Treatment of Pain in Methadone-Maintained Patients

MICHAEL M. SCIMECA, M.D.[1], SEDDON R. SAVAGE M.D.[2], RUSSELL PORTENOY, M.D.[3], AND JOYCE LOWINSON, M.D.[4]

Abstract

Patients with opioid dependency experience trauma, acute medical illness and chronic diseases, and may have to undergo surgery to the same extent as other individuals. They need to be treated for relief of symptoms, including pain. Undertreatment or inadequate treatment of pain for these individuals is a particular problem because of opioid dependency and/or methadone maintenance treatment. The guiding principles governing treatment of these patients are to maintain the methadone treatment and to use short-acting narcotics administered at higher doses, and to do so as often as necessary, preferably on a fixed schedule, to relieve the pain. Supplemental analgesic medication may also be employed, except that opiate antagonists must be avoided.

Key Words: Tolerance, methadone, analgesic, methadone maintenance, pain, pain treatment, opiate, opioid, heroin, analgesia.

Introduction

OPIOID AGONIST THERAPY is an accepted medical treatment for opioid addiction, with documented efficacy. Methadone maintenance treatment of addiction (MMT), the most common form of opioid agonist therapy, is approved by all major medical and professional organizations concerned with addiction treatment. Approximately 179,000 persons (1) in the United States are currently enrolled in methadone treatment. The federal government advocates expanded availability of the modality. Although some individuals require opioid treatment of addiction on a time-limited basis, others require treatment on a long-term basis and may, during the course of treatment, present with medical disorders associated with acute or chronic pain. Although the problem of pain management during methadone maintenance has received little systematic attention, pain is a common problem in this population and likely to become more so as the population ages and a larger number of medically ill patients are enrolled in programs.

Undertreatment of pain, which is a recognized problem in all populations, occurs with relatively greater frequency in those with histories of chemical dependency, including patients enrolled in MMT (2). The barriers to effective pain treatment are multiple and complex. Its undertreatment may be related to deficiencies in clinician practice, including the failure to assess pain and co-morbid disorders adequately, and to inadequacies in their knowledge and skills. Additionally, persistent pain may be ascribed to patient-related problems, such as under-reporting of pain, or to systems-related problems, such as

[1]Director, Department of Addiction Medicine, St. Barnabas Hospital, Bronx, NY and the Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY;
[2]Associate Professor of Anesthesiology, adjunct faculty of Dartmouth Medical School and Director, Pain Consultation Clinic at the Veteran's Administration Medical Center, Manchester, NH;
[3]Chairman, Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, NY and Professor of Neurology, Albert Einstein College of Medicine, Bronx, NY.
[4] Adjunct Faculty, The Rockefeller University, New York, NY

Address correspondence to Michael M. Scimeca, M.D., Director, Department of Addiction Medicine, St. Barnabas Hospital, Third Avenue and 183rd Street, Bronx, NY 10457-2594.

inadequate insurance or reimbursement for analgesic therapies.

In populations with chemical dependency, analgesic therapy using opioid drugs requires a high level of knowledge and skill on the part of responsible clinicians. In the case of methadone-maintained patients, effective analgesic therapy requires careful attention to both clinical and pharmacologic principles. Misinformation about the pharmacology of opioids, including methadone, may contribute to inadequate pain management. Misinformation about opioid tolerance is also common. Physicians may also believe erroneously that methadone taken for maintenance is sufficient to provide adequate analgesia. In addition, there are widespread concerns regarding possible legal sanctions related to physicians' use of state-mandated prescription forms for opioids.

When an MMT patient is in pain, aberrant drug-related behaviors may occur, and may raise concerns about relapse. A detailed assessment often indicates that desperation arising from the unrelieved pain is more likely to be the cause. In the context of a medical problem such as pain, simple labeling of aberrant behaviors as abusive "drug seeking" is inappropriate. Without a careful assessment by a concerned and knowledgeable clinician, behaviors can be misinterpreted.

Cycles of clinician concern and patient distress may be difficult to interrupt. The process requires the ability to perform a sophisticated assessment of both pain and drug use, and the ability to respond to unrelieved pain with appropriate interventions. Professionals working with addicted individuals need to become aware of their own possible biases, which may detract from their care of these patients. Examples of common biases include (3):

> "They are morally culpable for their addiction. It's their fault."
> "Pain is 'payback' for their own vices and for getting high."
> "They are deceitful and always manipulating to get drugs to get high."

All of these issues can become particularly daunting when the pain and clinical context suggest a role for long-term opioid analgesic therapy in patients receiving methadone maintenance. To address these issues, this article briefly reviews the principles of opioid agonist therapy of addiction and the principles of pain management for methadone-maintained patients.

Methadone as a Therapeutic Agent

Pharmacologic Aspects of Methadone

Basic Pharmacology

Methadone is a synthetic opioid with a long and variable half-life (between 12 and 100 hours (4). Although it can be administered intravenously or intramuscularly to treat pain, its utility as a maintenance medication in the treatment of opioid addiction is based on its long half-life and ready, reliable absorption when used as an oral medication. The slow onset of methadone taken orally does not produce a sudden "rush," and produces no euphoric effects in most patients (5). As a treatment for opioid addiction, it is effective in blocking craving and withdrawal for 24–36 hours.

For decades, methadone has also been used as an analgesic, and interest in the drug as a treatment for pain has been increasing because of recent evidence that the commercially available racemic mixture includes an isomer that does not bind to opioid receptors, but is an antagonist at the n-methyl-D-aspartate (NMDA) receptor. By blocking this receptor, this d-isomer could potentially yield analgesia by a mechanism that potentiates that produced by binding of the l-isomer to the opioid receptor. Moreover, NMDA-receptor antagonism reverses opioid tolerance, and this effect may explain the unexpectedly high analgesic potency of methadone when it is administered to patients who are receiving another mu agonist drug.

The analgesic effects of methadone typically last 4–8 hours after a dose. Although some patients are able to achieve stable analgesia with dosing every 12 hours, most patients require analgesic doses every 6–8 hours, and some can avoid end-of-dose failure only by dosing every 4 hours.

Single-dose, controlled analgesic studies indicate that methadone is slightly more potent, on a milligram per milligram basis, than morphine sulfate (6). These studies have limited relevance to chronic administration, during which the combination of kinetic factors (a slow and gradual increase of plasma concentration because of the long half-life) and dynamic factors (increased potency presumably because of the NMDA-receptor antagonism of the d-isomer) produce an unexpectedly high potency, gradual accrual of effects over days to a week or more, and variability in response based on the existing therapy. As a result of these factors, current guidelines indicate that the use of methadone for pain should be initiated at a dose that is 75–90% lower than the

calculated equianalgesic dose. This initial dose is usually co-administered with a short-acting opioid "rescue" medication. Close monitoring during dose titration is needed until sufficient time has passed at a stable dosing level to ensure that the plasma concentration has plateaued. This steady-state plateau, which requires 4–5 half-lives to achieve, can in the case of methadone require days to weeks.

Tolerance

Tolerance is the loss of drug effect over time, induced by persistent exposure to the drug (7). Alternatively, tolerance can be defined as the need to increase the dose to maintain the initial effects of the drug. Tolerance may develop to any opioid effect, and tolerance to different effects typically occurs at varied rates (8, 9). Tolerance to some adverse effects of a drug, such as respiratory depression and nausea, is clinically favorable and typically occurs within days to weeks. Tolerance to the respiratory depressant effects allows stepwise dose escalation to occur in a manner that is safe and can optimize analgesic outcomes (9). As a consequence of this phenomenon, some patients can be gradually titrated to very high doses of methadone — equivalent to many grams of morphine per day — in an effort to attain pain relief.

In contrast to tolerance to adverse effects, analgesic tolerance can be a clinical problem. Fortunately, however, extensive clinical experience has documented that the doses required to maintain analgesia typically stabilize in the absence of progressive disease. Although dose escalation may be needed periodically to sustain analgesia, tolerance is seldom a problem in the clinical setting. The corollary to this observation is equally relevant: when a need to increase the dose does materialize, the clinician should search for worsening disease, rather than assume that analgesic tolerance has occurred.

Physical Dependence

Physical dependence is an expected form of physiologic adaptation which occurs as a result of regular drug exposure and is reflected in the development of an abstinence, or withdrawal, syndrome when there is abrupt cessation of the drug, administration of an antagonist, or rapid decrease in dose (10). Physical dependence is not addiction, and much of the misunderstanding about the risk of addiction occurs because these terms are often mistakenly used as synonyms. Although physical dependence must be assumed to exist after a few days of opioid administration, it is, like the phenomenon of tolerance, neither necessary nor sufficient to yield an addictive disorder. Physical dependence that occurs in the course of therapeutic opioid use does not indicate addiction and should never be labeled in this manner.

Addiction and Drug Craving

Opioid addiction is a neurobiologically based disorder, with social and psychologic influences, characterized by a pattern of maladaptive behaviors, including: loss of control over use, craving and unwarranted preoccupation with non-therapeutic use due to craving, and continued use of the drug despite harm resulting from use. Physical dependency and tolerance may or may not be present in addiction.

Opioid addiction occurs as a result of neurobiologic changes within the limbic reward systems, changes that are induced in biologically vulnerable individuals through repeated use of rewarding drugs. The induced neurobiologic changes are protracted and appear to drive persistent drug craving. Addiction is associated with down-regulation of the hypothalamus-pituitary adrenal axis (11). Drugs with rapid onset of action are believed to pose the greatest risk for development of addiction in vulnerable individuals (11).

Treatment of Opioid Addiction with Methadone

Rationale

Opioid agonist therapy of addiction is based on the understanding that stable and continuous occupation of opioid receptors in the limbic system and other brain centers associated with addiction blocks opioid craving without causing euphoria or significant cognitive changes or sedation. This permits the user to focus on life activities unrelated to obtaining and using drugs, resulting in gradual return to normal function and a productive lifestyle.

Methadone has a relatively slow onset of action and a long half-life. With daily use of consistent doses, relatively stable blood levels of the drug are achieved. Methadone causes less stimulation of limbic reward centers than shorter-acting opioids, has a relatively low abuse potential, and, at relatively high stable blood levels, it blocks the "high" obtained from use of short-acting opioids. These attributes make methadone particularly effective as therapeutic opioid agonist agent. Recently, other agents, including buprenorphine and levomethadyl acetate (LAAM), have been

introduced as therapeutic agents. They appear to have good safety and efficacy profiles as therapeutic opioid agents in addiction treatment, and it is likely that their use in clinical practice will increase over time.

Documented Benefits

Methadone maintenance treatment for addiction normalizes the impairments associated with opioid addiction (2, 11). Methadone treatment has been documented to reduce the use of illicit opioids and to reduce morbidity and mortality among heroin addicts. Patients stabilized on methadone are able to take advantage of educational, vocational and employment opportunities. Increases in social stability and productive behavior have been documented in numerous studies over the past three decades (12). Outcomes of MMT for addiction are improved when combined with counseling, social support, and educational or vocational opportunities (12).

Methadone Maintenance for Hospitalized Patients

Under federal law, methadone may be prescribed for maintenance therapy of addiction in ambulatory patients only by physicians who have a special license to prescribe opioid therapy of addiction and who are affiliated with a licensed opioid treatment program. However, any physician with a standard, unrestricted Drug Enforcement Administration (DEA) license may prescribe maintenance methadone to a patient who is hospitalized for a cause unrelated to addiction. That is, if a patient is admitted for an acute medical illness such as pancreatitis or renal lithiasis, or for a surgical procedure, any treating physician may, and should, prescribe for the patient's maintenance methadone while the patient is hospitalized. It is imperative that maintenance methadone be continued during hospitalization in order to avoid withdrawal and potential complications in medical, surgical and pain treatment. The guiding principles for prescribing medications to MMT patients include:

- Avoid medications with antagonistic properties, such as naltrexone and agonist/antagonist opioids such as pentazocine
- Morphine or other opioids should be administered to control pain. The dosage may have to be increased because of tolerance induced by methadone.
- A fixed schedule of administration is preferable to a variable schedule.

Clinical Use of Methadone as an Analgesic Agent

Methadone has been used as an effective analgesic agent for decades. New information about NMDA receptor antagonist actions, combined with its relatively low cost, has generated increasing interest for use in pain management. The use of methadone as a treatment for addiction has complicated efforts to appropriately position the drug for analgesic therapy. For example, some physicians erroneously believe that a special license is required to prescribe methadone as an analgesic agent. This concern is particularly strong when the patient is receiving MMT and the use of methadone is being considered for pain. Physicians must be reassured that a specialized license to provide opioid therapy is required only when methadone is administered for the treatment of addiction, even if the patient is also receiving the drug as part of MMT. Methadone may be prescribed for the treatment of pain in any patient, including a patient on methadone maintenance therapy of addiction, without a specialized license other than a standard DEA license. Careful documentation is required if methadone is selected as an analgesic, especially in MMT patients.

Because of methadone's use on a once-a-day basis for the treatment of addiction, many physicians assume that methadone can be used once daily for pain. A very large clinical experience refutes this. Most patients will require a dose interval of 6–8 hours to maintain analgesic effects.

Although it is most often used orally both for maintenance therapy and as an analgesic, methadone may be used parenterally when the oral route is unavailable. Although methadone may be too irritating for continuous subcutaneous infusion, it can be administered by parenteral bolus injection or infusion, like any other opioid administered for pain.

Finally, some physicians believe that methadone has a unique profile of analgesic actions and side effects, although this has not been clearly documented from studies of long-term therapy for pain. There is very large intra-individual variability in the response to opioids, and a single patient may experience different patterns of analgesic responses and side effects to each of the pure mu agonist opioids. When methadone and other drugs are compared at equianalgesic doses, there is no evidence for systematic differences between them; however, an individual patient may or may not find a switch to methadone to be a favorable intervention.

Principles of Pain Management in MMT Patients

Common Problems in the Management of Pain in Patients on MMT

Patients receiving MMT for addiction often receive sub-optimal, or even negligible, treatment of acute pain while hospitalized. A series of approximately one hundred reports indicates the following common errors in management:

- Methadone doses were lowered in the hospital, and as a result, patients experienced withdrawal symptoms.
- Pain medication was denied because the clinician believed that the patient's chronic maintenance methadone doses would provide adequate analgesia.
- Patients for whom analgesics were prescribed were usually inadequately dosed because clinicians feared that medication in addition to the patient's prescribed methadone would cause respiratory depression.
- Patients were told to withdraw from methadone prior to surgery or other procedures because of the incorrect belief that methadone may interfere with the procedures and/or impair their general health.
- During hospitalization, patients' maintenance dose was increased in an attempt to achieve analgesia. Patients were then released from the hospital on excessively high doses of methadone.
- Patients reported that opioid antagonists were inappropriately administered, inducing severe withdrawal.
- Because of the stigma associated with MMT, many methadone patients had negative experiences with health professionals when their status as patients became known (12, 13). As a result, some methadone patients admitted to an emergency room or a hospital concealed their status from staff, with occasional dire consequences (e.g., administration of pentazocine or other agonist/antagonist drugs, which can precipitate sudden withdrawal) (14).

Clinical Issues Affecting Pain Management in MMT Patients

Role of Opioid Therapy in Pain Treatment

There is widespread consensus that opioid therapy is the mainstay approach for the treatment of moderate-to-severe acute pain, and moderate-to-severe chronic pain associated with cancer or AIDS. As noted previously, undertreatment is common despite this consensus, and chemically dependent patients are more likely to be undertreated than those without this history. Although a history of addiction and MMT for addiction may yield challenges during opioid therapy for pain, there is clinical agreement that opioid drugs should still be considered the major approach in these settings.

The role of long-term opioid therapy for non-cancer-related pain is evolving rapidly. There are now consensus statements from major professional societies, including the American Society of Addiction Medicine, that acknowledge the appropriateness of this treatment for selected patients. Although the use of this therapy for those with a history of chemical dependency has barely been studied, it is clear from a clinical perspective that, when opioids are required to relieve significant and persistent chronic pain in this population, they must be utilized with appropriate care and structure to avoid complications of use.

Careful assessment must be done when opioid therapy of chronic pain is contemplated for individuals with addictions, in order to clarify the state of the addictive disorder (active, at risk or recovering); to determine the presence or absence of co-morbid psychopathology; to assess the degree to which unrelieved pain may be driving aberrant drug-related behaviors; and to establish a means to structure treatment in a way that would reduce the risk of inappropriate use. The active abuser may be very different from the patient in MMT or in stable drug-free recovery, and the decision to consider long-term opioid therapy for chronic pain in these patients presumably carries very different degrees of risk.

When deciding whether to consider long-term opioid therapy for chronic pain in patients with a history of chemical dependency, the clinician should also recognize the difficulties that the patient may experience because of anxiety about relapse, abandonment by friends, or challenges from addiction treatment programs. In all cases, the treatment requires a detailed assessment, including an open discussion with the patient, concerning all risks and benefits.

Anxiety Regarding Treatment

Many patients who are receiving MMT for addiction recognize that pain is often inappropriately managed in patients on MMT, and this may cause significant anxiety among those confronting injury, illness or surgery. Patients often fear ineffectively treated pain, loss of effective maintenance therapy, and the emergence of acute withdrawal, as well as the possibility of disrespectful treatment by health-care personnel. Anxiety related to these fears may in turn result in behaviors that become challenging to clinicians. Reassuring the patient that pain management is a high priority, including the patient in decision making, and adhering to good basic principles of pain management are critical to providing effective pain treatment.

MMT patients may also experience anxiety about using opioid medications for pain. Some believe they should "grin and bear" their pain because of concern that taking an opioid analgesic constitutes a relapse and will lead to re-addiction (15). These patients and their families and physicians often need reassurance and encouragement to accept the analgesic treatment. It is sometimes helpful to point out that medications prescribed for acute pain are most often time limited and that relief of pain is essential for a quick and healthy recovery.

Many former illicit drug users fear losing control over medications and thus refuse any analgesia. Methadone patients receiving a blockade dose can be reassured that their daily dose of methadone will generally block any euphoric effects of the analgesic medications and that analgesics will only produce relief of pain. Methadone patients on lower doses can similarly be advised of a partial blockade and assured that in all probability they will feel very little euphoria, if any at all, from pain medication. If patients persist in declining medication, their request for no pain medication should be respected and non-medication approaches to pain control implemented whenever possible. However, in some patients, pain may eventually overcome this fear, and a request for pain medication may be made.

Some methadone patients fear that use of analgesic opioids will result in the need to increase their maintenance dose of methadone. It has been documented, however, that use of opioids for analgesia does not result in increased dose requirement for maintenance therapy once acute pain is resolved (16). With treatment, methadone patients will most likely continue with their usual maintenance treatment.

Adequacy of MMT

In order for pain management to be effective, patients who require maintenance therapy of addiction must be on an effective dose of methadone for their addiction treatment. Patients receiving subtherapeutic doses, who are experiencing early symptoms of withdrawal or craving, will be much more difficult, or impossible, to treat for pain. It may be difficult for patients on subtherapeutic doses to distinguish between the pain from surgical procedures and the pain from withdrawal syndrome. Opioid blockade may reduce the risk of euphorigenic effects and provide relative protection against re-addiction and relapse associated with the therapeutic use of an opioid analgesic.

Pain Sensitivity and Analgesic Responsiveness in MMT Patients

Although supporting data are inconclusive, there is suggestive evidence that methadone-maintained patients may be more sensitive to noxious stimuli — i.e., experience a relatively high level of pain following a noxious event — than non-maintained individuals. A study by Compton et al. (17), which examined pain, pain thresholds and pain tolerance in the presence of experimentally induced cold-pressor pain in humans, demonstrated that stable doses of methadone used as maintenance therapy appear to provide no analgesic effect and that methadone maintenance patients overall have lowered pain thresholds (increased pain sensitivity) and less pain tolerance than non-maintained individuals.

This research affirms that the usual dose of methadone used chronically for opioid therapy of addiction does not relieve pain and that individuals receiving MMT for addiction may require more aggressive pain management because of a predisposition to pain. If opioid analgesia is selected for the MMT patient, relatively high doses may be needed, both to overcome whatever level of analgesic tolerance the MMT has produced and to address the predisposition to pain (17).

Co-morbid Psychiatric Disorders

Studies suggest that 30–80% of substance abusers suffer from co-existing psychiatric illness (14). Anxiety, panic disorder, and the range of mood disorders (depressive and bipolar) which have a high prevalence in the addiction population may all be associated with bodily discomfort, pain itself, or distorted somatic perception (14). Psychiatric evaluation and effective treatment can be crucial to relieving the pain syndromes in many of these people.

Structure of Pain Therapy in Methadone-Maintained Patients

Discussion and Documentation of Benefits, Risks and Structure of Therapy

Unless there is compelling evidence suggesting otherwise, all patients presenting with complaints of pain, including those with addictive disorders, should be evaluated and treated for their presenting pain complaint. Most often, individuals seeking opioids for non-medical uses will declare themselves eventually, through a pattern of aberrant behaviors.

If opioid therapy is selected as an intervention for pain in the patient with addictive disease, it is important to establish a clear understanding with the patient. Appropriate discussion and documentation of the potential risks and benefits of therapy, as well as the structural guidelines of treatment, should be made. If therapy takes place in the ambulatory setting and is expected to continue for a prolonged period of time, it may be helpful to detail this understanding in the medical record and have it signed by both treatment provider and patient. This is often referred to as a "contract," agreement, or covenant (18). A number of structural supports may facilitate effective pain therapy in patients with addictive disorders and should be noted in any agreement between patient and provider. These are discussed below.

Single Prescriber

In the ambulatory setting, it is best for the patient to have one physician prescribe all the analgesics and, preferably, all controlled medications. This provides continuity of care, eliminates overlap of medications, reduces the risk of drug interactions, and is reassuring to both the patient and the clinicians. In this arrangement, the physician prescribing analgesic medications should inform other doctors who are prescribing for the patient, including the methadone prescriber, primary care physicians and any consultants who see the patient on a regular basis.

Team Approach

For those patients in MMT for addiction, it is essential that their team of counselors, nurses and others participate in the evaluation and treatment-planning process. The treatment staff must know what medications the patient is prescribed in order to observe for effects and side effects, be aware of potential drug interactions, and support the individual in his or her recovery.

Some MMT patients who are receiving opioids for chronic pain choose to drop out of their formal MMT program. Although using the opioid for pain may continue to block craving, the physician prescribing the drug for pain must carefully document that the intention of therapy is analgesic and not addiction management. A decision to leave the MMT program should be carefully discussed with the patient and members of the treatment team. It may be convenient, but such a decision may eliminate an important source of support for the patient.

Appropriate Controls on Medication Dispensing

When possible, it is best for the patient to obtain all prescriptions from one pharmacy. This facilitates tracking of medications. The patient should be asked to consent to ongoing contacts between the prescriber and the pharmacist. When a patient has difficulty controlling the use of medications, he or she should be given medications in small quantities, at frequent intervals. Some patients require daily dispensing from their pharmacy. This is often impractical, and sometimes a trusted other may dispense medications to a patient.

Documenting Use of Medications

It is often helpful to ask patients to bring their medications to each clinic visit so that care providers can observe whether the patient is using medications as prescribed. If concerns arise regarding whether or not a patient is using the prescribed medications, urine screens may be helpful for documentation. However, the clinician must be aware of the usual ranges that the particular laboratory utilizes when specific tests are requested, and what the reporting cutoff limits are for particular drugs; there is great variability among laboratories.

In rare instances, if a patient appears highly tolerant to medications and requires very high doses, use of the medication can be confirmed by asking the patient to take the prescribed dose while under observation. An opioid antagonist should be available in case the patient has been diverting medications and demonstrates no tolerance to the sedative or respiratory effects of the opioid. In patients on blocking doses of opioids, such side effects are not expected, but caution is appropriate nonetheless.

Managing Reported Losses

On occasion, clinicians who are prescribing long-term opioid therapy to a patient with a history of chemical dependency are asked to replace a prescription that is reported as lost or stolen. From the start, there should be a clear agreement

about how such circumstances will be managed, and this should be documented in the agreement. It is helpful to advise patients that they are responsible for keeping the prescriptions and medications safe. One way to handle the problem of lost or stolen medication is to request that all losses or thefts be reported to the police. The police report will have to be presented and placed in the patient's record before any replacement medication can be prescribed. Some clinicians follow a practice of replacing only a single reported loss or theft and advising the patient that he or she will have to accommodate to any subsequent loss or, if the occurrence is frequent, therapy may be discontinued.

Clinical Principles of Pain Treatment for the Methadone-Maintained Patient

Continuation of Maintenance Methadone at Unchanged Dose

A patient on MMT who presents with pain should be continued on his or her usual dose of methadone for maintenance. This should usually be given orally in one daily dose. However, if the dose cannot be verified, it is safest to give the reported daily dose in three to four divided doses at appropriate intervals and observe the patient's response, to assure that a potentially dangerous dose is not given. If the daily dose cannot be confirmed and if the oral route is unavailable, one-half the usual daily oral, in divided doses, should be given parenterally. Continuing treatment thereafter should be based on the patient's response.

Measurement of Pain

Opioid analgesics should be titrated according to reported pain, as with all patients reporting pain. Use of pain scales such as a numeric pain scale (0 – 10) or a visual analogue is recommended in order to evaluate both pain and responses to pain treatment. Because of relative tolerance to opioids and possibly lowered pain thresholds, MMT patients often will require higher-than-standard analgesic doses given at more frequent intervals. This must be established with clinical observations (17).

Choice of Opioids to Provide Analgesia

Although methadone is an effective analgesic, it is generally preferred to select an alternative mu agonist opioid such as morphine, hydromorphone or oxycodone, to provide analgesia in methadone-maintained patients. This allows clear distinction between treatment of addiction and treatment of pain, and lessens possible confusion over clinical issues of pain and addiction. In addition, because of its relatively slow onset of action and long half-life, methadone may be difficult to titrate rapidly enough to meet acute pain needs.

In some cases, however, methadone will be the preferred analgesic (this usually relates to cost). If the patients remains in MMT, the treatment must include visits to the MMT program to receive a single daily dose for addiction, and visits to the physician who treats the pain, for a prescription that will be filled by a regular pharmacy; the latter will provide analgesic methadone, to be administered several times per day on a fixed schedule. This approach is not pharmacologically necessary, of course, but is required by regulation if the methadone is still being used to treat the addiction. There are anecdotal reports of former MMT patients who receive prescriptions for analgesic methadone.

Long-acting opioids, such as controlled-release oral morphine, oxycodone, or hydromorphone (soon to become commercially available) or controlled-release transdermal fentanyl, provide consistent pain relief for continuous pain, while short-acting opioids are more rapidly effective for addressing intermittent, incident or breakthrough pain.

Titration and Scheduling of Analgesic Medications

A fixed schedule is preferable to a variable "prn" schedule. For an inpatient, this avoids the request for opioids, which may be interpreted by some staff as pathologic drug-seeking behavior, rather than the seeking of pain relief. For ambulatory patients, it avoids the situation where the individual with an addictive disorder has to make a decision as to whether or not to take a potentially rewarding or reinforcing drug based on subjective pain level, a situation which may cause confusion, distress or, possibly, an escalating pattern of pain and medication use.

If only intermittent analgesia on an irregular basis is required, it is helpful, when possible, to link doses with activity or time, rather than increased pain alone, in order to avoid the potentially reinforcing effects of opioids on pain perception. In the case of the ambulatory MMT patient requiring additional opioids for analgesia, therefore, treatment may consist of a single methadone dose per day as addiction therapy, plus a fixed schedule of the opioid as used for pain.

It is important to be aware that individuals on methadone maintenance therapy of addiction and those using opioids chronically for analgesic pur-

poses will often require relatively high doses of opioids at relatively short intervals, due to tolerance. Opioids should be titrated to reported effect while observing for improvement in pain and function versus signs of overuse, abuse or addiction. Ambulatory patients should be given medications in quantities that both they and their providers are confident that they can control.

When planning long-term opioid therapy in the ambulatory setting, it is often useful to begin with a small prescription, such as a seven-day supply. Before increasing the dose independently, the patient should be given instructions to contact the prescribing physician if the medication is not effective. The frequency of future prescription refills should be determined by effective dose, adherence of the patient, and the nature of the illness.

Use of Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) may be used with MMT patients who are believed to be in secure addiction recovery. A continuous background infusion may be used with the PCA component, if indicated. PCA allows patients to titrate their own analgesic needs without frequent medication requests to health-care staff. These requests, in an individual with addictive disease, are often perceived as drug-seeking behaviors. Doses should be titrated to effective reported analgesia, while observing for side effects such as intoxication or persistent sedation, which may occur with overuse. Caution is indicated if a patient is not securely in recovery, may be at risk for relapse, and/or has visitors who are actively abusing opioids, since PCA makes IV forms of opioid reasonably available to tamperers.

*Avoid Agonist-Antagonist Drug*s

A patient using methadone or other mu agonist opioids on a regular basis must avoid the use of opioids with agonist-antagonist properties, such as butorphanol (Stadol®), pentazocine (Talwin®), nalbuphine (Nubain®), and dezocine (Dalgan®). Such drugs provide analgesia through activity at non-mu opioid receptors, but act as antagonists at the mu receptor, thus reversing the actions of methadone or other therapeutic mu agonist opioids. Therefore, they may precipitate an acute withdrawal syndrome in patients using mu agonist medications such as methadone (16).

Avoid Meperidine and Propoxyphene

Because individuals on MMT may be relatively tolerant to the effects of opioids, thus requiring high-dose therapy, meperidine and propoxyphene should not be used when prolonged or high-dose analgesia is anticipated. Normeperidine, a metabolite of meperidine, and norpropoxyphene, are potentially neurotoxic agents that may accumulate in such circumstances, causing tremors, agitation and even seizures in some cases. Meperidine is also very short acting, is poorly absorbed after oral administration, and provides only transient analgesia. It has few indications in the treatment of pain.

Non-opioid Approaches to Pain Treatment

Non-opioid pain treatment approaches may provide effective analgesia for patients with pain, in many settings, either alone or as a complement to opioid therapy. Non-opioid medications with analgesic activity include nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, anticonvulsants, corticosteroids, and local anesthetics, among others. Antidepressants and anticonvulsants may be especially helpful in treating neuropathic pain, which may be less responsive to opioids than is nociceptive pain. Non-opioid pharmacologic treatments should be dosed in the standard amounts used for analgesia in nonmethadone-maintained patients, since individuals on MMT are not expected to have tolerance to the effects or side effects of these medications. Only the opioid analgesic may need to be used in higher doses for the methadone patient, unless the patient has developed tolerance to non-opioid substances. For example, an MMT patient with concurrent alcoholism also may have developed tolerance to sedative-hypnotics. Another approach is that offered by anesthesiologists, such as nerve blocks and intraspinal infusion.

There are numerous non-medication approaches to pain treatment, beyond the scope of this paper, which may be helpful in individuals on MMT. These include psychological (e.g., cognitive, behavioral and other therapies) and physical modalities (e.g., physical therapy, analgesic modalities such as cold or heat, and neurostimulatory modalities such as transcutaneous electrical nerve stimulation, acupuncture and dorsal column stimulation). Attention to nutrition and weight (loss or gain) may also have a role in pain treatment.

Special Populations

Pregnancy

Treatment of the pregnant woman demands special physiologic considerations according to trimester, and attention given to the well-being of the fetus. It is generally agreed that the pregnant

patient should receive as high a maintenance dose of methadone as is necessary to achieve blockade, so that she will cease using illicit opioid. The physiologic changes of pregnancy including slowed gastrointestinal absorption, expanded fluid load, and increased glomerular filtration, all indicate a possible need to increase the amount of methadone for maintenance, especially in the third trimester. As with other patients on MMT, it may be necessary to use higher analgesic doses of opioids to treat pain; opioids utilized to provide analgesia should be titrated to effect.

AIDS, HIV Infection and Cancer

The special needs of patients who have a history of illicit drug use and are infected with HIV are of critical relevance when considering pain management. It has been well documented that pain associated with HIV-related disease is routinely undertreated (2). The World Health Organization and U.S. Agency for Health Care Policy recommend that a cancer pain model of pain treatment be utilized in managing pain in patients with HIV-related illness. The complexity of the issues in treating these patients requires that the first step in their management be a comprehensive assessment. Careful attention to addiction recovery and to principles of pain management in MMT patients, as discussed above, is requisite to providing effective pain management for HIV-infected patients on MMT.

Care of Patients with Active Addiction

Patients with active drug addiction who present with acute or chronic pain due to injury, illness or surgery present special challenges to the pain treatment provider. It has been documented that periods of acute illness often represent opportunities for meaningful intervention in addictive disease, as patients are often confronted with their vulnerability to illness and, sometimes, specifically to the harmful sequelae of their disease. Attempts to engage the patient in addiction treatment should therefore be aggressive at these times. Clinicians not knowledgeable in addiction treatment should seek professional expertise when treating patients who are active drug users.

Pain management for all patients with addiction requires relatively tight controls, monitoring and documentation, while at the same time meeting the individual's analgesic needs through appropriate titration of medications and use of other modalities. A smooth course of analgesic therapy is often facilitated when addicted patients are reassured that the staff is aware of their addictive disorder and that every effort will be made to treat their pain; their addiction will not be an obstacle, if they are willing to work with the team. Opioid-addicted individuals should be assured that they will be given enough methadone to prevent withdrawal and craving while they are hospitalized. The relative tolerance to the analgesic effects of opioids in opioid abusers must be considered when titrating medications. The use of a written contract that is kept in the medical record, defining the regimen and explicitly stating the responsibilities of both the patient and the physician, may be especially helpful in treating these patients.

Summary

The methadone-maintained patient experiences as much pain in association with illness, injury, and surgery as do other individuals. Methadone used chronically for maintenance does not treat acute or chronic pain. Therefore, the methadone patient needs adequate analgesic medications prescribed to relieve pain.

Methadone-maintained patients who have pain often require relatively large doses of opioids at relatively short intervals to control their pain, since they have some level of tolerance to opioid medications. At a blockade dose of approximately 80–120 mg/day, the methadone-maintained patient has relatively high tolerance to the respiratory depressant effects of opioids, and will not experience drug craving or euphoric effects in association with short-acting opioids prescribed for relief of pain. Clinicians should therefore not feel apprehensive about the relatively large doses of analgesics often required to treat pain in methadone patients, but should observe patients carefully and adjust analgesic doses according to reported relief and observed effects. Methadone will not interfere with analgesic responses to opioids, although dose requirements may be higher than in non-maintained patients.

The simplest approach to the treatment of acute pain in the methadone patient is to prescribe adequate doses of an alternative mu opioid, while maintaining the maintenance dose of methadone. The type and dosing pattern of the opioid used should be determined with consideration of the type, intensity, and temporal pattern of the patient's pain.

When an opioid is used for chronic pain, successful therapy is predicated on a careful assessment of the pain, a detailed history of chemical dependency, and awareness of co-morbid physical

and psychosocial factors. Treatment requires a knowledgeable and committed physician who will administer the opioid in doses required to attain analgesia, while monitoring the patient for other critical outcomes, including function, drug-related behaviors, and side effects. A team approach is often helpful.

Patients should generally not be withdrawn from opioid medications while they are experiencing acute pain. If it is necessary to change the maintenance dose of methadone for any reason, this should be done in consultation with the patient and the clinician who is treating the patient for his or her drug dependence. If basic principles of pain management are followed, analgesic management of the methadone patient should be as effective and safe as for any other patient treated for acute or chronic pain.

References

1. American Methadone Treatment Association Survey. 1998. Tel #: (212) 566-5555. This report may be obtained at 217 Broadway, Room 304, NY, NY 10007
2. Portenoy R, Dole V, Joseph H, et al. Pain management and chemical dependency. Evolving perspectives. JAMA 1997; 278:592–593.
3. Pankratz L, Hickam DH, Toth S. The identification and management of drug-seeking behavior in a medical center. J Drug Alcohol Dependence 1989; 24:115-118.
4. Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman's The pharmacological basis of therapeutics. 9th ed., New York: McGraw Hill; 1996. p. 544.
5. Kreek MJ. Clinical update of opioid agonist and partial agonist medications for the maintenance treatment of opioid addiction. Semin Neurosci 1997; 9:140–157.
6. Portenoy RK, Payne R. Acute and chronic pain. In: Lowinson J, Millman R, Ruiz P, Langrod J, editors. In: Substance abuse. A comprehensive textbook. 3rd ed. Baltimore: Williams & Wilkins; 1997. pp. 563–589.
7. O'Brien CP. Drug addiction and drug abuse. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman's The pharmacological basis of therapeutics. 9th ed., New York: McGraw Hill; 1996. pp. 557-577.
8. Stimmel B. Basic concepts of dependence, addiction, tolerance, and withdrawal. In: Pain and its relief without addiction. New York: Haworth Press; 1997. p. 54.
9. Kreek MJ. Tolerance and dependence: Implications for the pharmacological treatment of addictions. In: Harris LS, editor. Problems of drug dependence. NIDA Research Monograph #76. Rockville, MD: NIDA; 1986.
10. Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman's The pharmacological basis of therapeutics. 8th ed. New York: Pergamon Press; 1990. pp. 485–521.
11. Stimmel B, Kreek MJ. Neurobiology of addictive behaviors and relationship to methadone maintenance. Mt Sinai J Med 2000; 67:375–380.
12. NIH Consensus Conference. Effective medical treatment of opiate addiction. JAMA 1998; 280:1936–1943.
13. Umbricht-Schneiter A, Ginn DH, Pabst KM, Bigelow GE. Providing medical care to methadone clinic patients: Referral vs on-site care. Am J Public Health 1994; 84(2):208–210.
14. Savage SR. Management of acute pain, chronic pain and cancer pain in the addicted patient. In: Miller NS, editor. Principles of addiction medicine. Chevy Chase, MD: American Society of Addiction Medicine ASAM; 1994. Sec. VIII 1, p. 4.
15. Stimmel B. Adequate analgesia in narcotic dependency. In: Hill CS, Fields WS, editors. Advances in pain research and therapy. New York: Raven Press; 1989. pp. 131–138.
16. Payte J, Khuri E. Principles of methadone dose determinants. In: State Methadone Treatment Guidelines CSAT Tip #1, DHHS Public # (SMA) 93-1991. Parrino, MW, Chair, U.S. Department of Health and Human Services, SAMHSA CSAT, Rockwall II, 5600 Fishers Lane, Rockville, MD 20857. pp. 47–58.
17. Compton MA. Cold-pressor pain tolerance in opiate and cocaine abusers. In: Correlates of drug type and use status. J Pain Symptom Manage 1994; 9:462–473.
18. Wesson DR, Ling W, Smith DE. Prescription of opioids for treatment of pain in patients with addictive diseases. J Pain Symptom Manage 1993; 8:289–296.