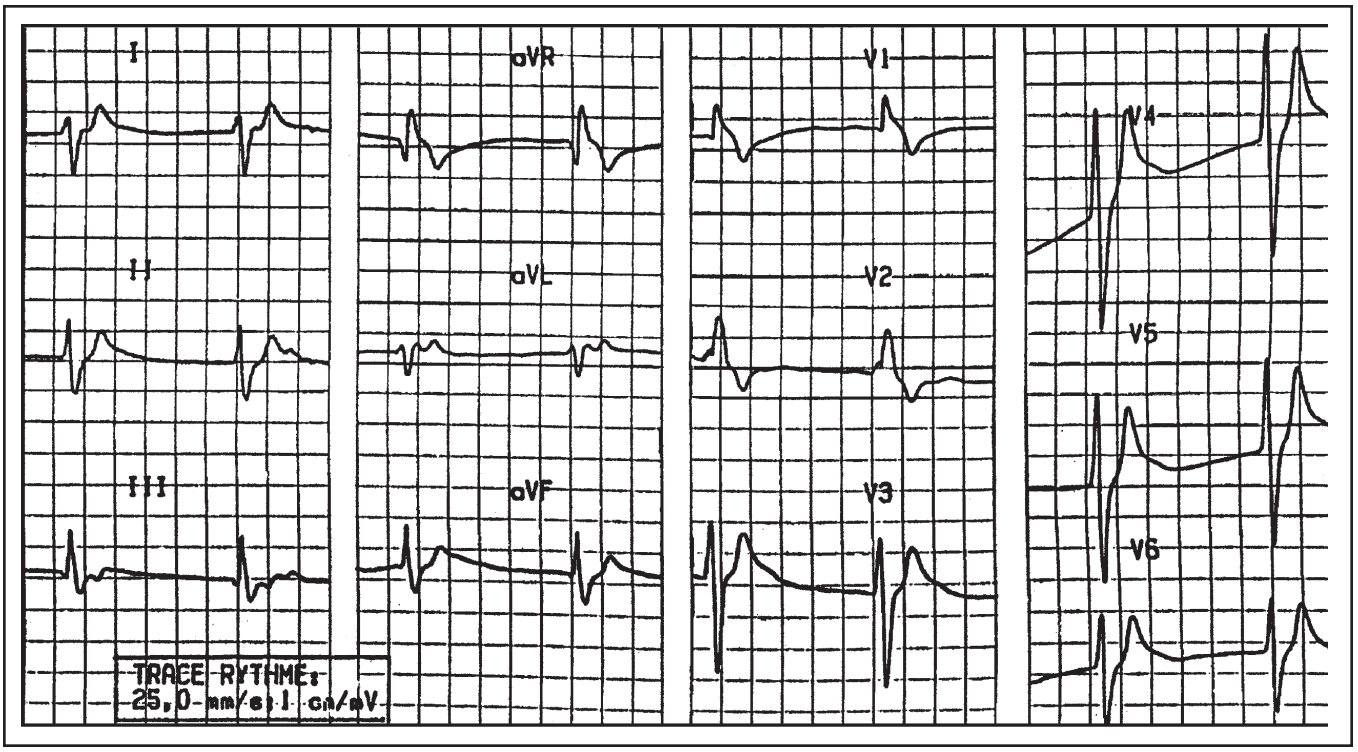

Figure 1: Dextropropoxyphene overdose, Case 1. ECG abnormalities on admission: Regular junctional rhythm (55 beats per min), absence of P waves, and broad QRS complexes (0.16 mm per sec) with aspect of right bundle-branch block.

period (ERP) without modifying the ERP/APD ratio.[9] On an isolated guinea pig atrium, they have exerted negative inotropic and chronotropic actions[9] that have been confirmed in vivo on pentobarbital-anesthetized pigs.[10,11] The depressant effect on myocardial contractility is more important with NP than with DP. Other in vivo animal experimentation has shown depressant effects on the cardiac conduction (PR interval, QRS complex and QT interval prolongation) and a biphasic effect on the cardiac frequency (bradycardia, then tachycardia).[10] DP and its metabolite have also slowed down the auriculoventricular node and His-Purkinje system conduction on endocavitary explorations.[9] Thus, it is clearly suggested that DP and NP cardiotoxicity is the result of a local anesthetic action that is twice more significant for NP.[10] Hypoxemia and lactate or respiratory acidosis that can be observed during DP poisoning are known to exacerbate the DP membrane-stabilizing effect. Whitcomb et al. have demonstrated that DP and its metabolite are a potent blocker of inward sodium currents in cardiac myocytes[12]; Ulens et al. have suggested that inward potassium current block may also contribute to the nonopioid effects of these molecules.[13] DP also exerts a negative inotropic effect by its blockage of the inward calcium current.[14] Moreover, DP and NP dilate the systemic and coronary vascular beds.[10]

The clinical use of naloxone to reverse DP cardiotoxicity is still being discussed.[8] On the isolated papillar cardiac muscle, the negative inotropic effect of DP has not been prevented by pretreatment with naloxone.[7] In an experimental study on pigs with cardiogenic shock induced by DP, naloxone led to a transitory improvement of the ejection volume that has not been reproducible with supplementary doses[11]; this action was secondary to increased cardiac frequency and myocardial contractility. Moreover, naloxone has not reversed the systemic vasodilatation after DP overdose. In healthy men or men with hypertension and who had not received opioid substances, the naloxone did not involve any modification of hemodynamic indices or catecholamine concentrations. Nevertheless, during the reversion of narcotic effects, an immediate increase of the cardiac frequency, myocardial contractility, and arterial pressure mediated by the sympathoadrenal system has been described.[15] In experimentation as well as clinical situations, naloxone does not modify ECG abnormalities, even in cases in which hemodynamic effects were reported.[8]

Animal experiments have shown the capacity of positive inotropic drugs to improve cardiovascular function during severe DP intoxication.[16] Similar results have been observed in human subjects with dopamine and dobutamine.[17] Nevertheless, arterial hypotension can resist dopaminergic and adrenergic drugs, and it has been suggested that DP has its own capacity to inhibit the calcium channels of vascular smooth muscle fibers.[12]

To summarize, the relevance of the use of naloxone in the treatment of DP-induced cardiotoxicity is still debated. Moreover, because of naloxone-induced withdrawal manifestations, its use must be circumspect in addicted

patients. Most authors have found it ineffective, and it must be emphasized that supportive therapy (e.g., mechanical ventilation, fluid replacement, inotropic drugs) is of primary importance. Gastric lavage and activated charcoal may be useful, while dialysis is of little value. No data support the use of antiarrhythmic drugs such as phenytoin or β-blockers to correct DP-induced ECG disturbances. Lidocaine has been successfully used in the management of cardiac conduction abnormalities, even though this therapeutic approach seems paradoxical because DP and lidocaine exert a common inhibition of the inward sodium currents.[12] The association of two sodium-channel inhibitors would allow the production of a less-significant sodium-channel inhibition as observed with each drug because of a difference of affinity for sodium channels. The use of sodium bicarbonate has also been reported to be successful in one case in the literature.[18]

DP has a narrow therapeutic index. Death can result from an overdose with relatively few tablets, especially when alcohol has also been taken. The rapid gastrointestinal absorption of DP explains that cardiorespiratory arrest can occur 15 minutes after an acute ingestion. Regarding fatal poisoning by DP, strict regulation in prescription with a close attention to the patient's risk category (e.g., suicidal patients, drug addicts, drinkers) is well advised.

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Methadone in end-of-life pain management

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INTRODUCTION

Pain is a complex symptom which, at times, challenges even the best clinician.[1,2] In patients with cancer, pain is a pervasive and difficult problem[3] that encompasses psychological, social, spiritual, and physical realms.[4] Palliative care clinicians must understand the psychosocial and spiritual domains in addition to the physical aspects of pain treatment to truly alleviate suffering. Thus, being adept with opioid dosing and titration is essential in comprehensive palliative care,[5] as it often requires rapid escalation and continual reevaluation. There is a general lack of comfort and understanding concerning the use of many opioids, however, which often leads to undertreatment of pain—even among patients receiving care for terminal diseases.[6] This is particularly true of methadone. Methadone is well known among addiction specialists for its use as maintenance therapy in opioid-dependent patients.[7] Increasingly, methadone's unique properties and economic advantages[8-10] are being realized by those within the palliative care community, whose practice settings often involve homebound patients with limited funds or difficult-to-control terminal pain. Because of its potential for serious adverse effects, however, methadone should only be prescribed with knowledge of its intricacies.

PHARMACODYNAMICS AND PHARMACOKINETICS

Methadone is a synthetic opioid, which exists as a racemic mixture. L-methadone provides analgesia in part via activation of the body's endogenous analgesia system: μ-, δ-, and κ-opioid receptors in the ascending pain pathway are agonized. L-methadone also modulates the descending pain pathway via inhibition of serotonin and norepinephrine reuptake. This monoamine reuptake inhibition dampens pain pathways. Finally, both D- and L- enantiomers are noncompetitive antagonists of the N-methyl-D-aspartate (NMDA) receptor. The reverse process, agonism of the NMDA receptor in the spinal cord, contributes to opioid tolerance. Hence, methadone's unique property of antagonizing this untoward process contributes to its notably higher milligram-for-milligram equianalgesic potency compared to morphine.[11]

Methadone has been used to treat neuropathic pain.[12] As well, some authors have theorized that NMDA receptor antagonism could offer a unique mechanism of added efficacy for neuropathic pain, whereas opioids without NMDA activity would not. However, a retrospective chart review suggested methadone affords no additional efficacy for neuropathic pain versus non-neuropathic pain when compared to equianalgesically dosed hydromorphone.[13] An evidence-based review of the current limited literature of eight randomized trials has revealed no research support for methadone's theoretical benefit in neuropathic pain treatment.[14] Whereas methadone has the complex pharmodynamics already mentioned, morphine is almost exclusively a μ-receptor agonist. Such variability among individual opioid analgesic receptor profiles contributes to the phenomena of incomplete opioid cross-tolerance. Occasionally a change in opioid agent will yield notably better analgesia, even when equianalgesic dosing is taken into consideration.[15]

Clinical onset of analgesia is within 30 to 60 minutes after oral administration; the plasma level peaks in four hours, and peak analgesia is achieved in 2.5 to 4.0 hours. Because methadone is stored in tissues and then subject to redistribution, repeat dosing may extend the initial analgesic effect from three to six hours initially to eight to 12 hours after a steady state is achieved. Methadone's tissue binding (to muscle, liver, kidney, lungs, and brain) is more extensive than its plasma binding. Methadone in the plasma is highly protein bound via α-1-acid glycoprotein (AAG). AAG is an acute-phase reactant, which is often elevated in cancer patients. Unbound methadone is metabolized in the liver primarily via cytochrome P-450 (CYP) 3A4, CYP2C8, and CYP2D6. Hence, hepatic clearance of methadone is decreased and half-life is increased among cancer patients.[17] CYP activity is important when considering potential drug interactions (Table 1). Numerous drugs that either inhibit or activate the CYP system can lead to opioid toxicity or withdrawal with methadone. The elimination half-life has a mean of 22 hours, but an extremely variable range of 15 to 190 hours has been reported.[18] This comparatively long half-life is beneficial for chronic pain management.[19] Elimination is predominantly via liver

Table 1. CYP activity and potential drug interactions								
2C8 substrate	**2C8 inducer**	**2C8 inhibitor**	**2D6 substrate**	**2D6 inducer**	**2D6 inhibitor**	**3A4 substrate**	**3A4 inducer**	**3A4 inhibitor**
repaglinide	rifampin	gemfibrozil	amitriptyline	dexamethasone	amiodarone	alprazolam	barbiturates	amiodarone
torsemide		glitazones	aripiprazole	rifampin	bupropion	amlodipine	carbamazepine	cimetidine
		montelukast	carvedilol		celecoxib	aripiprazole	glucocorticoids	ciprofloxacin
		trimethoprim	chlorpromazine		chlorpromazine	atorvastatin	modafinil	diltiazem
			clomipramine		cimetidine	buspirone	oxcarbazepine	erythromycin
			codeine		citalopram	cisapride	phenobarbital	grapefruit juice
			desipramine		clomipramine	clarithromycin	phenytoin	norfloxacin
			duloxetine		diphenhydramine	diazepam		verapamil
			flecainide		doxepin	erythromycin		
			fluoxetine		duloxetine	estradiol		
			haloperidol		escitalopram	felodipine		
			imipramine		fluoxetine	fentanyl		
			metoclopramide		hydroxyzine	finasteride		
			metoprolol		metoclopramide	haloperidol		
			risperidone		paroxetine	hydrocortisone		
			thioridazine		quinidine	lovastatin		
			tramadol		sertraline	nifedipine		
			venlafaxine			ondansetron		
						propranolol		
						quinidine		
						testosterone		
						trazodone		
						verapamil		
						zaleplon		
						zolpidem		

metabolism and subsequent renal and fecal excretion. There are no active metabolites. Methadone needs to be titrated with additional caution in patients with hepatic or pulmonary impairment. Approximately 40 percent of methadone is eliminated renally. If urine pH is less than 6, then the percent renal elimination increases. Nonetheless, renal dosing is almost never clinically necessary.

FORMULATIONS

In the United States, methadone is commonly dispensed as a tablet, dispersible tablet, liquid, or liquid concentrate for oral administration. Additionally, it may be administered via sublingual (SL), intravenous,[20,21] rectal, subcutaneous (SC), epidural, or intrathecal routes. Given orally, methadone has

a bioavailability of 80 percent (range, 41 to 99 percent), whereas morphine's is approximately 25 percent. In palliative care, providing pain relief in the least invasive manner is preferred. The oral route is used when at all possible. Most lipophilic drugs such as methadone can be given via the SL route. Methadone's SL bioavailability can be 75 percent when taken with bicarbonates.[22] Methadone can be given rectally as a suppository or microenema solution. Microenema preparations of methadone can have onset of action at 30 minutes and duration of effect up to eight hours.[23] Rectal administration has the potential to provide increased bioavailability compared to oral routes; however, many palliative patients experience constipation or impaction. The presence of fecal material in the rectal vault can severely affect absorption. Although many patients may refuse this route of administration, it does provide an alternative in difficult clinical management situations. For patients who have no other means of pain control, such as in cases of bowel obstruction, hospice care uses SC routes for opioids in place of painful intramuscular or invasive intravenous routes. In these settings, SC is reserved for opioids such as morphine and hydromorphone. Methadone is usually not given SC, as it can cause adverse skin reactions and increased pain at the site of administration[24]; however, if needed, this route is available and useful. Dexamethasone added to the methadone syringe has been reported to increase the interval between changing the needle from 2.6 days in the methadone-only group to 4.9 days in the dexamethasone plus methadone group.[25] In particular cases in which acute inpatient hospice care is provided for intractable pain intolerant to other opioids, injectable methadone may have a strong role. Rotating patients onto injectable methadone in a hospitalized setting has been shown to be safe and effective.[26]

DOSING

There are many options for methadone dosing. Choice for dosing is dependent on the clinical scenario, ability to monitor a patient, and experience of the provider. Many clinicians are familiar with common methadone initiation strategies, but rotation with rapid titration is often fraught with confusion for providers due to differing published equianalgesic conversions and ratios. The following are some commonly accepted schematics.

Initiation

Methadone can be the initial opioid used to mitigate severe pain. Initial dosing can vary from 2.5 to 5.0 mg by mouth every four hours, as needed (p.r.n.), for several days. The total p.r.n. doses consumed over those days are then converted to scheduled doses, divided over every eight or 12 hours. An alternative to this consists of beginning with both scheduled and p.r.n. dosages. A recent prospective randomized trial by Bruera involving 103 patients compared the initiation of oral methadone 7.5 mg every 12 hours and 5.0 mg every four hours p.r.n for breakthrough pain versus slow-release morphine 15 mg twice daily and immediate-release morphine 5.0 mg every four hours p.r.n. for breakthrough pain in cancer patients.[27] The primary objective of the study was to evaluate the difference in pain intensity at four weeks. Methadone was not found to be superior to morphine and had higher dropout rates at eight days owing to side effects such as sedation, vomiting, and myoclonus. The investigators postulated that the true dose ratio between methadone and morphine may be lower than the ratio of 0.5 (7.5:15) used in the study. Moreover, they added that it is possible methadone is more toxic than morphine when it also is used as a breakthrough opioid at the doses used in the trial.

Opioid rotation

Often a clinician may find a need to rotate from one opioid, such as morphine, to another. For example, when a patient develops renal insufficiency, neurotoxic morphine metabolites may accumulate, leading to myoclonus. Switching from one opioid to another is a worthwhile strategy, because incomplete cross-tolerance between the two agents may mitigate better analgesia at a lower dosage with the second agent. Toxicity owing to methadone occurs more commonly among patients using high-dose opioids, not among the opioid naïve.[28] Cross-titration, consisting of discontinuing the current analgesic and beginning methadone, is done in a so-called slow or rapid manner.[29]

Slow rotation. Changes occur over three days for patients on > 100 mg morphine equivalent (ME) at baseline. A progressive substitution of one-third of the previous opioid, using an equianalgesic dose ratio based on the prior morphine dose, is used as follows:

- Day one: The current opioid is decreased by 30 to 50 percent over 24 hours. Equianalgesic methadone dosage is given orally or rectally, divided over every eight hours.
- Day two: The original opioid is decreased by another 30 to 50 percent. Scheduled methadone is increased if the patient has moderate to severe pain. Breakthrough pain is addressed with a rescue dose of short-acting opioids or methadone at 10 percent of the daily dose, given as frequently as every two hours if needed, up to three doses.
- Day three: The original opioid is discontinued.

Variations of this slow-rotation scheme are used around the world. Among patients on < 100 mg ME, however, rapid rotation is used.

The conversation ratio of morphine to methadone

Table 2. Equianalgesic ratios of oral morphine to oral methadone			
	Method	**Initial daily morphine equivalence**	**Morphine:methadone conversion ratio**
Model 1	slow route	0 to 1,000 mg per day	10:1
		> 1,000 mg per day	20:1
Model 2	stop-go	30 to 90 mg per day	4:1
		90 to 300 mg per day	8:1
		> 300 mg per day	12:1
Model 3[29]	fixed	< 400 mg per day	5:1
Model 4[30]	fixed	< 300 mg per day	10:1

varies inversely per the current magnitude of MEs. Various authors suggest differing equianalgesic ratios. Table 2 is adapted from work by Bruera and colleagues, Ripamonti and colleagues, and others. Of note, there are many additional equianalgesic tables not reported here.

Rapid rotation. The current opioid is completely and abruptly stopped. In a randomized trial using this method, there was a reported effectiveness of the stop-and-go method when rotating from morphine to methadone in patients with uncontrolled pain.[30] A dose ratio of 1:4 (1 mg of oral methadone = 4 mg of oral morphine) was used for patients receiving less than 90 mg of morphine. Patients receiving 90 to 300 mg per day received methadone at a ratio of 1:8. Finally, a ratio of 1:12 was used for patients receiving morphine doses greater than 300 mg per day. The authors concluded that higher doses of methadone are not dangerous initially, because the pharmacokinetics of methadone require priming before achieving a pharmacologic effect. Appropriate monitoring of methadone dosing is necessary in the days that follow, however, when methadone accumulation could occur and dosing may need to be reduced. Eighty percent of the patients were successfully converted using this method and had improved pain and adverse symptom reports (assessed via the self-reported Visual Analog Scale for pain and a self-reported four-item, 4-point Likert scale devised by the authors, respectively). Constipation was also noted to be less in the methadone group.

Fixed-dose rotation

Conversion to methadone is set at a fixed ratio. Mercadante examined the feasibility of a rapid substitution of morphine with methadone at 20 percent (ratio of 1:5) of the previous morphine dosage to assess if this could improve the opioid response in terms of global effect (i.e., balance between analgesia and adverse effects) in patients with poor pain control.[31] Most of the patients in this study were on lower-dose morphine (< 90 mg per day) and tolerated the switch with efficacious analgesia and low morbidity. It was noted that patients on higher doses of morphine (median, 256 mg) required methadone dose reduction. There is no significant literature support for use of this method among patients using high-dose morphine.

Morley offers an alternative fixed-dose rotation using one-tenth of the previous morphine dose with a maximum initial dose of 30 mg, dosed not more than every three hours.[32] After six days, the amount of methadone taken over two days is converted to a daily dose given in 12-hour intervals. Additionally, there are many more fixed-dose models that are reported among European communities but are not commonly used in the United States.

SIDE EFFECTS

As with all opiates, methadone can exhibit side effects that limit its use by the general community. Methadone is highly lipophilic and easily accumulates in tissues. Among clinicians naïve to methadone prescribing, this tissue accumulation can lead to iatrogenic sedation, respiratory depression, delirium, and seizures. Other reported adverse effects include constipation, hallucinations, QTc prolongation,[33,34] and torsades de pointes.[35] Reports of QTc prolongation in the literature have not been correlated with any linear relationship to the methadone dose. Currently, there are no consensus recommendations on electrocardiogram monitoring among cancer patients on chronic methadone therapy.

Additionally, sexual dysfunction and decreased sex hormone levels have been reported with chronic methadone use. A clinical trial of heroin addicts treated with a single daily dose of methadone reported decreased levels of testosterone and increased levels of erectile dysfunction.[36] Additionally, a study of 92 opioid-dependent men using methadone surveyed reported a direct correlation with increased orgasm dysfunction and methadone dose.[37]

COSTS

Methadone is generally reported to be less expensive

than other long-acting opiates. As of 2004, methadone costs a fraction of sustained-release morphine, oxycodone, or transdermal fentanyl.[8] Sample wholesale prices for morphine sulfate controlled-release tablets (MS Contin, Purdue Pharma LP, Stamford, CT) at 100 mg every 12 hours for one month averages $328, whereas methadone hydrochloride (Methadose, Mallinckrodt, Inc., St. Louis, MO) 40 mg every 12 hours for the same period averages $17. With the availability of methadone in scored form, it can be easily fractionated, which further decreases the financial costs in most formulary-limited hospice systems.[38]

CONCLUSION

Methadone is an old drug that is increasingly providing new meaning among the pain community. It can be a powerful tool in the treatment of terminal pain symptoms. With knowledge of its pharmacokinetics, drug interactions, and variable equianalgesic potency, it can prove a powerful analgesic in our armamentarium against end-of-life pain.

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ORIGINAL ARTICLE

A comparison of oral and implant naltrexone outcomes at 12 months

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ABSTRACT

Naltrexone's current use has been limited by compliance. Subcutaneous implants would seem to offer a solution to this problem and improve long-term outcomes. The aim of the present study was to compare groups of patients who had received oral naltrexone or a naltrexone implant after detoxification and to follow their progress. Forty-one patients received an implant, and 42 patients received oral naltrexone. They were surveyed at one, three, six, and 12 months after detoxification. Their designated support person was also contacted to confirm the self-reports of the participants. Patients were compared on gender, age, and length of time since detoxification. Implant patients showed much higher abstinence rates, while those in both groups who were abstinent showed greater compliance to naltrexone (time spent in treatment) and attended more counseling sessions. Although the participants were not randomly allocated to each treatment condition, the preliminary evidence indicates that implants can improve compliance rates and outcomes.

Key words: naltrexone, implant, social support, compliance, opiate addiction

INTRODUCTION

Naltrexone, a potent opiate antagonist, has been shown to have valuable properties for the treatment of addiction to opiates such as heroin and methadone. The most important property is its ability to completely block the effects of heroin,[1] making relapse to regular opiate use almost impossible while it is being taken. Research has shown that a dose of 50 to 100 mg of oral naltrexone provides effective protection against heroin for two to three days, and with chronic dosing, no accumulation of naltrexone or its metabolites has been observed.[2,3] Naltrexone is nontoxic[2-4] and produces no clinically important side effects.[2,4-6] The main factor restricting naltrexone's widespread use in opiate dependency treatment is rate of noncompliance.[7-11]

The ability to resist and ignore drug misuse cues is not easy. Indeed, 50 percent of clients who left a three-week inpatient opiate detoxification program had misused opiates within several days of doing so.[12] This early relapse undermines any chance of success, as it does not allow the user the chance to implement new opiate-free behaviors and thoughts. Naltrexone offers no immediate reinforcement after use and discontinuation produces no adverse effects, making it easier to stop using it. This is in contrast, however, to heroin and methadone, which offer strong immediate reinforcement after use and adverse effects and withdrawal if they are discontinued.[13] Noncompliance to naltrexone-based treatment is of particular concern because tolerance is reduced after a period of abstinence from opiate use and, as such, patients who relapse are at an increased risk of overdose and death.[14]

Poor outcomes in the treatment of opiate dependency using naltrexone relate to shortened time in treatment; conversely, longer time in treatment has been related to better long-term outcomes.[15,16] Moreover, with no aftercare counseling, compliance strategy, or social support in place, studies have shown predictably poor long-term outcomes.[9,17,18] When naltrexone is combined with an effective aftercare program and social support to enhance compliance, however, results have been promising.[19,20] This view has been supported empirically for other drug addiction treatment services.[21,22]

One approach to the issue of noncompliance in naltrexone treatment has been the development of subcutaneous naltrexone implants. The latest development with these implants enables a slow release into the body.[3,23] This frees the patient of the mental battle they face when trying to remain compliant with oral naltrexone use and the need to sustain a support-person relationship as part of a compliance strategy. Several studies have indicated the excellent bioavailability of naltrexone in subcutaneous form.[6,13]

In summary, clinical studies of patients recovering from opiate addiction indicate that patients who are retained in counseling and who continue to take naltrexone tend to have better long-term outcomes compared to those who spend less time in counseling and who take naltrexone for shorter periods of time. The issue of compliance has led to poor outcomes when support is lacking and there is little or no follow-up counseling, and these problems persist because of low retention among those using oral naltrexone. In the context of the present study, it was hypothesized that patients using naltrexone implants would have improved compliance rates, increased total time in treatment, and with aftercare counseling, improved long-term abstinence rates, as compared to those taking oral naltrexone.

METHODS

Participants

As part of the present follow-up study, 83 patients and their support people were interviewed, with approximately one-half of the patients receiving implants and the other one-half receiving oral naltrexone. All participants had completed the program over an eight-month period 12 to 20 months before data collection was completed in September 2004. As part of the practice of Addiction Treatment and Psychology Services' treatment program, all patients had undergone some counseling and were kept in regular contact via telephone. Their appointed support person was also contacted. Data collection involved a telephone survey of the patient and their support person for corroboration of the patient's self-report regarding their drug use and compliance to naltrexone.

Implant

Implants produced by Go Medical Industries Pty, Ltd. (Subiaco, Australia; International Patent Application Number: PCT/AU01/01107), in cooperation with the Department of Pharmacy at Curtin University (Bentley, Western Australia) were used. Each implant was designed to contain approximately 1.7 g naltrexone hydrochloride that had an in vitro release rate ranging from 0.2 to 0.8 percent of their residual mass per day.[24] The naltrexone was encapsulated in poly-DL-lactide—a polymer similar to that used in dissolvable surgical sutures and screws—microspheres compressed into pellets. Each implant consisted of 10 pellets. Subjects were given a single (10 pellets; 1.7 g naltrexone) or double (2 x 10 pellets; 3.4 g naltrexone) implant, which was surgically inserted into the subcutaneous tissues on the right or left side of the lower abdomen, in the fat tissue below the waistline. The length of time the implant was expected to release therapeutic doses of naltrexone was three months (approximately 100 days) for a single implant and up to five months (approximately 150 days) for a double implant.[3,23]

Procedure

Before detoxification, all patients underwent a psychosocial assessment to determine whether or not they were suitable for the program. Suitability was determined by the client's motivation to be opiate free, their level of social support, any serious psychiatric diagnoses of mental illness, and any medical issues that would make the detoxification process dangerous.

Part of the psychosocial assessment also entailed the completion of two psychometric tests, the Beck Depression Inventory-II (BDI-II) and the Symptom Checklist-90-Revised (SCL-90-R). The BDI-II is a short inventory designed to measure depression. As a general rule, a BDI-II score ranging from 0 to 13 is considered minimal, 14 to 19 is considered mild, 20 to 28 is considered moderate, and 29 to 63 is considered severe. The SCL-90-R is a broad, multidimensional measure of psychological distress. Only one of the scores on the SCL-90-R was included for comparison between the two groups—the Global Severity Index (GSI). The GSI is the best indicator of overall psychological distress, combining the breadth and intensity of symptoms that are experienced. As an operational rule, a GSI T-score of 63 or greater is considered to indicate a positive risk for an actual psychological disorder. All participants were asked to rate their self-esteem and the quality of their primary relationships on a 0 to 10 Likert scale before and after treatment.

All patients were told before detoxification about the costs and benefits of oral naltrexone and naltrexone implants. Each patient signed informed consent forms before detoxification and another consent form before insertion of the implant, in accordance with the Helsinki Declaration of 1975. One of the consent forms included permission to release the data collected for research purposes and other information relating to the nature and risks attached to the detoxification procedure and the use of naltrexone. No patient received an implant at the time of detoxification, but did so a number of days later. This was to ensure that consent was given while they were drug free and to rule out any possible complications that may have arisen after the implant was inserted. Use of the implant was authorized under the Special Access Scheme of the Therapeutic Goods Administration.

Analysis

The data were collected over a period of 20 months and were based on self-report. Researchers called the patients and their support people, often in the evening,

Table 1. Characteristics of patients before detoxification from opiates compared with oral and implant naltrexone groups

Characteristics	Naltrexone implant	Oral naltrexone
Total male patients (percent)	25 (61)	26 (62)
Total patients detoxed from methadone (percent)	8 (20)	5 (12)
Total patients detoxed from heroin (percent)	26 (63)	30 (71)
Total patients detoxed from heroin/methadone (percent)	5 (12)	6 (14.5)
Total patients detoxed from other opiates (percent)	2 (5)	1 (2.5)
Mean years using opiates (± SD)	7.2 (5.0)	9.6 (8.8)
Mean years of education	10.6	10.8
SCL-90-R GSI T-score (mean ± SD)	68.7 (16)	63.5 (10.3)
BDI-II score (mean ± SD)	22.2 (10.3)	17.9 (11.7)
Mean heroin use (g)	0.66	0.75
Mean methadone (mg)	60	53.5
Mean counseling sessions	8.5 (SD 2.7; 2 months duration)	6.4 (SD 2.5; 1.5 months duration)
Age range (yr)	20 to 40	22 to 48
Mean age (yr)	26.2	32.3

BDI-II, Beck Depression Inventory II; SCL-90-R GSI, Symptom Checklist-90-Revised Global Severity Index; SD, standard deviation.

to verify information. If an individual used opiates only a few times (i.e., once or twice) since their detoxification (e.g., to test if the naltrexone was working), this was not considered a relapse. Rather, a relapse was defined as occurring in those people with opiate use daily or on most days, sporadic opiate use (weeks or months of regular use followed by weeks or months of abstinence), and/or a few days of use followed by nonuse on a regular basis.

Data were compared for significant differences using two-tailed t-tests with an α level set at 0.05.

RESULTS

Table 1 presents the characteristics of patients in the two groups (naltrexone implant and oral naltrexone) in terms of several variables, including age, gender, BDI-II scores, SCL-90-R GSI T-scores, years of education, length of time using opiates, whether detoxification was from heroin or methadone, and the number of days since detoxification (at the time these statistics were compiled). T-tests were conducted to see whether the groups differed significantly on mean age, years using opiates, years of education, daily heroin and methadone dose, SCL-90-R GSI T-scores, BDI-II scores, and days since detoxification. The differences were found to be nonsignificant with an α level of 0.05 for all of these variables.

Table 2 compares the two groups in terms of the social factors of self-esteem and general relationship quality pre- and post-detoxification for those people who were successful in their attempt to cease opiate use. The statistics reported are the means for the two groups. T-tests were conducted to determine whether the changes (i.e., improvements) in self-esteem and relationships were statistically significant for both groups. Statistical analysis comparing ratings pre-detoxification and at six and 12 months post-detoxification were highly significant with an α level of 0.01, showing the psychosocial benefits of abstaining from opiate use. T-tests showed that the differences in scores on a scale from 0 to 10 for the two groups in relationships (approximately 2.3) and self-esteem (approximately 3.8) before their detoxification were nonsignificant ($p = 0.81$ and 0.86, respectively). However, at six months the differences in the groups after detoxification were significant for self-esteem with an α level

Table 2. Mean ratings on social factors before and after detoxification		
Social factors measured	**Naltrexone implant**	**Oral naltrexone**
Self-esteem rating predetoxification	3.9	3.8
Self-esteem rating postdetoxification (six mo)	7.9	9.1
Self-esteem rating postdetoxification (12 mo)	8.7	8.3
General relationship quality predetoxification	2.4	2.2
General relationship quality postdetoxification (six mo)	7.8	9
General relationship quality postdetoxification (12 mo)	8.1	8.8
All ratings are based on a scale where 0 = disastrous and 10 = excellent.		

of 0.05 ($p = 0.018$), while the relationship ratings approached significance ($p = 0.055$), with the oral naltrexone group tending to do better. The differences between the groups when ratings were compared in the period from six to 12 months post-detoxification and for scores at 12 months were all nonsignificant, indicating that improvements in self-esteem and relationships tended to be maintained and also evened out over time. Average scores on self-esteem and quality of relationships at 12 months were approximately 8.5 for both groups.

Table 3 shows the reports by the patients and their support people of the time compliant to naltrexone, which is equated with time spent in treatment. Those who had an implant and relapsed to opiate use tended to do so after they believed the implant(s) had ceased being effective—the difference in time compliant to naltrexone between the abstinent and relapse groups was statistically significant at six and 12 months. Those with implants who were abstinent at six and 12 months estimated the implant was effective for approximately six months, whereas those who relapsed on the implant estimated the effective time as approximately four months. These differences were statistically significant. For those on oral naltrexone who maintained abstinence, the time compliant to naltrexone averaged four months, whereas those who relapsed took naltrexone for only three to six weeks on average. The time spent using oral naltrexone for those who relapsed was highly significant compared to the other three groups.

Table 4 shows the number of counseling sessions each group attended on average. None of the differences were statistically significant although, as expected, those who relapsed or were noncontactable attended significantly fewer sessions (four, on average) than those who were known to be abstinent (nine to 12 sessions).

Table 5 represents the number of people in each group who relapsed to opiate use. Follow-up reports showed that 19 of the 42 individuals taking oral naltrexone (45 percent) relapsed to opiate use or were noncontactable at six months, whereas only eight out of 41 individuals (19 percent) were using opiates or were noncontactable after receiving an implant at six months. This advantage was maintained for the implant group at 12 months, with relapse rates of 17 percent and 38 percent for that group and the oral naltrexone group, respectively.

DISCUSSION

In this study, patients received naltrexone implants, generally four days after detoxification, or else agreed to take oral naltrexone for a period of at least six months. For this latter group, a support person was identified who agreed to supervise the daily taking of the medication. As can be seen from Table 1, both groups were comparable in terms of age, gender, and mean number of days since detoxification. Table 1 also shows that the mean BDI-II scores were in the moderate depression range for the naltrexone implant group, and the moderate-severe depression range for the oral naltrexone group. There was a large amount of variance in depression scores, however, as indicated by the standard deviations for both groups.

One significant difference between groups related to gender and was common to both of them: women scored much higher in terms of depression (mean score 32, severe) compared to men (mean score 23, moderate). The mean SCL-90-R GSI T-scores were above the critical score of 63 for both groups (and for men and women), indicating that a large number of clients in both groups should be considered positive for diagnosis of a mental disorder.

Table 3. Group comparison of mean time using naltrexone		
Classification	**Naltrexone implant, mean days (SD)**	**Oral naltrexone, mean days (SD)**
Abstinent six mo	176.6 (68.1)	120.00 (104.8)
Abstinent 12 mo	187.3 (69.1)	123.21 (105.5)
Relapsed six mo	112.5 (50)	19.7 (31.7)
Relapsed 12 mo	120 (45.6)	30.1 (54.25)
SD, standard deviation.		

Both groups rated their self-esteem and general relationship quality comparably low before detoxification from opiates. As was hypothesized, both groups showed sharp increases in these ratings after detoxification; however, data were obtained only for those who were successful at abstaining from opiate use. It is interesting to note that the oral naltrexone group actually showed greater improvements on self-esteem and relationship ratings six months after detoxification; this may indicate a greater resolve within this group to "stay clean" and also closer reliance on their support people.

Compliance with naltrexone use was the main point of interest of this study (Table 3). It proved difficult to obtain precise information for those in the implant group who were abstinent, however, as the duration for which the implant was considered effective was based on their expectations about coverage and did not necessarily relate to the actual release of naltrexone. Information gathered from those who relapsed and who had the implant during the time of effective coverage was somewhat more accurate, as some patients tried using opiates for a period before they became aware that they could "feel it" and could therefore pinpoint the date it was no longer effective. Obviously the time spent using oral naltrexone was much more accurate to determine, as patients and support people were both clearly aware of when a patient stopped taking the tablets, although in many cases they had done so well before they relapsed. The expectation of those having a double implant was that it would be effective for up to six months. Estimates for this group were therefore higher than for those with a single implant, although in both groups many felt the implants were effective for longer than the actual duration patients were told the implants had.

A comparison of those in the oral group who maintained abstinence and those who relapsed show very clear differences in time spent taking naltrexone. At 12 months, those who were abstinent had taken naltrexone for an average of four months, whereas many of those who relapsed had ceased taking naltrexone within days of detoxification and the relapse group, on average, took naltrexone for only one month. Inspection of the results show that of those in the oral group who were abstinent at six months, only four (19 percent) stopped taking naltrexone less than one week after detoxification, and two (11 percent) had done so at 12 months. On the other hand, of those in the oral group who relapsed, 14 out of 21 (67 percent) had ceased taking naltrexone within a fortnight of detoxification, whereas at 12 months, 17 of 24 (70 percent) had stopped within two weeks.

The other result of note was that many still relapsed in the implant group despite being compliant to naltrexone for a similar period to those who were abstinent in the oral group. It seems there was a group who relapsed shortly after they believed the implant had stopped working and who possibly would have relapsed even sooner had they been on oral naltrexone. For both groups, it may be that some participants were not ready or were not suitable candidates for detoxification, and relapse was more likely among these individuals. It seems that if some of these potential relapsers are able to stay in treatment long enough, however, then better results are achievable given the overall better outcomes in the implant group.

The data in Table 4 show that participants who remained abstinent attended significantly more counseling sessions than those who relapsed and, while those who attended longer reported feeling better, it was also the case that if they relapsed they tended to drop out of treatment. However, because there was a cost to receive counseling, it may be that those who opted for oral naltrexone for financial reasons were also not able to afford counseling, thus compromising their outcomes.

The most important data to come from this study appear in Table 5, showing the clear advantage of a naltrexone implant over oral naltrexone. The difference between the two groups was quite striking, particularly when compared to traditional detoxification and rehabilitation programs.[15,16]

Table 4. Group comparison of mean number of counseling sessions attended		
Classification	**Naltrexone implant**	**Oral naltrexone**
Abstinent	12.7	9.0
Relapsed	4.0	4.9
Noncontactable	4.0	3.2
Total	8.5	6.4

Closer analysis of the relapse groups showed that those in the implant group who relapsed to heroin in particular had sold the drug before detoxification and continued selling afterward, had experienced early sexual or physical abuse and reported being able to get "over the top" of the naltrexone if they used enough, or else agreed that it didn't do anything, but used it anyway. They also reported that although they thought the heroin had only a weak effect, they still felt compelled to use, even while the implant was actively antagonizing the effect of the drug. This motivation contrasts with that found in the oral naltrexone group, as the participants knew they need only avoid taking the naltrexone tablets to receive the strong reward component associated with heroin use.

A large number in each group admitted to using heroin once or twice; however, the majority soon realized that it had no subjective effect, and knowing that it would only be a waste of time and money, went on to achieve abstinence during the study period. If any insight can be derived from this study, it is that those who were criminally inclined with a history of early delinquency and ongoing criminal behavior, irrespective of the need to obtain their drug (mainly men), and those who experienced abuse early in life and were inclined to use opiates to self-medicate (mainly women), seemed more likely to relapse. Notwithstanding, time spent in treatment had the effect of improving outcomes in general.

The other prominent feature of this study was the large number of people who were noncontactable, especially in the period from six to 12 months, during which this figure represented almost one-fourth of the participants in each group. These individuals may have been abstinent, but this could not be confirmed.

The present study would seem to provide strong preliminary evidence that the use of naltrexone implants is an effective solution to the problem of compliance, and that the effect tends to last for some time after the antagonistic effects of the implant have worn off. It seems that the lack of positive reinforcement (i.e., no subjective effect), strong negative reinforcement (i.e., wasting money) associated with using opiates, and lack of craving while an implant is releasing naltrexone into the body, are sufficient to prevent drug use. This allows time for the development of more adaptive coping behaviors, and for the patient, time to deal with the underlying psychological issues that so often compel people to use these drugs. It remains to be seen how many patients remain abstinent at longer follow-up intervals, although the trend seems to be that with more time spent in treatment and the ability to effect change in lifestyle, the more chance that long-term recovery will be sustained.

Overall, this study demonstrates the potential for naltrexone implants to improve compliance rates, increase time spent in treatment, and improve abstinence rates, as opposed to oral naltrexone.

Study limitations

This study would have produced more robust results if subjects had been randomly allocated to each treatment condition, whereas here patient groups were self-selected. Perhaps the patients who chose oral naltrexone might have been less motivated, selecting a treatment method that they felt they could opt out of at any point. Alternatively, this group may have felt they wanted to take responsibility for their own recovery and not proceed with the "easy way" of an implant, or as mentioned previously, it may have simply been that they could not afford the implant.

It is interesting to note that at the time of collecting these data, the ratio of people opting to use oral naltrexone compared to the implant has changed dramatically. Very few patients, who now come to our clinic for treatment, choose oral naltrexone (less than 10 percent), and many come to have an implant inserted after completing detoxification elsewhere. Reasons for not having an implant in the group we studied may have reflected some misgivings about the relative effectiveness of the implant or misunderstandings about how it worked, rather than financial concerns, as we assumed at the time. It seems that as word about the effectiveness of the implant has spread, financial concerns have not had as much influence.

This study also was comprised of patients who were screened for serious psychiatric problems, levels of motivation, and social support. Motivation was defined as the demonstration by intrinsic signs, and not by extrinsic signs, of behavioral hurdles placed in the path of a person who is already low on self-esteem and self-efficacy. As can be seen from our results, most patients were

Table 5. Group comparison for number of patients relapsed to opiate use		
Classification	**Naltrexone implant**	**Oral naltrexone**
Abstinent six mos	33 (80.5)	23 (54.5)
Relapsed six mos	6 (15)	15 (35.5)
Noncontactable six mos	2 (5)	4 (10)
Abstinent 12 mos	25 (61)	17 (40.5)
Relapsed 12 mos	7 (17)	16 (38)
Noncontactable 12 mos	9 (22)	9 (22)
Numbers in parentheses are percentages.		

moderately to highly depressed, and therefore tended to lack motivation. It has always been our contention that the use of naltrexone should be limited to those who have a reasonable chance of long-term recovery. That notwithstanding, it can also be seen that the patient group presented with a range of psychological problems that must be attended to, a history of multiple detoxification attempts, and often polydrug use. None of these problems was considered a bar to inclusion in the program. As other researchers have pointed out, naltrexone should be targeted to those who can most benefit, and the aim of research is to clearly define the best way to use this medication.[24]

In the present study, we relied on self-report and corroboration of support people to verify patient compliance to naltrexone and abstinence from opiates. Having patients give regular urine drug screens would also have lent more certainty to our reported results, especially effective levels of naltrexone.

Future research

Future research should include random allocation of subjects to each treatment condition, although matching on significant confounding variables may be warranted before random allocation. It is also important to maintain other strategies that have been shown to enhance outcomes and maintain the safety of the patients. Neither group maintained counseling for as long as it was felt desirable, and this often related to patient financial concerns. Not only is this in keeping with the research, but there is also a strong ethical argument to proceed in this manner and to ensure equal access to supportive counseling. Even with the provision of counseling, however, there appears to be a group of patients who are not likely to benefit from use of naltrexone and for whom methadone or buprenorphine is the preferred treatment.

To obtain valid data, it is important that future research also includes biological tests of opiate and other drug use to verify self-reports. Although regular checks of naltrexone levels and screening for opiates would lend more credence to the results, we are confident about the accuracy of the data collected. The timeframe for collection of data should also be extended to a point some years beyond the end of implant effectiveness. It is believed that the longer a person is in treatment the better the outcome, and certainly the use of implants facilitates this. However, it has yet to be shown that the use of naltrexone implants translates directly into long-term improvement.

The present study indicates the potential of the use of these devices in the treatment of opiate dependency. Clinical trials that are properly constituted with ethical approval and that extend well beyond the blocking effect of the implant, combined with biological testing of drug use, are necessary to confirm the results of this study.

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ORIGINAL ARTICLE

Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the Pain Assessment and Documentation Tool

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ABSTRACT

The increasingly common practice of long-term opioid therapy for chronic noncancer pain must be guided by ongoing assessment of four types of outcomes: pain relief, function, side effects, and drug-related behaviors. Our objective was to gather initial pilot data on the clinical application of a specialized chart note, the Pain Assessment and Documentation Tool (PADT), which was developed and tested with 27 physicians. This pilot test provided the means to collect cross-sectional outcome data on a large sample of opioid-treated chronic pain patients. Each of the physician volunteers (located in a variety of settings across the United States) completed the PADT for a convenience sample of personally treated chronic pain patients who had received at least three months of opioid therapy. Completion of the PADT required a clinical interview, review of the medical chart, and direct clinical observation. Data from the PADTs were collated and analyzed. The results suggested that the majority of patients with chronic pain achieve relatively positive outcomes in the eyes of their prescribing physicians in all four relevant domains with opioid therapy. Analgesia was modest but meaningful, functionality was generally stabilized or improved, and side effects were tolerable. Potentially aberrant behaviors were common but viewed as an indicator of a problem (i.e., addiction or diversion) in only approximately 10 percent of cases. Using the PADT, physician ratings can be developed in four domains. In this sample, outcomes suggested that opioid therapy provided meaningful analgesia.

Key words: opioids, noncancer pain, assessment, documentation, outcomes

INTRODUCTION

The use of opioid analgesics is a cornerstone of pain management. Although still controversial, chronic opioid therapy for noncancer pain is becoming a more widely accepted therapeutic option.[1-5] A large gap exists between the empirical literature on the safety and efficacy of long-term chronic opioid therapy and the expanding use of this approach in clinical practice.

To use opioids safely and effectively, candidates for therapy should be appropriately selected, drug administration should be optimized, and ongoing monitoring should provide detailed information in multiple domains. Based on extensive clinical experience, four domains have been proposed as most relevant: pain relief, side effects, physical and psychosocial functioning, and the occurrence of any potentially aberrant (or nonadherent) drug-related behaviors.[6] These domains have been summarized as the "Four As" (analgesia, activities of daily living, adverse side effects, and aberrant drug-taking behaviors).[7] The monitoring of these outcomes over time should inform therapeutic decision-makers and provide a framework for documentation of the clinical use of these controlled drugs.

Suboptimal physician monitoring and documentation during opioid therapy is a significant problem[8] and may have adverse clinical, medicolegal, and regulatory implications.[9] In an effort to improve the approach to monitoring and simultaneously provide a standardized chart note for the purposes of documentation, a brief, physician-rated Pain Assessment and Documentation Tool (PADT)

was developed and successfully field tested.[10] The PADT was developed from a series of questions and checklists that together assessed each of the Four As.

PADT items that evaluated pain relief and function were modeled on the Brief Pain Inventory,[11] a validated patient-rated instrument. Side effects were tabulated. A list of potentially aberrant drug-related behaviors was developed from descriptions in the medical literature[3] and clinical experience. The list included drug-related behaviors that are illegal (e.g., altering of prescriptions, lying to obtain a controlled substance, drug diversion), those that strongly suggest addiction (e.g., continued use despite harm), and those that raise concern about drug abuse or addiction but are not, in themselves, diagnostic (e.g., multiple requests for higher doses, repeated visits to an emergency room).

The process by which the PADT was developed and refined, using application of the tool clinically by physicians, has been described previously.[10] The pilot clinical application itself yielded outcomes data on a large and diverse patient sample. These data, described later, reflect the perceptions of treating physicians pertaining to a broad set of outcomes achieved by a selected population of opioid-treated chronic pain patients. As such, they represent a type of survey data that has not heretofore been explored as a means to define the spectrum of responses observed in clinical practice. Our objective was to gather initial pilot data on the clinical application of a specialized chart note, the PADT, which could then be used in the design of future validation and reliability trials.

METHODS

Procedure

Twenty-seven physicians attending a training program for a pain-oriented speakers' bureau were recruited to participate in the pilot study. The physicians practiced in all regions of the continental United States and spent at least part of their clinical practice time caring for patients with chronic noncancer pain. They were chosen for their collective expertise in pain management and their ready access to patients with chronic pain issues being maintained on opioid therapy. Although this is a potential source of bias, it was felt that having physicians with interest and expertise in pain administer the PADT was important for gathering initial data on the tool.

The physicians were given the checklists that together constituted the first draft of the PADT and were asked to identify patients from their practices who had been receiving opioid therapy for a period of at least three months. They were then instructed to obtain the information necessary to complete the PADT from a clinical interview, review of the medical chart, and direct clinical observation.

A total of 388 patients with a diverse assortment of pain syndromes and a wide variety of opioid and adjuvant medications were interviewed for the study. As stated previously, all patients with chronic noncancer pain were eligible to be selected as long as they had been on opioids for a period of three months or longer. This selection criterion was chosen in the hopes of obtaining a patient sample that was not new to the various physicians so they could render judgments based on some established relationship. In addition, it was hoped that this time period would also maximize the chance that any "dose-finding" for opioids would be well underway or stable in those who were selected. After the checklists were completed by the physician, the forms underwent removal of identifying information and were sent to the lead investigator for analysis.

Study instrument

The PADT was developed by the investigators with input from a group of experts in pain and addiction medicine.[10] The tool has four sections: physician demographics, patient demographics, assessment of the Four As, and the physician's diagnostic impression of the patient. The physician demographics section includes information such as age, mode of practice, practice location, and the number of prescriptions written for opioids in the last month. The patient demographics section includes gender, ethnicity, employment status, pain diagnosis, and medical history.

The section on the Four As requires the physician to rate the effectiveness of the analgesic regimen, the presence of side effects and their severity, the current impact of the pain on function, and the presence of any aberrant drug-taking behaviors. The last section, physician impression, asks the physician to note whether aberrant drug-related behaviors, if present, most likely owed to addiction, unrelieved pain, criminal intent (diversion), or nonaddiction-related psychiatric disturbance (e.g., depression, anxiety, personality disorder).

Analysis plan

The goal of the study was to characterize the impressions of physicians who were treating patients on chronic opioid regimens according to the PADT. To this end, the data analysis plan was to collate and describe the participating physicians and the patients they interviewed. A series of descriptive analyses was conducted, including frequency and mean calculations. Overall, the objective was to simply tally and report the findings from the clinical application of the PADT. However, we were also interested in some exploratory areas that might lead to future research questions. Exploratory analyses were conducted on how each of the Four As related to each

other and to demographic information through a series of Pearson correlations and t-tests. To accomplish this, global scores for each of the Four As were created by summing the items from each section of the instrument. As a final analysis, a series of one-way analysis of variance (ANOVA) tests was conducted to determine whether or not the opioid regimen chosen for the patient had an effect on any of the Four As.

RESULTS

Physician data

A total of 27 physicians volunteered to participate in the trial. Physicians interviewed an average of 14.4 patients, for a total sample of 388 patients (described later). The majority of physicians were in the 41- to 50-year-old range (n = 15, 55.6 percent), followed by those in the 51- to 60-year-old range (n = 6, 22.2 percent), and then the 30- to 40-year-old range (n = 5, 18.5 percent). Specific ages were not requested to avoid potential identification of the physicians, given the small physician participant pool. Most were male (n = 21, 77.8 percent), and all were board certified (n = 27, 100 percent) in their specialty areas. The most common mode of practice was family practice (n = 10, 45.5 percent), followed by anesthesia (n = 7, 31.8 percent), and neurology (n = 2, 9.1 percent).

Most physicians were located in an urban setting (n = 18, 69.2 percent), followed by those in suburban (n = 7, 26.9 percent) and rural settings (n = 1, 3.9 percent). Most practice settings were in an office (n = 10, 50 percent) or university hospital (n = 5, 25 percent). The physicians reported an average of 14 years in practice (SD = 10.6). Most stated that more than one-half of their patients had chronic pain (mean = 62.7 percent, SD = 36.6); overall, they treated an average of 912.6 patients per year with chronic pain (SD = 1,211.9).

The physicians reported that they managed more than one-half of their chronic pain patients with an opioid regimen (50.6 percent, SD = 31.3), and that they treated an average of 576.9 patients per year with opioids (SD = 927.2). Table 1 lists the estimated number of prescriptions for opioids that were written by the physicians during the month prior to completion of the PADT. Oxycodone-containing products (mean = 39.2, SD = 71.9), hydrocodone-containing products (mean = 31.9, SD = 37.2), and methadone (mean = 16.4, SD = 27.6) were the most frequently prescribed opioid analgesics.

Patient data

A total of 388 chronic pain patients were interviewed and rated by the physicians. The sample was comprised of 233 women (63.7 percent) and 133 men (36.3 percent), and had a mean age of 50.1 years (SD = 13.6, range = 21 to 87 years, median = 47.0). Most were white (n = 322, 84.1 percent), followed by African American (n = 29, 7.6 percent) and Hispanic (n = 23, 6.0 percent). Most had some college experience (n = 115, 30.5 percent), followed by those who were high school (n = 93, 24.7 percent) or college (n = 63, 16.7 percent) graduates. Many were disabled (n = 160, 41.2 percent), while others were working full-time (n = 80, 20.6 percent), or retired (n = 60, 15.5 percent). Before their pain diagnosis, most of the patients were working full-time (n = 250, 67.4 percent) or part-time (n = 32, 8.6 percent). They were most likely to be married (n = 218, 56.2 percent), followed by divorced (n = 76, 19.6 percent), single (n = 47, 12.1 percent), and widowed (n = 32, 8.3 percent). Most lived with a spouse (n = 208, 53.9 percent) and the next largest group lived alone (n = 95, 24.6 percent).

Nearly one-half of the sample (n = 178, 45.9 percent) reported only one source of chronic pain; the remainder endorsed two or more causes of pain. Somatic pain was documented for 291 patients (75 percent), followed by mixed/other sources (n = 160, 41.2 percent), neuropathic pain (n = 125, 32.2 percent), and visceral pain (n = 37, 9.5 percent). Only 17.8 percent of the sample (n = 69) stated that the pain was related to a past job, and an additional 4.4 percent (n = 17) stated that the pain was related to their current job.

Outcomes: The Four As

Analgesia. On a scale of 0 to 10 (0 = no pain, 10 = worst pain imaginable), patients rated their average pain for the prior week as 5.4 (SD = 2.2) and their worst pain during that time as 7.9 (SD = 2.1). When asked what percentage of pain had been relieved since starting treatment, the average response was 57.8 percent (SD = 24.4). More than three-fourths of the patients (n = 301, 77.6 percent) stated that they had a meaningful degree of pain relief, and 85.1 percent of the physician responses (n = 330) also indicated that they believed the degree of pain relief from the analgesic regimen was clinically meaningful.

Activities of daily living. Physicians rated aspects of functioning as "better," "same," or "worse" compared to a baseline defined as before the current opioid therapy (Table 2). Overall, physicians rated their patients' physical (n = 307, 79.1 percent), psychological (n = 250, 64.4 percent), and social functioning (n = 214, 55.2 percent) as improved since starting their current regimen.

An index of declining function was created by adding all the domains of function that were scored by the physician as declining since the opioid regimen was begun. The domains included physical functioning, mood, family relationships, social relationships, sleep pattern, occupational functioning, and overall functioning. Therefore, a range of 0 to 7 was possible for domains that had worsened. Overall, only 16.3 percent (n = 63) of the sample

Table 1. Frequency of opioids prescribed in the past month				
Item	**n**	**Mean (SD)**	**Median**	**Range**
Morphine products	27	14.50 (18.00)	8	0 – 80
Oxycodone-containing products	27	39.23 (71.85)	15	0 – 350
Fentanyl patch	27	15.54 (25.62)	5	0 – 125
Methadone	27	16.42 (27.55)	6.5	0 – 100
Hydromorphone	27	5.50 (6.49)	3.5	0 – 20
Tylenol #3	27	3.92 (3.43)	3	0 – 10
Tylenol #4	27	1.27 (2.44)	0	0 – 10
Hydrocodone-containing products	27	31.85 (37.23)	15	0 – 125
Tramadol	27	12.92 (16.02)	5	0 – 50
Levorphanol	27	0.15 (0.46)	0	0 – 2
Dihydrocodeine	27	0.08 (0.27)	0	0 – 1
Butorphanol	27	0.35 (0.69)	0	0 – 2
Pentazocine	27	0.31 (0.68)	0	0 – 2
Others	27	0 (0)	0	0

SD, standard deviation.

was rated as worsening in one or more domains of function. This was broken down as follows: one (n = 31, 8 percent), two (n = 9, 2.3 percent), and three (n = 15, 3.9 percent).

Adverse effects. The most common side effects and ratings of their severity by the patients are listed in Figure 1. A total of 132 (34 percent) patients required treatment for constipation, 23 (5.9 percent) for nausea, 14 (3.6 percent) for sedation, and seven (1.8 percent) for mental clouding. Forty-nine patients (12.6 percent) stated that side effects forced them to cut down their medications, and five (1.3 percent) stated that they had to stop taking the medications entirely. Ninety percent (n = 349) considered the side effects of the medications tolerable.

Only 32.8 percent (n = 127) of the sample rated one or more of the possible adverse side effects as moderate or severe in nature. Most reported only one (n = 97, 25 percent) or two side effects (n = 25, 6.4 percent) as being moderate or severe.

Potentially aberrant drug-related behaviors. When asked whether there was concern about a patient's responsibility in the use of the current analgesic regimen, physicians reported 71 times (18.3 percent) that they were concerned, 299 times (77.1 percent) that they were not concerned, and 13 times (3.4 percent) that they were uncertain. When asked whether the patients' families raised concerns over their use of medications, the physicians responded "yes" 53 times (13.7 percent) and "no" 330 times (85.1 percent).

In a series of related questions, physicians rated the degree to which they suspected problematic behaviors on the part of their patients. Table 3 lists the behaviors as well as the physicians' impressions. Overall, the physicians believed that their patients answered clinical questions in a completely truthful (n = 308, 79.4 percent) or somewhat truthful (n = 74, 19.1 percent) manner. In only two cases (1.0 percent) was it felt that their patients were "not at all truthful." In 46 cases (11.9 percent), physicians concluded that their patients had exhibited worrisome aberrant drug-taking behaviors, and in 40 cases (10.3 percent) they felt that the aberrant behavior was related to unrelieved pain.

Nearly one-half of the sample (n = 173, 44.6 percent) was rated as having engaged in at least one of the 29 listed aberrant drug-related behaviors. The range of aberrant behaviors was from 0 to 17, with a mean of 1.48 behaviors per patient (SD = 2.65). Most often, patients engaged in one (n = 62, 16 percent) or two (n = 36, 9.3 percent) aberrant drug-related behaviors. When examining the percentage of patients engaging in multiple behaviors, 19.3 percent of the sample engaged in three or more potentially aberrant behaviors, with 10.8 percent of the

Table 2. Results of patient interviews and physician impressions on activities of daily living (N = 388)				
	Better	**Same**	**Worse**	**Missing**
Patient interview				
Physical functioning	303 (78.09)	67 (17.27)	14 (3.61)	4 (1.03)
Mood	368 (69.07)	96 (24.74)	22 (5.67)	2 (0.52)
Family relationships	219 (56.44)	151 (38.92)	16 (4.12)	2 (0.52)
Social relationships	194 (50.0)	171 (44.07)	20 (5.15)	3 (0.77)
Sleep pattern	226 (58.25)	129 (33.25)	30 (7.73)	3 (0.77)
Occupational functioning	155 (39.95)	176 (45.36)	19 (4.90)	38 (9.79)
Overall functioning	289 (74.48)	81 (20.88)	12 (3.09)	6 (1.55)
Physician impression				
Physical functioning	307 (79.12)	64 (16.49)	13 (3.35)	4 (1.03)
Psychological functioning	250 (64.43)	112 (28.87)	22 (5.67)	4 (1.03)
Social functioning	214 (55.15)	137 (35.31)	29 (7.47)	8 (2.06)
Numbers in parentheses are percentages.				

sample having engaged in five or more of these behaviors.

Table 4 indicates the aberrant drug-related behaviors recorded by the physicians and the average number of occasions on which a behavior occurred. Because this was a cross-sectional survey, physicians noted the number of times an aberrant behavior occurred over the course of treating the given patient. Requests for frequent early renewals (n = 69) and insisting on a particular medication (n = 63) were the most common potentially aberrant behaviors. Five patients (1.3 percent) had been arrested or detained by the police, four (1.0 percent) had associates who were arrested or detained by the police, and six (1.5 percent) were victims of abuse or violence.

Exploratory analyses of the Four As

It was of interest to determine whether the Four As were correlated and how they were associated with psychological, alcohol, or drug problems or demographic variables. For purposes of determining analgesia level, the question pertaining to the percentage of pain relieved was selected for the analysis. For the remaining domains, summary scores (i.e., total score of each item in that domain) were used as global representations of outcome. Only the activities of daily living domain was significantly related to the other three. Decreased functioning as measured by activities of daily living was associated with a smaller degree of reported pain relief ($r = –0.20$, $p < 0.01$), as well as more problems with side effects from medications ($r = 0.17$, $p < 0.01$) and a greater number of aberrant drug-related behaviors being endorsed ($r = 0.10$, $p < 0.05$).

Several other relationships were significant and noteworthy. Concerning the demographic variables, gender was associated with reported pain relief ($t1, 361 = 2.09$, $p < 0.05$), with women (mean = 55.8 percent, SD = 25.5) experiencing a lesser percent of pain relief from treatment than men (mean = 61.4 percent, SD = 22.3). Younger age was also found to be significantly related to an increase in the number of aberrant drug-related behaviors recorded ($r = –0.21$, $p < 0.01$).

With regard to psychiatric issues, a past psychiatric history of any kind was associated with engaging in more aberrant drug-related behaviors ($r = –0.14$, $p < 0.01$). A final set of interesting correlations concerned the smoking status of the patients. A history of having smoked cigarettes was associated with poorer functioning in their activities of daily living ($r = –0.14$, $p < 0.01$). Current smoking activity was associated with a greater number of aberrant drug-related behaviors ($r = –0.17$, $p < 0.01$).

Exploratory statistics based on medication

Another key area of interest concerned the effect of

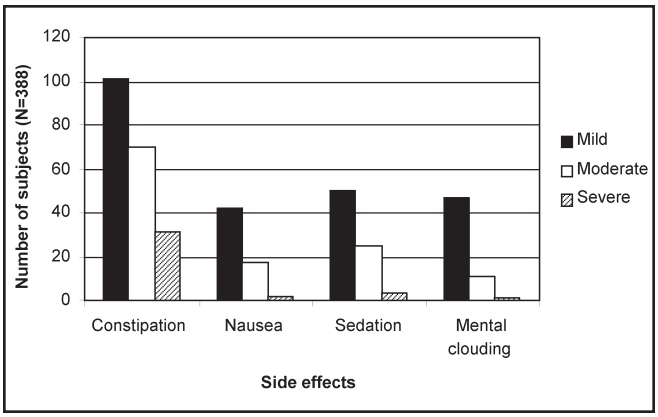

Figure 1. Side effect severity of opioid therapy (N = 388).

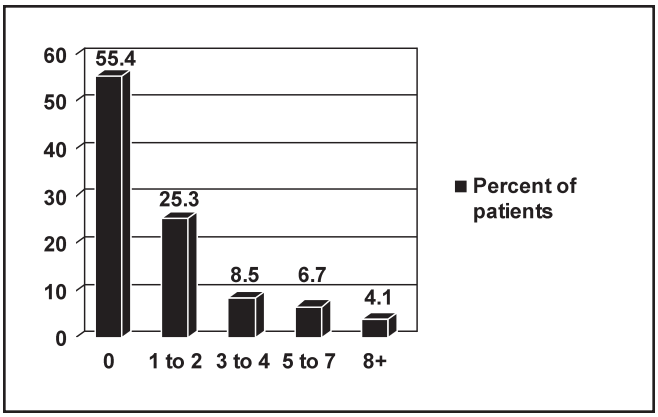

Figure 2. Total number of aberrant behaviors endorsed by each patient (N = 388).

medication choice on the Four As. Using the summary scores and analgesia items mentioned in the previous section, a series of one-way ANOVAs was conducted to compare long- and short-acting opioids. Long-acting opioids were associated with more adverse side effects than short-acting opioids ($F1, 381 = 11.86$, $p < 0.01$). There were no significant differences between these categories of opioids concerning percent pain relief, number of impairments in activities of daily living, or number of aberrant drug behaviors exhibited.

DISCUSSION

The use of opioids for noncancer pain must be accompanied by a careful and ongoing assessment of outcomes supported by documentation. In this work, we examined outcomes using a tool designed to guide this assessment and generate a comprehensive note to improve record-keeping. We attempted to put this tool into the hands of busy clinicians and examine perceptions of outcome. It is important to note that these results do not represent an epidemiological survey of outcome in chronic opioid therapy—it was neither designed (i.e., sampling) nor powered to be interpreted in this fashion.

Thus, it is important to recognize the limitations of this design to better appreciate what can be learned from such a naturalistic cross-sectional observation of pain therapy with opioids. The physicians who took part in this study were not selected at random, and all had some expertise and familiarity with chronic pain management. Indeed, chronic pain patients made up more than one-half of their respective medical practices. In addition, the patient sample was one of convenience, needing to be on an opioid regimen for a period of at least three months. In addition, the physicians interviewed the patients directly and completed all of the assessment, which could lend to a bias for under-reporting on the part of patients, especially concerning the aberrant drug-taking behaviors. Indeed, we should expect that the patients were not totally forthcoming to their physicians, although a number of aberrant behaviors were reported. Thus, the data reported in this paper are subject to multiple selection biases and may not be representative of outcome in chronic opioid therapy; in this respect, it is not terribly different from many short, often industry-sponsored, community-based studies of opioid therapy in the extant literature. However, this type of design does involve a naturalistic look at pain practice as opposed to a more contrived clinical trial and also offers some insight into how doctors perceive outcomes in their long-term opioid-treated patients.

The PADT does appear to describe outcome in a comprehensive fashion and might prove to be a useful addition to record-keeping in chronic opioid therapy. It may also aid in improving the adherence to guidelines for opioid use and the safe use of opioids for noncancer pain. However, replication studies focusing on more stringent reliability and validity data for the tool are needed. We conclude that this study is an important first step toward creating a clinically applied tool for documentation.

In describing outcomes in these patients, the PADT helps to explicate the Four As of pain outcomes. The patients described in this study overall were assessed as having moderate to severe pain while on opioid therapy. Their degree of pain relief is best described as modest, but meaningful, in that it was overwhelmingly felt to make "a real difference" in patients' lives. The actual degree of relief noted was a diminution of approximately 58 percent from baseline pain. This is an important and telling observation, one that says much about the need to set appropriate expectations for opioid therapy. With most patients attaining this level of pain relief, a figure which compares favorably with those previously reported in the literature,[12,13] it is clear that the average patient will have significant residual pain with which to cope. Patients should be informed of this when first going into treatment, thus helping them to see they will likely require lifestyle changes, fitness enhancement, coping strategy acquisition, etc. to realize a satisfying outcome. Patients who have the capacity to improve in their function with

Table 3. Physician-reported impressions of behaviors			
Behavior	**Yes**	**No**	**Do not know**
Opioid prescription abuse/addiction	23 (5.93)	342 (88.14)	18 (4.64)
Prescription opioid dependence	92 (23.71)	261 (67.27)	19 (4.90)
Prescription drug abuse/addiction	11 (2.84)	358 (92.27)	9 (2.32)
Prescription drug dependence	6 (1.55)	349 (89.95)	10 (2.58)
Alcohol abuse/addiction	5 (1.29)	364 (93.81)	11 (2.84)
Alcohol dependence	9 (2.32)	349 (89.95)	12 (3.09)
Other illicit drug abuse/addiction	7 (1.80)	356 (91.75)	17 (4.38)
Any illicit drug dependence	0	351 (90.46)	15 (3.87)
Drug-taking behavior related to criminal intent	2 (0.52)	367 (94.59)	10 (2.58)
Drug-taking behavior resulting from family dysfunction	16 (4.12)	346 (89.18)	17 (4.38)
Has a psychiatric disorder that may be causing or contributing to aberrant drug-related behavior	21 (5.41)	344 (88.66)	16 (4.12)
Numbers in parentheses are percentages.			

this degree of relief are probably fairly uncomplicated and could be considered for opioid therapy in routine medical management settings. Patients who do not functionally improve with this degree of relief are likely to have other clinical problems, such as comorbid psychiatric issues (i.e., depression, anxiety, secondary gain issues, a deep-seated need to stay in the sick role), and would require specialized attention for a satisfying outcome to be realized.

Additionally, nearly four of five patients were seen as improved in overall functioning with this rather gross approach to assessment and documentation. This is an important consideration in the wake of the negative attention focused on opioid therapy owing to OxyContin abuse.[14-15] There is a suggestion of the validity of these ratings given that most of the improvement comes in the areas of physical functioning and mood where opioids have their most direct impact.

Opioid side effects were common in this study, but overwhelmingly seen as tolerable and manageable by patients and physicians. Constipation was the most common side effect and was severe in one-third of patients, which is similar to results found elsewhere.[16,17] Side effects can detract from ability to function and must be aggressively managed.

The results from this study in the area of aberrant drug-related behavior, should they be replicated in an adequately designed and powered epidemiological survey, are powerful. For many years, pain experts have argued that addiction is rare in people receiving adequate and appropriate opioids as part of the medical management of pain.[18,19] While this may be true, large-scale studies are, in fact, lacking.

Addiction may not be the central issue facing pain clinicians. In the phenomenology of the pain clinician, the management of noncompliance behavior arising from multiple causes is the central issue. These results suggest that noncompliance is fairly common and challenges the clinician to note, understand, and react to it in nearly 50 percent of patients. Noncompliance has a complex "differential diagnosis," including addiction, uncontrolled pain (pseudoaddiction), self-medication of psychiatric and physical symptoms other than pain and situational stressors, family dysfunction, and diversion.[6,20-22] The clinician must know how to assess and come to decisions about the meaning of this behavior and importantly, document about it. Physicians noted noncompliance in 45 percent of patients but considered it worrisome only one in 10 times, and so must have a repertoire for responding to psychiatric and other causes of noncompliance.

Behaviors varied tremendously in their frequency. The very aberrant and illegal behaviors were rare and occurred in less than 2 percent of patients overall. The less obvious behaviors were common, seen in the cases of nearly one in five patients in some instances. Most behaviors were seen in approximately 6 percent of

Table 4. Noted aberrant drug-taking behaviors and mean number of occasions observed by physician or through reports from family/outside sources (N = 388)		
Behavior	**n**	**Mean number of occasions noted per patient (SD)**
Requests frequent early renewals	69	2.88 (2.35)
Asks for medication by name	63	2.68 (1.79)
Increases dose without authorization	51	2.59 (2.38)
Requests higher dose in a worrisome manner	33	3.29 (2.45)
Reports lost/stolen prescriptions	32	1.36 (0.54)
Oversedation	31	4.92 (13.12)
Negative mood change	30	3.05 (2.23)
Attempts to obtain medication from other doctors	30	1.98 (1.33)
Successfully obtains medications from other doctors	27	1.80 (1.13)
Misses appointments except for medication renewal	22	2.23 (1.57)
Does not comply with other recommended treatments	21	3.26 (2.65)
Reports no effect of other medications	18	2.78 (1.77)
Uses medication for purpose other than described	17	2.21 (1.10)
Declining physical function	16	2.38 (1.82)
Declining social function	13	2.15 (1.63)
Declining psychological function	13	2.04 (1.51)
Intoxicated seeming	13	2.62 (1.82)
Contact with street culture	13	1.31 (0.63)
Abusing alcohol or street drugs	11	1.27 (0.47)
Staff splitting	10	2.70 (1.64)
Involved in motor vehicle or other accident	7	1.14 (0.38)
Increasingly unkempt or impaired	6	2.33 (1.21)
Hoarding of medications	6	2.00 (1.67)
Worrisome drug effects	5	2.30 (1.72)
Changes route of administration	4	3.50 (2.89)
Engaging in the sale of sex to obtain drugs	0	0
SD, standard deviation.		

patients, an interesting observation in that the rate of substance abuse/addiction in the United States is thought to be approximately 6 to 10 percent of the population,[23-25] and recent reports in chronic pain populations have ranged from 3 to 18 percent.[26] Thus, if this observation is replicated in larger epidemiologic surveys, it suggests that the subgroup of patients expected to be problematic on opioids could have been predicted from the baseline population norms.

Inter-relationships between the Four As and other patient variables

It is interesting that there was not a greater degree of intercorrelation among the Four As. Although they tap vastly different areas, overall we expected that the chronic pain experience would lend an overarching thread to combine these four important areas. Indeed, only the second "A," activities of daily living, was significantly correlated to the other aspects of the chart note. This may suggest a rather important role for paying attention to the functionality of patients being treated for chronic pain. Poor functioning in this sample was related to lesser amounts of pain relief, more adverse side effects, and a greater number of aberrant drug-related behaviors being engaged in by patients. It might be that assessing functionality is a rather innocuous means of getting a global impression of the patient and whether or not he or she is going to ultimately respond to opioid therapy. This notion has been at least initially supported by a recent study of 158 patients treated in an inpatient chronic pain setting.[27]

Regarding aberrant drug-related behaviors, it is important to highlight the predictors that were significant in this study. Those who were younger, had a psychiatric history of any kind, and were current smokers were all more likely to engage in a greater number of aberrant drug-related behaviors. Further assessment of psychiatric history, addiction history, and smoking status and the ability of these factors to predict aberrant behavior is warranted.

CONCLUSION

We attempted to implement a new documentation aid, the PADT, in a naturalistic study of outcomes in opioid therapy. Although subject to the types of selection biases that are common in the field of community-based trials in pain management, the study does suggest that the measure records a comprehensive view of outcomes. The study also suggests that, in general, patients on ongoing opioid therapy were seen as having favorable outcomes by their treating physicians. Future trials are needed to explore the factor structure, reliability, and validity of the tool.

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ORIGINAL ARTICLE

Electronically monitored single-use patient-controlled analgesia pumps in postoperative pain control

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ABSTRACT

The present study was performed to establish whether analgesic consumption in the first four postoperative hours is a suitable basis for selecting the demand dose and predicting the likely analgesic requirement over the next 20 hours with single-use patient-controlled analgesia (PCA) pumps, and to establish whether this method provides effective pain control.

Forty-two patients who had undergone a laparotic gynecological procedure (hysterectomy) were given an electronic PCA pump (Abbott Lifecare, Abbott Laboratories, Abbott Park, IL) for four hours (phase I) with a demand dose of 1 mg piritramide and a lockout period of five minutes for dose titration. Piritramide's potency is comparable with that of morphine. The patients then received single-use PCA pumps (Baxter Infusor/Watch, Baxter, Deerfield, IL) for the next 20 hours (phase II) with a demand dose of 0.75 mg in Group A and 1.5 mg in Group B, depending on whether more or less than 10 mg pritramide had been consumed in phase I. A specially designed electronic recorder was used to measure the exact amount consumed and number of demands. Patients experiencing pain were free to receive additional piritramide at any time as rescue medication; however, these patients were withdrawn from the study.

Ninety percent of the patients in group A said they were satisfied with or undecided as to the level of analgesia. The corresponding figure in group B was 95 percent. Piritramide consumption was significantly higher in group B than in group A. There were no significant differences between the groups regarding demographic data or duration of surgery, nor did either of these two parameters affect postoperative piritramide consumption. Significant alleviation of pain and improvement in visual analog scale scores from phase I [group A, 4.7 (range, 2.0 to 6.8); group B, 4.6 (range, 3.0 to 8.3)] to phase II [group A, 3.1 (range, 0.4 to 5.2); group B, 3.2 (range, 0.4 to 6.0)] was achieved in both groups. A significant difference in analgesic consumption up to 18 hours postoperatively was seen after dose titration. In the first four hours, the rate of successful demands was significantly higher in group A (80.9 percent) than in group B (40.9 percent). The number of successful demands was comparable in the two groups during phase II (A, 98.8 percent; B, 94.5 percent).

In summary, total opioid consumption during the first four hours after operation showed two groups of patients with significantly different needs for piritramide (< 10 mg per 4 hours or > 10 mg per 4 hours). Two different dose regimes were applied using a high and a low bolus size in the following 20 hours. We concluded that effective pain control without respiratory depression was achieved with single-use PCA pumps. Opioid consumption varied significantly, whereas pain levels did not.

Key words: postoperative analgesia, patient-controlled analgesia, single-use, demand-dose, acute analgesia

INTRODUCTION

Patient-controlled analgesia (PCA) is a highly effective means of providing postoperative pain management.[1] Patients can control their own individual analgesic requirements, thus enhancing user acceptance and satisfaction.[2,3] With proper monitoring, the method is also a safe means of handling strong opioids.[1,4-6] Routine use of electronically controlled PCA pumps is limited by the expense and technical problems involved,[7] and also a lack of available pumps. The need for improved postoperative pain management is amply documented in a number of national and international studies.[8-15] Mechanically operated single-use PCA pumps without electronic recording and control therefore constitute a rational alternative.[16,17] Because of their construction, the demand dose can only be adjusted with systems of this type when filling the pumps, and the lockout period is fixed at a set level. Also, because the demand dose is essential to successful PCA[18-20] and the postoperative analgesic requirement may vary greatly,[2] the present study was performed

to establish whether the postoperative analgesic requirement during the first four hours after surgery established using an electronic PCA pump accurately predicts the analgesic requirement during the subsequent 20 hours and can be used as a basis for setting the demand dose. Another objective of the study was to establish whether single-use PCA pumps provide effective analgesia with no added risk of respiratory depression.

METHODS

A total of 42 American Society of Anesthesiologists class I/II female patients undergoing abdominal hysterectomy were included in the study. Ethics committee approval from our institutional review board was obtained beforehand and written informed consent was obtained from all patients. Patients displaying opioid intolerance, suspected alcohol or drug dependency, analgesic abuse, or inability to understand the method were excluded from participation. All patients were instructed in the method on the day before surgery. The participants were taught how to operate both PCA pumps and when to administer a dose. A demonstration was also shown. The night before surgery, patients received oral premedication with diazepam of 5 to 10 mg. Midazolam 7.5 mg p.o. was administered on the day of surgery before transport to the operating room. General anesthesia was inducted by intravenous injection of pancuronium (1 mg), fentanyl (3 to 5 µg per kg), thiopental (3 to 5 mg per kg), and succinylcholine (1 mg per kg). The patients were intubated and ventilated with 0.5 to 1.5 vol% enflurane or isoflurane and O_2/air (FiO_2 = 0.35). After the surgical procedure, patients were wheeled to the recovery room and connected to an electronic PCA pump (Abbott Lifecare, Abbott Laboratories, Abbott Park, IL) containing pritramide (1 mg per mL, demand dose 1 mg, lockout period 5 min, maximum dose in 4 h = 30 mg). Pharmacological data on piritramide are comparable to those of morphine; its potency is 0.7 of that of morphine. The pharmacological duration of action is six hours. In our study, piritramide consumption was recorded over the four-hour period. According to the findings of Lehmann,[21] the average accumulated piritramide dose within four hours was 8.52 mg in postoperative pain with on-demand pumps. In relation to the type of operation, and to have objectives, we had to fix a certain quantity of opioid consumption from which patients received a low or high demand dose. Patients were allocated to one of two groups on the basis of piritramide consumption over the first four postoperative hours (< 10 mg or > 10 mg) and the demand dose for the subsequent 20-hour period delivered via the single-use PCA pump (0.75 mg or 1.5 mg per demand dose) was set based on these data. The only way that opioid consumption can be altered in single-use PCA pumps is to change the demand dose by the concentration of the administered opioid. Patients who had a higher opioid consumption in phase I were expected to continue this demand in phase II. Patients who had lower opioid requirements in phase I were also expected to have similar demands in phase II.

Group A received piritramide 0.75 mg per demand dose; group B received piritramide 1.5 mg per demand dose. The severity of pain was documented every four hours on the basis of a visual analog scale (VAS, range 0 to 10). A short infusion of piritramide 15 mg as rescue medication was available at any time to patients requiring additional pain relief, who were then withdrawn from the study. The single-use PCA pumps for phase II were from the Baxter Infusor/Watch line (Baxter, Deerfield, IL). The system was filled with piritramide 30 mg in 20 mL of 0.9 percent saline (group A) or with piritramide 45 mg in 15 mL of 0.9 percent NaCl (group B). The pumps were used without a basal infusion, in compliance with the recommendations in the literature on preventing risks and side effects of PCA therapy.[3,22-28] The Baxter systems have a default lockout period of six minutes. The fixed demand dose was set at 0.5 mL. The frequencies and times of demands and doses during the 20-hour observation period were documented on a dedicated electronic recorder; this allowed us to determine each patient's exact piritramide consumption. The patients were monitored continuously during the first four hours in the recovery room and the subsequent 20 hours in the postoperative intermediate care unit (electrocardiogram, blood pressure, pulse oximetry). SaO_2 levels were recorded every two hours. Patients exhibiting oxygen saturation below 95 percent on pulse oximetry were administered oxygen at a rate of 3 L per hour through a nasal tube. The number of such episodes and saturation levels below 90 percent were recorded. Other safety parameters according to the study protocol were spontaneous reports of nausea and episodes of vomiting. The patients were asked to rank the severity of their pain at intervals of no greater than four hours on the basis of the VAS used.

Patient demographics, duration of surgical procedure, and postoperative piritramide consumption were described as means with standard deviations and compared statistically with the U test. Incidences were compared by Chi-square analysis. The data concerning piritramide consumption were compared between the two groups (A/B) and among the two phases (I/II) with the Wilcoxon test. Also used were nonparametric tests for unpaired probes (comparison of groups) with the Wilcoxon test and paired probes (comparison of phases) with the Wilcoxon test. Continuous quantitative parameters were investigated by a correlation coefficient. A t-test was used to show any deviation from 0 of the correlation coefficient. The level of significance was $p < 0.05$.

Table 1. Piritramide use, patient satisfaction, reported side effects, and oxygen saturation			
	Group A (n = 20)	**Group B (n = 20)**	**Statistics**
Piritramide (mg in first four hours postoperative)	6.5 ± 2.6	13.6 ± 2.9	$p < 0.05$
Piritramide (mg in subsequent 20 hours)	16.5 ± 8.9	25.2 ± 14.3	$p < 0.05$
Patient evaluation of treatment effectiveness (percent)			
Satisfied	16 (80)	17 (85)	ns
Undecided	2 (10)	2 (10)	ns
Dissatisfied	2 (10)	1 (5)	ns
Patient side effects			
Nausea	8	3	$p < 0.05$
Vomiting	0	1	ns
Pulse oximetry (first four hours postoperative)			
$SaO_2 < 95$ percent	12	17	ns
$SaO_2 < 90$ percent	0	0	ns
Pulse oximetry (subsequent 20 hours)			
$SaO_2 < 95$ percent	1	2	ns
$SaO_2 < 90$ percent	0	0	ns
Statistics on piritramide use from U1-test and on incidences from Chi-square test; ns, not significant.			

RESULTS

The results of 40 of the original 42 patients were assessable. In one patient's case, the nursing staff threw away the counting module by mistake; in another case, the nurse forgot to open the three-way valve on the indwelling cannula after changing the drip at night. The latter patient required piritramide infusion for pain and was withdrawn from the study. The remaining 40 patients were allocated according to the stated criteria into two groups, depending on whether their piritramide consumption in phase I was more or less than 10 mg (demand dose: group A, 0.75 mg; group B, 1.5 mg). After the first four hours, it was possible to distinguish one group of patients with an average opioid consumption of piritramide of 6.5 ± 2.6 mg and another with a significantly higher consumption of 13.6 ± 2.9 mg (Table 1). There were 20 patients in either group. The two groups did not differ in demographics or duration of surgical procedure (Table 2).

Over the next 20 hours, cumulative consumption was significantly lower in group A (16.5 ± 8.9 mg) than group B (25.2 ± 14.3 mg) ($p < 0.05$). Figure 1 shows the exact time curve of piritramide demand. It can be seen that the difference between the two groups was significant only up to 18 hours postoperatively. No difference at all was discernible after 20 hours. The number of successful dose demands was twice as high in group A (80.9 percent) than in group B (40.9 percent) during phase I. There was no difference between the two groups in terms of the number of successful demands during the subsequent 20 hours (group A, 98.8 percent; group B, 94.5 percent). Significant alleviation of pain from phase I to phase II was achieved in both groups, with VAS in group A of 4.7 (range, 2.0 to 6.8) and 3.1 (range, 0.4 to 5.2) and in group B of 4.6 (range, 3.0 to 8.3) and 3.2 (range, 0.4 to 6.0) in the two phases, respectively.

Figure 2 shows that the patients in both groups were similar regarding severity of pain. There were no significant differences at any time. Only two patients in group A and one patient in group B were unsatisfied with the analgesic regimen. Eighty percent of patients in group A and 85 percent in group B said pain relief had been good (Table 1). Thus, the two groups did not differ significantly in this respect.

Table 1 also shows the observed side effects. The incidence of nausea differed significantly ($p < 0.05$) between

Table 2. Demographic data of patients and anesthesia			
	Group A (n = 20)	**Group B (n = 20)**	**Statistics**
Age (yr)	48.0 ± 8.0	48.0 ± 9.4	ns
Weight (kg)	66.0 ± 12.2	65.0 ± 12.9	ns
Operation duration (min)	133.0 ± 61.0	138.0 ± 59.0	ns
ns, not significant.			

group A (eight patients) and group B (three patients). Vomiting was seen in only one patient (group B). Decline in oxygen saturation measured by pulse oximetry to levels below 95 percent in the first four hours was seen in 12 patients in group A and 17 in group B. In the subsequent 20 hours, oxygen saturation measured below 95 percent was seen in only one patient in group A and two in group B. Saturation levels below 90 percent were not observed in any patient.

DISCUSSION

We found a significant correlation between analgesic consumption in the first four hours after laparotomy and consumption over the subsequent 20-hour period. Single-use PCA systems may represent an alternative to purchasing expensive electronically controlled PCA pumps. The only adjustable variable with single-use PCA pumps is the demand dose. The demand dose appears to be of greater significance for pain relief than adjustment of the lockout period.[2]

Because of their construction, currently available single-use PCA systems allow the demand dose to be set only when filling the pump. However, because the analgesic consumption in the initial postoperative phase may vary greatly,[2] we used an electronic PCA pump in this study to determine the precise individual analgesic requirement and use this as a basis for setting the demand dose for subsequent pain control with the single-use PCA system.

Sources in the literature[19] recommend use of the opioid amount needed in the recovery room as a basis for determining the following day's analgesic requirement for adjustment of conventional postoperative analgesia. On the basis of our own studies on postoperative opioid requirements, we decided on a study design with piritramide use in the first four postoperative hours as a cutoff point for allocating patients to one of two groups (low/high analgesic requirements).

Analysis of time curves showed that differences in dosing behavior persisted up to 18 hours after surgery. The results support the observations of other authors[18,29,30] who propose further graduations in the demand dose in the quest for optimum PCA therapy. Previous studies using single-use PCA pumps mention a single uniform level of 1 mg morphine per demand dose.[31,32] Limitation of demand dose and lockout period to a single standard level for all patients regardless of the type of surgery, gender, and body weight greatly limits the therapeutic potential of PCA pumps, thereby reducing the effectiveness of PCA therapy.

Our study results also corroborate those of other authors[18,19,30] in identifying considerable interindividual variation in analgesic requirements, which can best be addressed by providing individually adjusted demand doses. The specially designed recorder used in this study enabled us to determine the exact dosage behavior of patients using single-use PCA pumps after dose titration. The results showed a large percentage of successful demands by patients in group A (80.9 percent) on the basis of the uniform demand dose of piritramide 1 mg during the first four hours. However, demand failure was much higher in group B, with only 40.9 percent successful demands. During phase II, with different demand dose levels (group A, 0.75 mg; group B, 1.5 mg), there was no longer any difference between the groups regarding the rate of successful demands (98.8 percent and 94 percent, respectively).

Unlike the analysis of dosing behavior, evaluation of severity of pain by VAS disclosed no significant difference between the two groups. Use of the PCA pumps according to the stated regimen brought about continuous pain relief over a 24-hour period in both groups, while piritramide consumption was significantly higher in group B (1.5 mg demand dose) than in group A up to the 18th postoperative hour. Patient assessment of the effectiveness of pain control showed that only two patients in group A and one in group B were dissatisfied with the chosen procedure, showing that 90 percent and 95 percent of patients in each group, respectively, were satisfied with the method or were undecided.

Nausea was reported by eight patients in group A (low

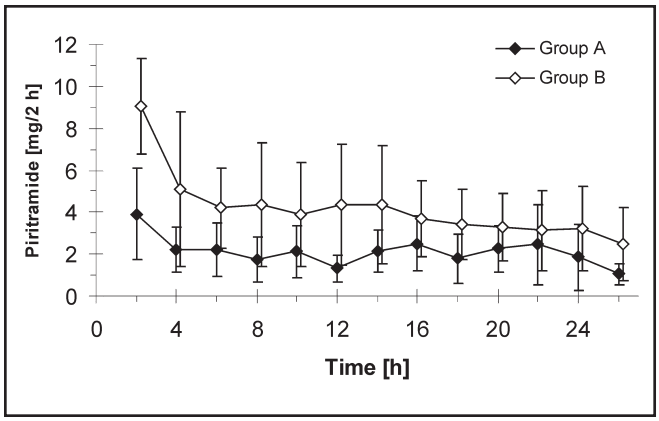

Figure 1: Piritramide consumption (average ± standard deviation) was significantly higher in group B than in group A up to the 18th postoperative hour.

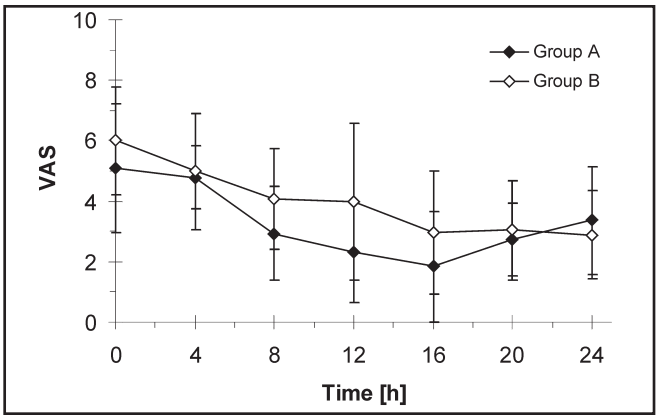

Figure 2: The level of change in the visual analog scale pain scores (VAS, range 0 to 10, average ± standard deviation) was the same in both groups.

demand dose) and three patients in group B. This contrasts with earlier studies in which nausea was more usually associated with higher opioid doses.[1] This observation may be attributable to slightly higher vigilance in the lower-demand dose group; our hypothesis is that the smaller amount of opioid consumption by this group causes lower blood levels of the medication, resulting in the higher vigilance. Interestingly, nausea and vomiting have the same incidence in morphine and piritramide treatment.[33]

One very important aspect in assessing the safety of an analgesic procedure using opioids is the potential to cause respiratory depression. Therefore, all the patients in this study were monitored by pulse oximetry throughout the entire period of observation. Oxygen saturation below 95 percent was seen during the first four hours in 12 patients from group A and 17 from group B. These patients were administered oxygen through a nasal tube. During phase II, oxygen saturation levels below 95 percent were seen in only one patient in group A and two in group B. There were no cases of oxygen saturation below 90 percent. The method thus appears to be safe under the conditions described here.

The results of our study confirm the hypothesis that use of an electronic PCA pump in the first four hours after laparotomy provides a suitable basis for predicting the analgesic requirement during the subsequent 20 hours and can be used to set a fixed demand dose to be administered by single-use PCA pumps. Dose titration can also be performed by manual means in clinical practice (e.g., in the recovery room).[34] Single-use PCA systems provided effective and safe postoperative analgesia in our study. Thirty-one to 75 percent of patients receiving standard analgesia on general wards report severe postoperative pain.[9] The postoperative pain control method presented here seems more effective than the previously described standard ward procedures. Direct costs are higher with the PCA, however, in contrast to standard intramuscular injections.[35]

Titration of the individual opioid requirement enabled us to identify and provide optimum postoperative care for two patient groups with significantly different postoperative piritramide consumption. The patients in both groups were able to steadily reduce their pain with the selected fixed demand dose. None of the patients with a PCA pump required rescue medication. Single-use pumps are not equipped with any kind of alarm function; therefore, dose titration is important to give patients a safe bolus size of opioids. Respiratory depression did not occur in any patient on either regimen during the study.

Single-use PCA pumps are small pumps requiring no main electricity supply or maintenance, which we tested for suitability in a postoperative setting. The pumps are user friendly, with little potential for error in administration. We divided the patients in our study into low- and high-analgesia groups based on prior dose titration and set them up with single-use PCA pumps, which were primed to provide demand doses of piritramide 0.75 mg or 1.5 mg according to group. In this study, we used a dedicated electronic recorder, which gave us important information on the use of those pumps in the postoperative period. Our data indicate that effective 24-hour pain relief was achieved in both patient groups. Based on this, we believe that single-use PCA pumps are suitable for use in conjunction with or as an alternative to electronic pumps and, as such, represent a useful addition to the postoperative pain control armamentarium.

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Cholecystokinin antagonists: Can they augment opioid-derived analgesia?

Gary McCleane, MD

INTRODUCTION

Cholecystokinin (CCK), originally thought to be confined to the gastrointestinal tract, is now known to be colocalized in the gastrointestinal tract and the central nervous system (CNS). In animal models, levels are increased after neural injury and with opioid administration. CCK acts as an antiopioid, and as its levels increase, the extent of opioid-derived antinociception decreases.

Coadministration of a CCK antagonist along with an opioid is associated with an improved level of antinociception. Furthermore, CCK antagonists may prevent antinociceptive tolerance with opioids and even reverse established tolerance. Human studies have now confirmed the proanalgesic effect of some CCK antagonists; however, human investigation of the effect of CCK antagonists on analgesic tolerance has yet to be performed.

Few would argue about the crucial role played by opioids in modern pain management. That said, concerns still remain regarding the partial analgesic efficacy of these opioids and issues such as analgesic tolerance with sustained use, particularly in the field of chronic pain management. Consequently, much investigation is focused on ways of minimizing these concerns.

One line of investigation has been into the role of CCK in the nociceptive processing systems. In contrast to many other areas of study, the insight into its function is matched by the availability of a group of therapeutic entities, the CCK antagonists, which are already extensively investigated. The initial findings from human studies confirm the strong impression from the animal literature that CCK has an integral part in nociceptive processing and that antagonists of its action have a useful proanalgesic effect.

The aim of this review is to outline the results of the extensive investigation that has already been made into the function and action of CCK and its antagonists and hopefully stimulate further interest in the application of this knowledge into human clinical practice.

ORIGINAL DESCRIPTION OF CHOLECYSTOKININ

Following work by Boyden in 1926,[1] which showed that transfusion of blood from cats that had just been fed into other cats made their gall bladders contract, Ivy and Oldberg[2] suggested the existence of a hormone released after feeding that causes gall bladder contraction. They showed that in anesthetized dogs whose carotid arteries were connected to allow cross-circulation between two animals, feeding of one led to gall bladder contraction in both. They named this hormonal substance "cholecystokinin."

CENTRAL LOCALIZATION OF CHOLECYSTOKININ

Some 50 years after the original description of CCK, immunochemical studies started to reveal that not only was CCK present in gut tissues, but also in the CNS.[3-5] In addition, nerves containing CCK were found to be particularly numerous in the guinea pig neocortex, hippocampus, amygdaloid nuclei, hypothalamus, and spinal cord.[6] Further work has confirmed the presence of cells containing mRNA encoding CCK in the rat[7] and human[8] CNS. Levels of CCK in the rostroventral medulla are elevated in cases of neuropathic pain and tolerance.[9] What emerges is that CCK has extensive CNS as well as gastrointestinal representation. There are, however, some differences in the structure of CCK found in the alimentary tract of rodents and that found in the CNS. That predominating in the alimentary system is known as "CCK A," while that localized predominately in the CNS is known as "CCK B" (brain).

In rodent and murine models, "peripheral" CCK, or CCK A, is indeed found predominately in the periphery, but also has some CNS representation. The localization of CCK A varies among differing rodents.[10] In contrast, the density of CCK A receptors in the CNS is significantly higher in primate models.[11] Indeed, Verge and colleagues have shown that 20 percent of monkey dorsal root ganglion neurones express mRNA for CCK irrespective of spinal level. In contrast, mRNA for CCK is found at very

low levels in uninjured rats, and it is only after neural injury that its levels increase substantially.[12] Tissue levels of CCK are unaltered at the site of neural injury, and it is only at the dorsal root ganglion level that increases in CCK are seen. This increase is in mRNA levels for CCK[13-15] and in the extent of CCK binding.[15]

Not only neural injury can increase CCK levels. Gustafsson and colleagues used microdialysis techniques to show that systemic administration of antinociceptive doses of morphine induces a dose-dependent release of CCK-like immunoreactivity in the dorsal horn of the rat spinal cord.[16] Similarly, Zhou and colleagues have demonstrated an 89 percent increase in CCK immunoreactivity in the perfusate of the rat spinal cord after morphine administration.[17] Wiesenfeld-Hallin and colleagues have confirmed these findings and shown that morphine causes release of CCK after axotomy but not during carrageenan-induced inflammation.[18] In rodents, even a single dose of morphine can cause up to a threefold increase in the concentration of brain and spinal cord CCK.[19]

EFFECT OF ELEVATION OF CENTRAL NERVOUS SYSTEM CHOLECYSTOKININ LEVELS

If we accept that CCK is found in both the gastrointestinal tract and CNS and that its levels are elevated after neural injury or opiate administration, then the question of the relevance of such elevated levels arises.

Xu and colleagues[20] studied rats, of which some had a spinal cord injury inflicted. Of these, some exhibited behavioral signs of allodynia. They measured the circulating level of CCK in the cerebrospinal fluid and found that the levels in uninjured animals were almost exactly the same as those in animals with a spinal injury, but not exhibiting signs of allodynia. In contrast, those animals that were spinally injured and did show evidence of allodynia were found to have a very marked increase in level of circulating CCK.

Kovelowski and colleagues[21] have also investigated the role of CCK in neuropathic pain. We know that the CNS exerts facilitatory and inhibitory drives that regulate pain. In animals, spinal section at T8 blocks tactile allodynia, but not thermal hyperalgesia after spinal nerve ligation, suggesting a supraspinal integration of allodynia. They found that injection of CCK-8 into the rostroventromedial medulla was associated with a robust tactile allodynic effect and produced a more modest hyperalgesia. They also showed that the antinociceptive effect of morphine injected into the periaqueductal gray region was substantially reduced in spinal nerve-ligated rats, but that its effect was restored by the concomitant administration of a CCK antagonist. They concluded that activation of descending nociceptive facilitatory pathways is important in the maintenance of neuropathic pain, and that this is dependent on CCK release.

If CCK is injected systemically or perispinally, the antinociception produced by morphine is antagonized.[22] Furthermore, if CCK is injected into the inflamed paws of rats, the antinociceptive effect of fentanyl is reduced and this reduction is blocked by CCK A, but not CCK B antagonists in this species.[23]

EFFECT OF CHOLECYSTOKININ ANTAGONISTS ON OPIOID–DERIVED ANTINOCICEPTION

The studies presented previously imply a role for CCK in nociceptive processing. Although this is of interest, it is of clinical relevance only if it suggests a therapeutic intervention that may produce patient benefit. In fact, there is a depth of evidence to support the concept that the use of CCK antagonists may improve opioid-derived antinociception in a variety of animal models. Perhaps the first of these pieces of evidence dates from 1985, when Watkins and colleagues showed that proglumide given systemically, intrathecally, or intracerebrally enhanced morphine-derived antinociception in a rat radiant heat pain model.[24] That this effect was mediated by CCK was confirmed by Suh and colleagues,[25] who showed that intracerebroventricular injection of CCK-8 antagonized the antinociceptive effect of morphine in a mouse tail-flick test. The antagonistic effect of CCK-8 on morphine was blocked by the specific CCK B antagonist PD135,158, but not by the CCK A antagonist lorglumide.

While the majority of studies suggest that CCK B antagonists such as L365,260,[26,27] PD134, 308,[28-30] and PD135, 158[31] have the greatest enhancing effect on opioid-derived antinociception, other isolated reports confirm an enhancing effect with the mixed CCK A and B antagonist proglumide[32,33] and even with the specific A antagonist L364,718.[34] Although this evidence tends to point toward CCK B antagonists as having the more pronounced effect on the antinociceptive effects of morphine, we will see later that there are important interspecies variations.

The magnitude of effect produced by a CCK antagonist on morphine antinociception is typified by the results of Nichols and colleagues.[27] They examined rats that underwent an L5-L6 spinal nerve ligation. Allodynia was assessed using von Frey filaments. Neither administration of morphine nor the CCK B antagonist L365,260 alone had any effect on allodynia. When they were coadministered, however, a significant antiallodynic effect was observed. The δ-opioid receptor antagonist naltrindole NTI blocked this antiallodynic effect.

CHOLECYSTOKININ AND OTHER NEUROACTIVE SUBSTANCES

Dynorphin

CCK is not the only antiopioid peptide found in the

CNS. Dynorphin A, when given in very small doses intrathecally, reduces the antinociceptive effects of morphine.[35,36] This effect seems not to be a direct action, but rather, one that is mediated by CCK. The antinociceptive effect of morphine is reduced by intrathecal dynorphin, producing a rightward shift of the morphine dose-response curve. This effect is prevented by administration of a CCK antagonist and by pretreatment with CCK antiserum. On the other hand, the antianalgesic effect of CCK is not affected by pretreatment with dynorphin antiserum, suggesting that dynorphin A has an indirect effect mediated by spinal CCK.[37] In a similar fashion, the antianalgesic effects of pentobarbital[38,39] and neurotensin[40-42] seem to be mediated by spinal release of CCK.

Enkephalins

Radioimmunoassay and immunochemical studies have shown that enkephalins and CCK 8 have a similar distribution within many areas of the CNS.[43,44] Enkephalins act as endogenous opioids, while CCK has antiopioid properties. This has produced interest in the possible combined use of CCK antagonists and enkephalinase inhibitors, such as RB101, a complete inhibitor of the enkephalin-catabolizing enzymes.[45] Valverde and colleagues[46] have shown that RB101 does indeed have antinociceptive properties and that coadministration of the CCK antagonists L365,260, RB211, and PD134,308, along with RB101, increases the antinociception by 300, 500, and 800 percent, respectively, as compared with RB101 alone. The duration of action of RB101 is short, however, and this may limit its clinical usefulness. RB3007 has a longer duration of action, and recent work has confirmed its long-lasting antinociceptive properties and a significant potentiation by the CCK B antagonist PD134,308.[47]

Vanderah and colleagues[48] confirmed that the addition of a peptidase inhibitor (thiorphan) to L365,260 produced marked antinociception, while application of either alone produced no such decrease in nociceptive signaling. The effect of the combination of CCK antagonist and peptidase inhibitor was blocked by naltindole (a δ-opioid antagonist) and by antisera to [Leu5]enkephalin, but not by antisera to [Met5] enkephalin. This suggests that CCK may tonically inhibit [Leu5] enkephalin, which results in a subsequent enhancement of morphine activity.

This raises the question of the effect of CCK antagonists on placebo-mediated analgesia. It has been observed that the opioid antagonist naloxone is capable of reversing placebo analgesia.[49-52] Benedetti[53,54] examined human subjects with experimentally induced ischemic pain. He found that while the placebo response was indeed reversed by naloxone, proglumide enhanced it. This enhancement was seen only in placebo responders.

Opioid agonists

The knowledge of an interaction between CCK levels and the antinociceptive action of opioids has led to interest in the design of a novel peptide ligand for the CCK B receptor, which has potent agonist-binding affinity and bioactivity at δ-and μ-opioid receptors and simultaneous antagonist activity at CCK receptors.[55]

EFFECT OF CHOLECYSTOKININ ANTAGONISTS ON ANTINOCICEPTIVE TOLERANCE TO OPIOIDS

In keeping with much of the evidence relating to the actions of CCK and the effects of administration of its antagonists, referring to its effects on antinociceptive tolerance to opioids is not new. In 1984, Tang and colleagues demonstrated that the antinociceptive tolerance that developed after only seven or eight subcutaneous injections of morphine can be curtailed by treatment with proglumide without altering the half-life of the morphine.[56]

Similarly, in 1987, Panerai and colleagues studied rats that were fed morphine alone, morphine with proglumide, or morphine and benzotript (both CCK antagonists) dissolved in their drinking water.[57] The experiment lasted 27 days. The presence of tolerance to morphine was assessed by an evaluation of the analgesic responses evoked by graded doses of acutely injected morphine in the tail-flick and hotplate tests. Both proglumide and benzotript shifted the dose-response curve for morphine to the right when compared to those treated with morphine alone, suggesting that they had curtailed the development of tolerance. Neither proglumide nor benzotript had any effect when administered alone.

A recurring theme from animal experiments examining antinociceptive tolerance to opioids is that almost-complete tolerance is relatively easily obtained. This contrasts with human practice, in which many still maintain that even prolonged treatment with opioids is not commonly associated with such tolerance.

Tortorici and colleagues[58] have given some insight into the possible central location where tolerance is mediated through. They introduced a cannula into the periaqueductal gray area of rats. Microinjections of morphine produced antinociception, as quantified with the tail-flick and hotplate tests. When morphine microinjection was repeated twice daily, the antinociceptive effect disappeared within two days. If each morphine microinjection was preceded by a microinjection of proglumide into the same site, however, the microinjection of morphine always produced antinociception and did not induce tolerance. If the proglumide microinjections were suspended, subsequent morphine microinjections induced tolerance. In morphine-tolerant rats, a single microinjection of proglumide was enough to restore the antinociceptive effect of morphine.

The work of Idanpaan-Heikkila and colleagues[59] confirms that the CCK B antagonist L365,260 curtails tolerance in a rat model of peripheral neuropathy, while the studies by Zarrindast[60,61] show that both the CCK A antagonist MK329 and the B antagonist L365,260 curtail antinociceptive tolerance to morphine in mice. Dourish and colleagues also show that both the CCK A antagonist L365,031 and the B antagonist L365,260 curtail antinociceptive tolerance in a rat radiant heat tail-flick model, although they did show the morphine-enhancing effect was greater with L365,260 than with L365,031.[62]

The majority of studies investigating antinociceptive tolerance have concentrated on morphine. Kissin and colleagues,[63] in contrast, studied the effect of intravenous infusion of the short-acting opioid analgesic alfentanil in a rat model. Within four hours of commencement of alfentanil infusion there had been an approximate cumulative reduction of initial analgesic effect of 95 percent. L365,260 administered with alfentanil attenuated this reduction to a value of approximately 65 percent after four hours. Most impressively, proglumide, when given with alfentanil, had the effect of allowing a cumulative reduction of initial analgesic effect of only 45 percent.

REVERSAL OF ESTABLISHED TOLERANCE

The majority of studies addressing the issue of antinociceptive tolerance have concentrated on prevention. In contrast, Hoffmann and Wiesenfeld-Hallin[64] looked at the effect of a CCK antagonist, CI988, on established tolerance. This was induced by twice-daily subcutaneous injections of morphine in rats. By this stage, tolerance was almost complete. Administration of further morphine with saline did not improve the level of antinociception as judged by a hotplate test. When CI988 was given with morphine, however, marked antinociception was observed, suggesting that this CCK antagonist had reversed established antinociceptive tolerance. Similarly, Watkins and colleagues[65] showed that proglumide not only increased the antinociceptive effect of morphine in a rat model, but also seemed to reverse established tolerance.

SAFETY OF CHOLECYSTOKININ ANTAGONISTS

As has been shown, a considerable body of evidence supports the contentions that CCK has an antiopioid effect, its levels are increased after neural injury and chronic opioid administration, and CCK antagonists have a pro-opioid analgesic effect. The use of opioids is not without risk, however, with the major concern after acute administration being respiratory depression. Efficacy matters little in the promotion of better analgesia if additional risk to the patient is accrued from their use. Dourish and colleagues[66] provide a degree of reassurance from one of the few studies actually done in primates. They examined the effect of morphine on respiratory depression in squirrel monkeys and demonstrated a reduction in respiratory frequency after morphine administration, as would be expected. Addition of devazepide, a CCK A antagonist to a similar dose of morphine, increased the antinociception obtained from morphine alone, but did not decrease the respiratory rate any more than morphine alone. It is also interesting that they demonstrated such an increase in antinociception with a CCK A antagonist, given that the majority of studies done in rodent and murine models suggest that the B antagonists have a greater effect on nociception than the A antagonists.

To date, only one study has been undertaken in human subjects addressing the issue of safety. McCleane[67] studied nine subjects, all of whom were unresponsive to previous analgesic intervention, and in whom a trial of strong opioids was indicated. All subjects were given a twice-daily dose of sustained-release morphine. After stabilization of this dose, subjects were divided into three groups. All received L365,260, with the first three getting two doses of 10 mg separated by a four-hour interval; of the remaining six, three received 30 mg and the other three 60 mg, in a similar fashion. Cardiovascular and respiratory parameters were measured at regular intervals for the 10 hours after drug administration. No alterations in these variables were observed, and side effects were infrequent and mild.

HUMAN EVIDENCE

Despite the abundance of studies examining the concepts surrounding the issue of CCK in animal models, relatively few human comparisons have been made.

In 1985, Price and colleagues[68] used a human experimental pain model (radiant heat stimulus to the forearm) to examine the effect of proglumide on morphine-induced analgesia. Each subject received intravenous morphine at a dose of 0.04 or 0.06 mg per kg. They were then given intravenous saline and 10 or 100 mcg of proglumide. Morphine with saline had a very modest analgesic effect; however, the quality and duration of analgesia was substantially improved by coadministration of proglumide with morphine. Although this paper was the first to demonstrate a useful improvement in analgesia when a CCK antagonist is given with morphine, the dose of proglumide used was exceptionally small. The majority of other human studies examine the use of proglumide with doses measured in milligrams, rather than micrograms. If nothing else, this highlights the lack of dose-finding studies in humans with this and all of the other CCK antagonists currently available.

Lavigne and colleagues[69] studied 60 subjects undergoing impacted third molar extraction. Subjects received intravenous morphine at a dose of 4 or 8 mg or morphine

4 mg with proglumide at a dose of 0.05, 0.5, or 5 mg. Morphine 4 mg with proglumide 5 mg not only produced analgesia comparable to morphine 8 mg alone in terms of quality, but also of much greater duration.

In contrast to the studies with positive results, Lehmann and colleagues[70] were unable to demonstrate any improvement in pain scores or reduction in morphine consumption when they studied 80 subjects undergoing major abdominal or gynecological surgery. The morphine and proglumide administered in this study was given on demand using a patient-controlled analgesia device. It is hard to rationalize the failure to observe improvements in analgesic quality when proglumide was given, although four dose levels were examined. Also, the subjects were undergoing a variety of different procedures, so the comparability between subjects may not have been that great.

McCleane[71] studied 40 subjects who were already taking sustained-release morphine at a mean daily dose of 50 mg for a median time of 7.4 months (range, 0.3 to 72 months) for intractable pain. Subjects were blindly treated with proglumide 200 mg twice daily and placebo twice daily, in random order, for a two-week period each. Pain scores fell from a baseline of 8 on a 0 to 10-cm linear visual analog scale to 6 with proglumide treatment ($p < 0.002$), while no significant changes in pain score were seen with placebo. Side effects resultant from proglumide use were infrequent and minor. While morphine is occasionally considered as a possible treatment option in pain management, infinitely greater numbers of patients receive codeine-based preparations. McCleane[72] also examined the effect of proglumide on analgesia derived from a stable dose of dihydrocodeine in 30 adult subjects with pain of varied etiology using a double-blind, placebo-controlled crossover study. Pain scores were essentially unaltered by addition of placebo, but proglumide 200 mg twice daily produced a fall in pain scores of 1.23 on a 0 to 10-cm linear visual analog scale ($p < 0.05$).

Bernstein and colleagues[73] performed a double-blind, placebo-controlled crossover study of 60 subjects with cancer pain who were receiving morphine. Each patient received their usual daily dose of morphine along with placebo and half of their normal daily morphine dose with proglumide 50 mg. Forty-three patients completed the study. No differences in pain scores were observed between the two treatment periods, indicating that a substantially smaller dose of morphine could be used to achieve analgesia when proglumide was added. They also observed no side effects from the use of proglumide. The clinical implications of this study are obvious.

The majority of the murine and rodent studies suggest that antagonism of the CCK B receptors produces a more pronounced enhancement of opioid-derived antinociception. Few primate studies have been undertaken, but that of Dourish and colleagues[66] examined the effect of a CCK A antagonist in a squirrel monkey pain model. They observed impressive antinociception when the CCK A antagonist was added to morphine. McCleane[74] investigated the effect of the CCK B antagonist L365,260 on morphine-derived analgesia in humans with chronic neuropathic pain. Forty subjects were studied, all of whom were taking sustained-release morphine but obtaining incomplete pain relief. All subjects received placebo and L365,260 at three dose levels (30, 60, and 120 mg) in three divided doses daily for two weeks in random order separated by a washout period. Pain scores, activity levels, sleep, concomitant analgesic consumption, electrocardiographs, and serum biochemistry were all measured. No differences between the treatment periods (at any dose given) and the placebo period were observed, and few side effects were attributable to the use of L365,260. The study population was made up of patients with pain previously resistant to treatment, similar to other studies with proglumide in which definite reductions in pain levels were observed.[70,71] This implies that there may be species variations in the response to CCK antagonists and also raises the possibility that CCK A antagonists may be more efficacious in primate and human models.

To date, no randomized controlled trials have been reported that examine the effect of CCK antagonists on analgesic tolerance in humans. McCleane[75] reported an open-label series in which patients stabilized on proglumide 200 mg twice daily along with a fixed dose of morphine were followed for one year. At the end of this period all subjects were still receiving a similar level of analgesia from this fixed dose of morphine, and it was concluded that analgesic tolerance had not developed.

CONCLUSION

A significant body of evidence confirms that in animal pain models, CCK and its receptors play an important role in nociceptive processing. Again in these models, the addition of a CCK antagonist to an opioid enhances its antinociceptive effect and reduces the extent of antinociceptive tolerance with sustained use.

Human evidence is less complete and only partially suggests that the same effects are associated with CCK use. Therefore, the full story of the effect of CCK antagonists and their effects on opioid-derived analgesia in humans needs significant further research, but given the highly suggestive animal evidence, such human work is well merited.

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