■ REVIEW ARTICLE

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Perioperative Management of Acute Pain in the Opioid-dependent Patient

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PAIN is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] In settings where pain is poorly controlled, patients suffer needlessly and may develop untoward emotional and cognitive responses that negatively affect behavior, rehabilitation, and quality of life. Providing rapid and effective relief of pain remains a humanitarian issue, whereas allowing patients to suffer as a result of analgesic undermedication may be considered a breach of fundamental human rights.[2–4]

Noticeable shifts in attitude have occurred in recent years regarding the use of opioids for the treatment of benign and malignancy-related pain. Primary care physicians and pain specialists prescribe opioids to a greater number of patients and in doses appropriate to needs.[3–7] A variety of opioid analgesics and delivery systems have been introduced that have increased patient satisfaction, physician acceptance, and overall use. Concomitant with improvements in pain relief and quality of life, an increasing number of patients are affected by issues related to opioid tolerance and physical dependence. There have been only a small number of published reviews that address the treatment of acute pain in patients with substance abuse disorders,[3–5] and fewer have focused specifically on perioperative pain management in opioid-dependent patients.[6,7] This review outlines factors responsible for opioid tolerance, physical dependence, and addiction and provides perioperative analgesic dosing guidelines for this specialized subset of patients.

Many patients who present for surgery and anesthesia may be opioid dependent or at least moderately tolerant to the therapeutic effects of opioid analgesics.[5–7] Causal factors underlying dependency include substance use disorder and, more commonly, legitimate use of opioid analgesics for treatment of chronic benign pain or malignancy-associated pain. Perioperative management of opioid-dependent patients poses a special challenge to primary caregivers, anesthesiologists, and pain specialists alike. This problem emanates from the often-conflicting needs to balance the rights of the patient on one hand and concerns of safety, diversion, and abuse on the other,[6,7] thus raising important ethical issues.[6–9]

The percentage of patients to whom opioid analgesics for chronic pain are prescribed has increased dramatically in recent years. An Australian study found that in 83% of patients with chronic pain, including back pain, other forms of benign pain, and cancer pain, opioids were prescribed by the patients' general practitioners at the time of referral to a multidisciplinary pain center.[10] Moreover, 47% of these patients were treated with strong opioids, such as morphine, oxycodone, and methadone. In another study, long-term opioid use and dose escalation was noted in one third of patients with chronic noncancer pain.[11] Factors responsible for the increased acceptance and prescription of opioid analgesics include physician education, concerns of analgesic undermedication and inadequate pain control, the favorable side effect profiles of newer semisynthetic and sustained-release opioids, and morbidity associated with nonsteroidal antiinflammatory drugs.[3,4,10]

Opioid-dependent patients, particularly substance abusers, may present with organ damage, infectious diseases such as human immunodeficiency virus, tuberculosis, hepatitis, associated psychological disorders, and drug-specific adaptations such as tolerance, physical dependence, and withdrawal.[5,12] These variables alone or in combination may diminish opioid analgesic effectiveness in the perioperative setting. The following issues should be considered to provide a comprehensive pain management strategy: (1) key concepts and definitions including substance abuse, physical *versus* psychological dependence, and tolerance development; (2) clinical differentiation of opioid dependency; (3) preoperative assessment issues; and (4) postoperative management issues.

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Table 1. Criteria for Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) Tolerance, as defined by either of the following:
   (a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect
   (b) Markedly diminished effect with continued use of the same amount of the substance

(2) Withdrawal, as manifested by either of the following:
   (a) The characteristic withdrawal syndrome for the substance (refer to criteria A and B of the criteria sets for withdrawal from the specific substances*)
   (b) The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

(3) The substance is often taken in larger amounts or over a longer period than was intended
(4) There is a persistent desire or unsuccessful efforts to cut down or control substance use
(5) A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
(6) Important social, occupational, or recreational activities are given up or reduced because of substance use
(7) The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

With physiologic dependence: evidence of tolerance or withdrawal (*i.e.*, either item 1 or item 2 is present)
Without physiologic dependence: no evidence of tolerance or withdrawal (*i.e.*, neither item 1 nor item 2 is present)

Criteria for opioid withdrawal*

A. Either of the following:
   (1) Cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer)
   (2) Administration of an opioid antagonist after a period of opioid use

B. Three (or more) of the following, developing within minutes to several days after criterion A:
   (1) Dysphoric mood
   (2) Nausea or vomiting
   (3) Muscle aches
   (4) Lacrimation or rhinorrhea
   (5) Pupillary dilation, piloerection, or sweating
   (6) Diarrhea
   (7) Yawning
   (8) Fever
   (9) Insomnia

Modified with permission from the DSM-IV.[13]

Basic Aspects of Substance Use Disorder

Criteria and Definitions

Substance use disorders have been classified according to clinical manifestations of psychological dependence with physical dependence or tolerance or both. Specific definitions can be found in table 1[13] and table 2.[13,14] It may be noted that the terms and their distinctive boundaries are not always clear, especially terms such as *addiction*, *dependence*, *abuse*, and *substance abuse*. This is partly because these terms have evolved over time in varying historical and sociocultural contexts.[12,13,15] They also reflect conflicts regarding appropriate terminology for the complex medical and psychosocial issues that underlie chronic and compulsive substance-using behavior. For example, the strict medical or biologic viewpoint that characterizes substance use disorder essentially as a disease or a disorder conflicts with the strictly sociocultural viewpoint that tends to "demedicalize" such behavior and explain it from a social and cultural context.[14-16] For the purpose of this review, the terms *addiction*, *substance use disorder*, and *psychological dependence* will often be used interchangeably.

Physical Dependence

The term *physical dependence* describes alterations in physiologic response that result from opioid binding and receptor-mediated activity.[15,16] Abrupt discontinuation of oral or parenterally administered opioids leads to opioid withdrawal or abstinence syndrome. This syndrome is characterized by increased sympathetic and parasympathetic responses mediated *via* the myenteric plexus, brainstem vagal and hypothalamic nuclei, resulting in hypertension, tachycardia, diaphoresis, abdominal cramping, and diarrhea, as well as physiologic and behavioral responses such as shaking ("wet dog shakes"), yawning, and leg jerking ("kicking the habit").[15-18] Opioid-dependent patients use the term "cold turkey" to describe the appearance of their cold, pale, goose-bumped skin when opioids are acutely discontinued.[14,16] These symptoms, although very unpleasant, are rarely life threatening; however, they can often confuse clinical diagnosis and care.[17] The time course of withdrawal is variable, depending on the opioid used.[17] The onsets and peak intensities of withdrawal symptoms for different opioid analgesics are presented in table 3.

Opioid Tolerance

Opioid tolerance is a predictable pharmacologic adaptation. Continued opioid exposure results in a rightward shift in the dose–response curve, and patients require increasing amounts of drug to maintain the same pharmacologic effects. The phenomenon of tolerance develops to analgesic, euphoric, sedative, respiratory depres-

Table 2. Substance Use Disorder: Related Definitions[12–14]

Term	Definition
Addiction	Commonly used term meaning the aberrant use of a specific psychoactive substance in a manner characterized by loss of control, compulsive use, preoccupation, and continued use despite harm; pejorative term, replaced in the DSM-IV[11] in a nonpejorative way by the term *substance use disorder* (SUD) with psychological and physical dependence
Dependence	1. Psychological dependence: need for a specific psychoactive substance either for its positive effects or to avoid negative psychological or physical effects associated with its withdrawal
	2. Physical dependence: A physiologic state of adaptation to a specific psychoactive substance characterized by the emergence of a withdrawal syndrome during abstinence, which may be relieved in total or in part by readministration of the substance
	3. One category of psychoactive substance use disorder
Chemical dependence	A generic term relating to psychological and/or physical dependence on one or more psychoactive substances
Substance use disorders	Term of DSM-IV[13] comprising two main groups:
	1. Substance dependence disorder and substance abuse disorder
	2. Substance-induced disorders (*e.g.*, intoxication, withdrawal, delirium, psychotic disorders)
Tolerance	A state in which an increased dosage of a psychoactive substance is needed to produce a desired effect; cross-tolerance: induced by repeated administration of one psychoactive substance that is manifested toward another substance to which the individual has not been recently exposed
Withdrawal syndrome	The onset of a predictable constellation of signs and symptoms after the abrupt discontinuation of or a rapid decrease in dosage of a psychoactive substance
Polydrug dependence	Concomitant use of two or more psychoactive substances in quantities and frequencies that cause individually significant physiologic, psychological, and/or sociological distress or impairment (polysubstance abuser)
Recovery	A process of overcoming both physical and psychological dependence on a psychoactive substance with a commitment to sobriety
Abstinence	Non-use of any psychoactive substance
Maintenance	Prevention of craving behavior and withdrawal symptoms of opioids by long-acting opioids (*e.g.*, methadone, buprenorphine)
Substance abuse	Use of a psychoactive substance in a manner outside of sociocultural conventions

sant, and nauseating effects of opioids but not to their effects on miosis and bowel motility (constipation).[16,17]

The degree or gradation of opioid tolerance is generally related to duration of exposure, daily dose requirement, and receptor association/disassociation kinetics.[16-18] Opioid agonists binding to the same receptor may show asymmetric cross-tolerance depending on their intrinsic efficacy.[14,16] For example, patients treated with sufentanil, an agonist having high intrinsic efficacy and requiring low receptor occupancy for a given analgesic effect, develop tolerance more slowly than to opioids having low intrinsic efficacy, such as morphine.[18,19] Although there are no clear gradation guidelines, individuals requiring the equivalent of 1 mg or more intravenous or 3 mg or more oral morphine per hour for a period greater than 1 month may be considered to have high-grade opioid tolerance.[20,21]

Table 3. Time Course of Opioid Withdrawal[17]

Opioid	Onset	Peak Intensity	Duration
Meperidine Fentanyl	2–6 h	6–12 h	4–5 days
Morphine Heroin	6–18 h	36–72 h	7–10 days
Methadone	24–48 h	3–21 days	6–7 weeks

Tolerance is observed in patients to whom opioids are legitimately prescribed for pain management as well as in those abusing this class of drug. In general, the higher the daily dose requirement, the greater is the degree of tolerance development.[16,19,20] This is of importance for many patients and caregivers who perceive an increasing opioid dose requirement as reflecting harmful addiction rather than a normal adaptation to this class of analgesics.[4,20,21]

Several types of opioid tolerance, including innate and acquired, have been characterized.[14-16] *Innate tolerance* refers to preexisting insensitivity, which is genetically determined and hence is present before drug exposure. True tolerance is acquired after multiple exposures.[16,21] This can be of three types: pharmacokinetic tolerance, learned tolerance, and pharmacodynamic tolerance. *Pharmacokinetic tolerance* refers to changes in distribution or metabolism of the drug, usually by enzyme induction and subsequent acceleration in metabolism. Opioids are biotransformed in the liver by two types of metabolic processes. Phase I reactions include oxidative and reductive reactions, such as those catalyzed by the cytochrome enzyme system (P-450), and hydrolytic reactions.[22,23] Phase II reactions involve conjugation of a drug or its metabolite to an endogenous substrate, such as D-glucuronic acid, generating highly

hydrophilic molecules that are excreted primarily by the kidneys. With the exceptions of the *N*-dealkylated metabolite of meperidine and the 6- and possibly 3-glucuronides of morphine, opioid metabolites are generally inactive.[16,17,22,23] Because P-450 is inducible by a host of compounds including opioids, barbiturates, and antiepileptics, patients exposed to these drugs for long terms can metabolize some opioids faster, thus producing pharmacokinetic tolerance.[16,22] There is good evidence that drug metabolism by genetically variable P-450 can also influence the development of tolerance and dependence.[22]

A second type of tolerance, termed *learned tolerance*, refers to a reduction in the effects of a drug due to compensatory mechanisms that are learned. For example, an opioid abuser learns to behave normally (*e.g.*, walking in a straight line) in spite of intoxication. Learned tolerance is also observed in methadone maintenance programs where abusers mask the effects of methadone so that a higher dose will be prescribed.[21,23]

Perhaps the most important form of tolerance relevant to opioids is pharmacodynamic tolerance. Pharmacodynamic tolerance has been related to neuroadaptive changes that take place after long-term exposure to the drug. These include changes in receptor density and alterations in receptor coupling to G proteins and signal transduction pathways.[16,21,24] Basic research has provided a better understanding of the cellular and molecular mechanisms mediating pharmacodynamic opioid tolerance.[16,21,25] These mechanisms occur at two distinct levels. The first occurs at the level of the opioid receptor and involves receptor desensitization on long-term or repeated exposure to opioids.[25] The concept of receptor desensitization underlies the classic hypothesis of opioid tolerance.[16,25] Opioid receptors on the cell surface become gradually desensitized by various mechanisms such as reduced transcription and subsequent decreases in the absolute number of opioid receptors (down-regulation), reduction in the number of opioid receptors on the cell surface by active endocytosis and receptor trafficking from cell surface to the interior of the cells (internalization), and the uncoupling of opioid receptors from underlying G proteins.[16,21,25,26] However, this classic hypothesis that tolerance is primarily related to receptor desensitization has yet to be proven.

A second mechanism proposed to explain pharmacodynamic tolerance involves up-regulation of the cyclic adenosine monophosphate (cAMP).[27] Acutely, opiates inhibit the functional activity of the cAMP pathway by blocking adenyl cyclase, the enzyme that catalyzes the synthesis of cAMP. However, with long-term opiate exposure, the cAMP pathway gradually recovers, and tolerance develops. Increased synthesis of cAMP may be responsible for physical dependence and physiologic changes associated with withdrawal. In this regard, the activity of the cAMP pathway increases far above baseline levels after abrupt discontinuance of opioid bind-

ing.[27,28] Up-regulation of cAMP has been most clearly demonstrated in the locus ceruleus of the brain,[27] but up-regulation within the dorsal horn of the spinal cord seems to be responsible for tolerance to opioid-induced analgesia.[28] Other areas where such cAMP up-regulation has been demonstrated include the nucleus accumbens, ventral tegmental area, periaqueductal gray, amygdala, dorsal horn of the spinal cord, and myenteric plexus of the gut.[28]

Long term-tolerance may represent a persistent neural adaptation.[26-29] This phenomenon may be observed in patients who discontinued prescribed or illicit opioid use many months or years previously but continue to exhibit opioid insensitivity. Long-term adaptations at the molecular and cellular level include (1) induction of transcription factors, such as δ Fos B, which regulate the function of several genes in a stable fashion, thus initiating neuronal plasticity; (2) activation of the central glutaminergic system; and (3) increased synthesis of spinal dynorphin.[26-29] Mao, Mayer, and coworkers[29-32] have provided strong evidence to suggest that glutamate and *N*-methyl-D-aspartate (NMDA) receptors play a critical role in the development of opioid tolerance and increased pain sensitivity. The role of NMDA receptor activation in the superficial laminae of the dorsal horn is particularly important.[30] Prolonged exposure to morphine indirectly activates NMDA receptors *via* second-messenger mechanisms and also down-regulates spinal glutamate transporters.[31] The resultant high synaptic concentration of glutamate and NMDA activation contributes to opioid tolerance and abnormal pain sensitivity, by various mechanisms. These include an influx of calcium, activation of protein kinase C, production of nitric oxide, and finally, neuronal apoptosis.[29,32] Spinal dynorphin also seems to play an important role in the development of opioid tolerance and hyperalgesia.[33] Concentrations of this endogenous opioid peptide increase after continuous exposure to μ-opioid receptor agonists.[33] Treatment with dynorphin antiserum[27,33] and NMDA receptor antagonists such as ketamine may attenuate the development of long-term tolerance to the analgesic effects of opiates.[30]

Clinical Differentiation of Opioid-dependent Patients

Anesthesiologists are likely to deal with a variety of opioid-dependent patients. The majority are those with chronic pain conditions who have been taking opioid analgesics for a prolonged period (months to years).[3-7] Clinical surveys of long-term opioid use in patients with both cancer and non–malignancy-associated pain have not shown escalating drug dosage to be inevitable; however, some degree of dose increase over time is often observed. This increase in dose requirement may be indicative of tolerance development, progression of disease, or both factors.[34] Nugent *et al.*[35] evaluated transdermal fent-

anyl (Duragesic; Janssen Pharmaceutical Products, Titusville, NJ) dose escalation in 73 patients with pain related to terminal malignancy. They noted that the initial fentanyl dose of 75 μg/h increased approximately 25% to a final median dose of 100 μg/h. Thirty-two of 73 patients initially enrolled continued the drug until or nearly until death (median, 2.9 months; range, 1–23 months). One criticism of this study is that the relatively short lifespan of patients enrolled did not allow sufficient time for the full extent of tolerance and dose escalation to be observed. A careful review of the data indicates that the Duragesic dose range was very wide (25–700 μg/h) and that patients with longer survival required the highest doses and exhibited the greatest degree of dose escalation.[35] Eight of 16 patients who received fentanyl for 3 months or longer required dose escalation, and 3 patients required dose increases to 300 μg/h or greater.

A second group exhibiting tolerance includes opioid abusers (opioid addicts). These patients are generally more problematic in terms of assessment and management.[3–6] The exact prevalence of opioid addicted patients presenting for surgery is not known but may be expected to vary depending on setting, type of surgery, prevalence in the local and regional population, and the ability of the physician to screen or detect these patients.

Heroin is the most commonly abused opioid. Approximately one adult among three who tries heroin becomes addicted to this drug.[21] Of patients entering treatment for heroin dependence in 1998 in the United States, 50% were non-Hispanic white, 25% were Hispanic, and 22% were non-Hispanic black.‡§‖[36] Heroin is readily available on the illicit market but has varying levels of purity. Each 100-mg bag of powder in early 1990 had only 4 mg (range, 0–8 mg) of heroin, and the rest was inert or sometimes contained toxic adulterants such as quinine. In the mid-1990s, street heroin reached 45–75% purity. In some large cities, 90% pure heroin was made available. Thus, heroin, which initially required intravenous injection, could be smoked or administered intranasally (snorted). Only 37% of new heroin abusers now inject the drug.§‖ Based on extrapolation of various data, including overdose deaths, applicants for treatment, and arrests, the number of heroin addicts in the United States is estimated to range from 800,000 to 1 million. Approximately 410,000 began using heroin be-

tween 1996 and 1998, underscoring a recent escalation in its incidence of abuse.§[36]

Heroin is a highly effective analgesic that is widely prescribed in the United Kingdom for control of acute and chronic pain.[16] Nevertheless, heroin's notoriety and perceived liability for abuse has prohibited its clinical use in the United States.

Prescribed opioids that provide a desirable "high," that is, a rapid onset to peak effect and pleasurable feelings of sedation or euphoria, are also commonly abused. These include rapid-acting semisynthetics such as oxycodone, hydrocodone, oxymorphone, and hydromorphone and nonmorphinian synthetics including methadone and fentanyl.[16,21,37,38] Only a small minority of abusers prefer drugs that produce dysphoria, such as meperidine and pentazocine.[16,21] Reports of oxycodone and hydrocodone abuse increased 68% and 31%, respectively, from 1999 to 2000.[36,39] The sustained-release opioid preparation OxyContin (Purdue-Pharma, Stamford, CT) has also gained notoriety for being abused. OxyContin was developed as a sustained-release opioid for moderate to severe pain that avoided peaks and troughs in analgesic plasma concentrations. OxyContin provides safe and effective pain relief; however, with tampering (i.e., crushing and powdering the preparation), it may be injected or used intranasally to provide a rapid and powerful opioid effect. Methadone (Dolophine [Eli Lilly, Indianapolis, IN]) is also abused. Oral methadone is not associated with euphoric or pleasurable effects but does provide effective analgesia in the setting of chronic pain and reliable maintenance for recovering addicts. Nevertheless, the oral tablet has high street value because after being crushed, placed into solution, and injected, addicts experience an intense and very prolonged "high."[21]

Drug addiction refers to a complex phenomenon with behavioral, cognitive, and physiologic components where the use of a particular drug assumes central importance in the user's life, even in the face of obvious physical or psychological harm.[20,21,37] Essentially, the life of the addicted patient centers on the repeated use of opioid and nonopioid narcotics to experience pleasure or to avoid displeasure (i.e., avoiding withdrawal). The matter, in actuality, is more complicated than classifying patients as abusers or legitimate users. For example, some patients to whom opioid analgesics are prescribed for chronic pain may actually become addicted to them. For user/abusers, pain control is only one of the motivations responsible for drug-seeking behavior and not the central theme, although it may superficially seem so.[15,21,37] It is difficult to ascertain the prevalence of opioid addiction in chronic pain patients, but a study performed by Fishbain et al.[37] found that 3–19% of chronic pain patients have an addictive disorder, which is comparable to the lifetime prevalence rate of addictive disorders in the general population. Savage[15] and others[12,37] have suggested that prevalence of addiction may

Table 4. Difference between Chronic Pain and Opioid-abusing Patients

Chronic Pain Patient	Opioid-abusing Patient
Appropriate use of opioid	Out of control with opioids
Opioids improve quality of life	Opioid impair quality of life
Aware of side effects	Unconcerned
Follows treatment plan	Does not follow plan
Has medication saved from previous prescriptions	Out of medication, "loses" prescriptions, has a "story"

be higher in chronic pain patients because of their background of emotional and psychological instability and conditioning behavior resulting from increasing pain intensity and relief resulting from opioid use.[12,15] Therefore, there may be a subgroup of patients presenting in the perioperative period who are an amalgam of user/abuser, who may not be easily diagnosed and may be difficult to treat (table 4).

A unique subset of opioid-tolerant patients, who are neither abusers nor those to whom opioids are prescribed for chronic pain, are former addicts enrolled in long-term methadone maintenance programs. Many of these individuals have not been users for many years, are gainfully employed, and enjoy normal lifestyles. Nevertheless, they are exposed to relatively large doses of methadone, 25–100 mg/day, and, as might be expected, exhibit high-grade tolerance to the antinociceptive effects of opioids.[15,38] There are no published research data on how to best address the concerns of this particular subclass. The anesthesiologist and pain specialist may devote time to allay patient apprehensions that they may lose control and possibly relapse or that their pain will be inadequately controlled. Patients may be reassured that despite a previous history of opioid dependency, effective pain control is an achievable goal and that the risk of relapse can be minimized.[3,15,37,39,40] The patient, addictionologist, and rehabilitation counselor may meet before surgery and develop a management plan. Together, they may formulate and agree to follow a realistic protocol that would minimize but not eliminate pain perception, while avoiding excessive opioid doses that might lead to recurrence of addictive disorder[15,40,41] (table 5). A practical approach might include the use of a medication agreement or contract, setting appropriate goals for pain intensity scores as well as daily dose of analgesic, and a method of analgesic administration. Patient monitoring may include drug screens, pill counts, and careful documentation of the postoperative course.[13,39,40]

A final subset of opioid-dependent patients is those who have well documented chronic pain and who, superficially, resemble opioid abusers by virtue of their often obsessive drug-seeking behavior. These patients

are usually found to have visited numerous physicians and have filled multiple prescriptions for opioids. In actuality, these individuals are not addicted but undermedicated and are only seeking adequate pain relief. This phenomenon was not recognized until recently, and has been termed *pseudoaddiction* by Weissman and Haddox.[42] Its prevalence is unknown, but it may result in the treatment team becoming negatively biased against the patient and denying him or her adequate opioid coverage. Pseudoaddictive behavior generally reflects patients' attempts to compensate for development of tolerance, progression of metastatic disease, or worsening of pain in settings where patients have become more functional. In general, pseudoaddictive patients can be differentiated from true drug abusers because increasing doses of opioids and improvement in pain control usually eliminate the drug-seeking behavior.[42]

Finally, it is relevant to note that methadone-maintained and other opioid-tolerant patients are relatively pain intolerant and demonstrate significantly increased sensitivity during cold pressor and thermal testing.[38,43] It has been hypothesized that continuous opioid receptor occupation produces hyperalgesia during less painful states; thus, these patients are unable to cope with sudden acute pain.[43–45] Therefore, after surgery or other settings of acute pain, caregivers should not restrict medicating opioid-dependent patients, but rather treat the pain aggressively, while being aware of the altered pharmacokinetic–pharmacodynamic and behavioral issues involved.[38,40,46] This necessitates a good assessment strategy and formulation of a perioperative management plan to provide adequate comfort to this particularly pain-sensitive population.

Patient Assessment Issues

There are several general principles that help to guide the anesthesiologist and pain specialist with perioperative pain management. First and foremost is to uncover the fact that the patient is an opioid user or an abuser and to recognize that issues related to physical and psychological dependence and opioid tolerance could

Table 5. Suggested Guidelines for Administration of Methadone[14]

1. Recovering opioid dependent patients enrolled in maintenance programs:
   Methadone—daily dose at the same time as usual (oral, s.c./i.m.; relationship between oral and parenteral methadone 2:1)[14]
2. Opioid dependent patients not enrolled in maintenance programs:
   Methadone—
   20–40 mg orally every 24 h
   10–20 mg subcutaneously/intramuscularly every 24 h
   1-25–2.5 mg intravenously every 5–10 min
   (Start with 20 mg orally/10 mg subcutaneously/intramuscularly, or 1.25 mg intravenously followed by titrated injections to diminish or to avoid withdrawal symptoms.)

Table 6. Opiate Abuse Checklist

1. The patient displays an overwhelming focus on opiate issues during pain clinic visits that occupy a significant portion of the pain clinic visit and impedes progress with other issues regarding the patient's pain. The behavior must persist beyond the third clinic treatment session.
2. The patient has a pattern of early refills (three or more) or escalating drug use in the absence of an acute change in his or her medical condition.
3. The patient generates multiple telephone calls or visits to the administrative office to require more opiates, early refills, or problems associated with the opiate prescription. A patient may qualify with fewer visits if he or she creates a disturbance with the office staff.
4. There is a pattern of prescription problems for a variety of reasons that may include lost medications, spilled medications, or stolen medications.
5. The patient has supplemental sources of opiates obtained from multiple providers, emergency rooms, or illegal sources.

Modified with permission from Chabal *et al.*[57]

profoundly influence the postoperative course. The importance of patient assessment and early recognition cannot be overemphasized, because failing this essential first step, principles that follow become less relevant.[5–7,41]

The assessment strategy aims at correct identification of the opioid-abusing patient from dependent individuals with chronic pain conditions.[15,47–49] The true abuser should be detected, whereas legitimate users are not to be falsely labeled as addicts. In other words, both "false-positive" as well as "false-negative" rates should be low.[49–51] However, this is easier said than done because of drug-seeking behavior associated with pseudoaddiction.[42,52] Alternatively, patients who achieve effective pain control may take extraordinary steps to maintain an adequate supply of medication. Although indicative of addictive drug seeking, such behavior may in actuality reflect the efforts of an extremely anxious patient to maintain tolerable pain relief and prevent undermedication.[47–49,52] Table 4 outlines the underlying principles that help clinicians to differentiate patients with chronic pain and opioid abusers.

Patients with substance use disorders to alcohol, marijuana, or nicotine show a higher incidence of dependence on other substances than the general population. This phenomenon has been termed *cross-addiction* or *polydrug abuse*.[21,48,50,51] Nearly 70% of opioid addicts in the United States are dependent on either cocaine or other habituating substances.[48,50] Opioid-dependent patients with superimposed cocaine dependence may present additional problems for acute caregivers, including hemodynamic instability and extreme emotional lability.[21,53] Some opioid-dependent patients are also codependent on benzodiazepines and other anxiolytics.[21] By simply focusing on opioid dependency issues and not accounting for or administering adequate doses of benzodiazepines, these individuals may experience

severe withdrawal reactions, including anxiety, agitation, and confusion.[46,47,52,53]

Applying *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition,[13] criteria for drug abuse to patients taking prescribed opiates for a chronic pain problem is difficult.[46,53,54] Therefore, special assessment criteria must be developed and applied.[54–56] A retrospective case review identified some patient characteristics, such as recent polysubstance abuse, early prescription abuse, especially oxycodone, and aberrant drug-seeking behavior, as predictive of later opioid abuse.[55] Two recently published studies addressed this assessment issue.[57,58] Chabal *et al.*[57] introduced a five-point prescription opiate abuse checklist that is easy to use, although it may lack sensitivity (table 6). Compton *et al.*[58] developed a more detailed 42-item screening tool called the Prescription Drug Use Questionnaire that may help clinicians to uncover opioid abuse in chronic pain patients. These assessment tools are still in preliminary stages of development, and large-scale multicenter trials are warranted before their widespread application. A major problem with abuse checklists and questionnaires is that some of the criteria used for assessment necessitate prolonged physician contact with the patient and hence may be difficult to apply in acute perioperative settings.[54,57,58]

During patient assessment, the anesthesiologist should recognize that the terms *opioid user* or *abuser* may be considered highly sensitive labels.[53,55,56] Patients are keenly aware of the significant social stigma surrounding opioid dependency and are entitled to privacy and the right to confidentiality. The anesthesiologist should develop a clear management strategy that maintains a balance: to gain patient trust with an understanding and caring approach while being prepared to overcome high-grade tolerance with liberal doses of opioid and nonopioid analgesics.[3–5,7,41]

The anesthesiologist should also be aware of the rapidly changing profile of opioid-based analgesia. Newly developed and marketed opioids often do not have names that are readily recognizable as opioids but represent potent or long-acting preparations that can confer a high degree of tolerance and dependence. Examples include (1) rapid-acting or novel-delivery preparations, Actiq (Cephalon Inc., West Chester, PA; fentanyl oralet), Nasal Stadol (Bristol-Myers Squibb, New York, NY; butorphanol), and Oxy-IR (immediate-release oxycodone) (Purdue-Pharma, Stamford, CT); (2) sustained-release preparations containing fentanyl, Duragesic (fentanyl transdermal patch) or morphine (Kadian; [Elan Corporation, Dublin, Ireland], Avinza [Mayne Pharma (USA), Paramus, NJ], MS-Contin [Purdue-Pharma]); and (3) less often prescribed preparations containing codeine (Fioricet with codeine, Fiorinal with codeine [Sandoz Pharmaceuticals, East Hanover, NJ]), hydrocodone (Hy-

codan [Endo Laboratories, Chaddsford, PA]), and methadone (Dolophine).

It should also be recognized that some patients presenting to the anesthesiologist or preadmission testing unit physicians may not realize that they are opioid dependent and may unintentionally deny the possibility. Patients may not know that opioids have been prescribed to them or may not recognize that escalations in their daily need for pain relievers reflects tolerance development.[15,21] Although most patients are aware that morphine and Demerol (Sanofi-Synthelabs, New York, NY) are narcotics, many are not aware that they may have been given opioids of even greater potency for treatment of arthritis and low-back pain.

Other patients may consciously deny or underplay reporting opioid use or the amount of drug consumed.[21,37,41,46] The latter scenario is likely to occur in patients highly addicted to opioids. In fact, these are the patients who must be identified before induction of anesthesia, to minimize postoperative risks of undermedication and inadequate analgesia. It should be understood that tolerance to any one opioid preparation results in clinically measurable insensitivity to most others. It does not matter whether individuals are using legally prescribed oxycodone or abusing street heroin—both exhibit a diminished response to intraoperative doses of fentanyl and postoperative doses of morphine.[38,46,56,59] In same-day surgical settings, not recognizing that a patient is highly opioid dependent may result in inadequate pain relief and an unscheduled hospital admission for pain management. In many cases, the onus of recognition falls on the anesthesiologist, either in preadmission testing or, in the worst-case scenario, just minutes before the scheduled start of the procedure. An increased clinical index of suspicion is useful especially with patients who exhibit a chronic pain condition, those to whom opioids have been recently prescribed, and others whose lifestyle, general appearance, or general physical examination (*e.g.*, multiple needle marks, thrombosed superficial veins, and skin abscesses) are suggestive of harboring an addictive disorder.[5–7,39]

Finally, it is worth emphasizing that the immediate perioperative period is not the optimal time to attempt detoxification or rehabilitation management for any patient abusing opioids.[7,41,49] Although obviously important, such issues should be dealt with later in the postoperative period, when the patient is stable and pain has declined in intensity.

Patient Treatment

Preoperative Period. There are few controlled studies or scientifically rigorous sources of data available to guide the anesthesiologist in optimizing anesthetic and analgesic care, despite the increasing prevalence of opioid dependency.[5–7,41,44] Perioperative management of opioid-dependent patients is not discussed in any major

anesthesiology textbook. The majority of scientific literature in this area is comprised of case reports that include recommendations for patient treatment, often based on the authors' experience and expertise. We have summarized pertinent clinical findings from a number of case reports and, together with suggestions provided by pain management specialists at major medical centers and our experience caring for opioid-dependent patients, developed guidelines that may improve postoperative analgesia and patient satisfaction. These guidelines, although not tested scientifically, have been advocated in settings of opioid dependency and receptor down-regulation and serve as a backdrop against which future controlled clinical trials may be planned.

Perioperative management of opioid-dependent patients begins with preoperative administration of their daily maintenance or baseline opioid dose before induction of general, spinal, or regional anesthesia. Patients should be instructed to take their usual dose of oral opioid on the morning of surgery. Because most sustained-release opioids provide 12 h or more of analgesic effect, baseline requirements will generally be maintained during preoperative and intraoperative periods. Thereafter, baseline requirements may be provided orally, particularly after ambulatory surgery, or parenterally for those recovering in the hospital from more invasive procedures.[5,41,44] Recovering addicts enrolled in a methadone maintenance program[59,60] or receiving buprenorphine maintenance[61] should continue taking those medications with one sip of water on the morning of surgery. The anesthesiologist usually need not be concerned about redosing baseline opioids during the intraoperative period because these preparations are also associated with prolonged durations of activity. Unless contraindicated, patients should also be instructed to take their morning dose of cyclooxygenase-2 inhibitor to reduce inflammatory responses to surgery and to augment opioid-mediated analgesia.[62]

Patients who are instructed not to take or those who forget to take baseline opioids may be treated with an equivalent loading dose of morphine or hydromorphone, administered preoperatively as an oral elixir (if time permits) or intravenously, either at anesthetic induction or during the operative procedure. Patients should also be instructed to maintain their transdermal fentanyl patch into the operating room. If the preparation was removed, an intravenous fentanyl infusion may be initiated to maintain baseline plasma concentrations. A new patch may then be applied intraoperatively; however, it may take 6–12 h to reestablish baseline analgesic effects.[63,64] The fentanyl infusion may be gradually decreased in rate and eventually discontinued during that time.

Baseline intravenous opioid infusions should also be maintained preoperatively and then converted to intravenous patient-controlled analgesia (PCA) after recovery

from anesthesia.[65] Epidural and intrathecal opioid infusions delivered by internally implanted devices are generally maintained throughout the perioperative period and are used to maintain baseline pain control. The only exception to this rule applies to patients receiving intrathecal infusions of the nonopioid relaxant Lioresal (baclofen) (Watson Laboratories, Corona, CA). It may be prudent to discontinue or reduce the intrathecal infusion rate of Lioresal during the immediate perioperative period because central effects and peripheral skeletal muscle relaxing effects of this agent may enhance neuromuscular blockade and increase the incidence of hypotension and excessive sedation.[66]

Intravenous or oral doses of methadone and morphine may be used as baseline and intraoperative analgesics for patients abusing heroin.[7,41,43,60] Baseline doses of intravenous methadone or morphine are also recommended for patients enrolled in a methadone maintenance program.[60] Before administering an intravenous loading dose, heroin addicts may require placement of a central line because they typically present with poor peripheral venous access.[15,41]

The importance of maintaining a baseline dose of methadone was underscored in a case described by de Leon-Casasola and Lema.[19] An opioid-dependent patient who required 1,000 mg methadone daily did not have her methadone continued after pelvic surgery. She developed agitation tachycardia, salivation, and lacrimation in addition to poor pain control. Her symptoms were diagnosed as acute opioid withdrawal, and she was given a morphine loading dose of 300 mg, followed by an intravenous infusion of 110 mg/h. Withdrawal symptoms disappeared, and she experienced good pain control. During the next several days, 30 mg methadone every 6 h was restarted, and her morphine infusion was decreased by 10 mg/h each day.

Recovering opioid abusers maintained on buprenorphine may continue on this partial opioid agonist for postoperative pain control. If the quality of analgesia provided by buprenorphine is inadequate, one may consider supplementation with methadone and morphine. Sublingual buprenorphine, 0.8 mg, is equianalgesic with 20 mg oral methadone.[16,67] Opioid antagonists, including naloxone and naltrexone, should be avoided in opioid-dependent patients.[67,68,69] Postoperative administration may precipitate withdrawal symptoms in patients who are dependent on potent opioids.[69] In addition, mixed agonist-antagonist–type opioids that block μ receptors, such as nalbuphine, butorphanol, and pentazocine, may precipitate acute opioid withdrawal in these individuals.[16,68] Similar abstinence symptoms have been reported in highly dependent patients who were treated with the weak μ-opioid α-adrenergic receptor agonist tramadol.[70] Naltrexone, a long-acting oral opioid antagonist often used in recovering opioid abusers, should also be discontinued at least 24 h before surgery.[71] After

abrupt discontinuation, a selective up-regulation of μ receptors with enhanced opioid sensitivity may develop. Perioperative opioids must be titrated carefully to avoid excessive sedation or respiratory depression in this setting.[71]

Intraoperative and Postoperative Periods. Patients recovering from ambulatory surgery should be initially treated with intravenous boluses of fentanyl or sufentanil. After stabilization in the postanesthesia care unit (PACU), they may be restarted on oral opioids in doses higher than baseline requirements, depending on the invasiveness of the procedure.[41,72] In most nonambulatory surgeries, oral opioids are discontinued after anesthetic induction and converted to a parenteral equivalent.[5,7,41,72] Judicious doses of morphine, hydromorphone, fentanyl, or methadone are used to augment intraoperative anesthesia and to provide effective postsurgical analgesia in addition to covering baseline requirements.[7,41,72] Precise dosing guidelines have not been developed, but opioid doses required to meet intraoperative and postsurgical analgesic requirements are affected by receptor down-regulation and may need to be increased 30–100% in comparison with requirements in opioid-naive patients[3,5,72] (refer to section on dosing guidelines). Some anesthesiologists prefer to slowly "front load" relatively large amounts of morphine or methadone to cover baseline and estimated intraoperative opioid requirements after applying full monitoring and mask oxygen and while maintaining active communication with the patient. Others prefer administering one half of the estimated dose during preinduction and induction periods and titrate the remainder as the case progresses.[72]

Differences in oral to intravenous dose equivalency need to be appreciated to estimate perioperative baseline and supplemental opioid dose requirements. Most intravenous or intramuscular doses of opioid can be adjusted downward from doses taken orally because parenteral administration bypasses gastrointestinal absorption variables and first-pass hepatic clearance and metabolism.[16,67,73,74] This is particularly the case with intravenous morphine and hydromorphone which have three and two times, respectively, greater bioavailability and systemic potency than equivalent oral doses.[67,73-75] In contrast, oxycodone and sustained-release OxyContin have high oral bioavailability that approaches 83% of an intravenous dose, and the baseline oral dose can be approximated by nearly similar doses of intravenous morphine (1–1.5 mg oral oxycodone = 1 mg intravenous morphine).[67,76,77] Patients treated with transdermal fentanyl (Duragesic) or receiving intravenous PCA morphine/hydromorphone at home or hospice are more straightforward because their baseline requirement may be supplied with an equivalent intravenous dose of opioid.[63,73]

Because there may be significant interpatient variability in opioid dose requirements, intraoperative vital

signs, particularly heart rate, respiratory rate, and degree of pupil dilation, should be closely monitored. The optimal intraoperative dose avoids undermedication and overmedication, both associated with negative perioperative outcomes.[6,7,41,72] One technique that may help to gauge the adequacy of intraoperative opioid dosing is to reverse neuromuscular blockade and allow patients to breath spontaneously at later stages of the general anesthetic. Patients with respiratory rates greater than 20 breaths/min and exhibiting slight to markedly dilated pupils generally require additional opioid dosing. Intravenous boluses of morphine, fentanyl, or hydromorphone are titrated as needed to maintain a rate of 12–14 breaths/min and a slightly miotic pupil.

The surgeon may consider infiltrating the surgical site with a long-acting local anesthetic (0.5% bupivacaine or 0.75% levobupivacaine to further block pain perception during the immediate recovery period (refer to the section on regional analgesia). The patient may also be maintained in a mildly sedated state to avoid agitation and pain on emergence from anesthesia.[7,72] This may be accomplished by administering additional opioid as needed before patient transport to the PACU.

Parenteral Analgesia for Postoperative Pain. A continuous parenteral opioid infusion or intravenous PCA provides useful options for effective postsurgical analgesia.[78,79] Initiation of intravenous PCA in the PACU minimizes the risk of undermedication and breakthrough pain that may occur during patient transport to the surgical care unit. To compensate for opioid tolerance and receptor down-regulation, higher than normal doses of morphine or hydromorphone should be considered.[41,72] A basal infusion equivalent either to the patient's hourly oral dose requirement or one to two PCA boluses per hour may be added to maintain baseline opioid requirements.[79] Basal infusions may not be required in patients receiving baseline analgesia *via* transdermal fentanyl patch.

Allowing substance abusers or recovering addicts to use intravenous PCA to control postoperative pain was initially considered controversial because caregivers worried that these individuals might self-administer excessive amounts of opioid or rekindle addictive behavior.[7,41,72] It is now recognized that intravenous PCA may be offered to selected patients provided that pain intensity and opioid consumption are carefully assessed and that such therapy is supplemented with baseline doses of methadone, neural blockade, and nonopioid analgesics.[7,41,80,81]

Boyle[80] reported on the successful use of PCA in a 23-yr-old woman undergoing cesarean delivery who had been using intravenous heroin until the seventeenth week of her pregnancy, when she switched to 25 mg/day oral methadone. At 32 weeks, it was decided to deliver the baby by cesarean delivery with general anesthesia. Postoperative analgesia was provided by patient-administered intravenous boluses of morphine (2 mg)

with a background (basal) infusion of 3 mg/h. Intravenous PCA provided adequate pain relief for this patient, although initial morphine requirements (mg/h) at 2, 4, and 6 h were high (15, 16, and 10 mg, respectively).[80] At 36 h after surgery, the basal morphine infusion was discontinued, and oral methadone was restarted. PCA boluses of morphine were continued for breakthrough pain until 48 h, whereupon oral morphine was substituted.[80]

Oral methadone has been advocated for use in patients who experience ineffective postsurgical analgesia despite administration of relatively high doses of morphine or synthetic derivatives of morphine. Sartain and Mitchell[82] recently described the case of a 25-yr-old man with a history of intravenous opioid abuse who was hospitalized with multiple fractures. The patient had dropped out of a methadone maintenance program and was being treated with a sustained-release morphine preparation, 100 mg twice daily. In the hospital, treatment with intravenous PCA morphine and supplemental doses of ketamine did not provide adequate pain relief. After receiving 100 mg oral morphine as well as 509 mg morphine and 769 mg ketamine by intravenous PCA over a 24-h period, his caregivers discontinued such therapy and initiated 50 mg oral methadone four times daily. This strategy was successful because the patient reported rapid and effective pain control. The improved analgesic efficacy observed in this case was probably related to the ability of methadone to activate a different spectra of μ receptor subtypes to which morphine tolerance has not developed.[83–86] In addition, the activity of methadone at α-adrenergic receptors may provide useful analgesic effects that are not influenced by high-grade opioid tolerance.[38,84] Finally, d-methadone has been shown to block morphine tolerance and opioid-induced hyperalgesia by virtue of its NMDA receptor antagonistic and α-adrenergic agonistic properties.[38,84,85] For these reasons, some have advocated methadone as the intravenous PCA opioid of choice in opioid-dependent patients.[4,80,81,86] Suggested guidelines for administration of methadone are presented in table 5.

Nonopioid analgesic adjuvants may also be used to reduce opioid dose requirements and provide multimodal analgesia, although relatively few evaluations have been performed in opioid-dependent patients. Nonopioid analgesics including nonselective nonsteroidal anti-inflammatory drugs and more specific cyclooxygenase-2 inhibitors to minimize inflammatory pain,[62,87,88] low doses of ketamine (0.5 mg/kg) or similar agents to antagonize NMDA receptor activation,[89,90] and clonidine patch (0.1 mg/h), which provides effective α-adrenergic–mediated analgesia, have been studied.[91]

Low-dose ketamine was used as an adjunct for parenteral opioids in highly tolerant patients with severe cancer pain[90] and as balanced analgesia for the management of pain associated with multiple fractured ribs in an opioid addict.[92] In the latter case, initial analgesic ther-

apy consisting of epidural boluses of morphine (5 mg) and bupivacaine (0.25%) did not provide pain relief. Epidural analgesia was then supplemented with intravenous PCA fentanyl, 40-μg bolus dose with a 5-min lockout time. Analgesia was still inadequate. The combination of a ketamine intravenous infusion at 10 mg/h plus 250 mg naproxen twice daily finally provided effective analgesia allowing active physiotherapy. The ketamine infusion was stopped, and the PCA fentanyl bolus was reduced to 20 μg on day 8. Thereafter, the patient was started on 40 mg methadone twice daily and made a good recovery.[92]

Finally, it may be worthwhile to consider the contribution of fear and anxiety to the overall pain syndrome.[21,41,72] This is especially true for opioid-tolerant patients and polydrug abusers. Anxiety and fear should be discussed and treated with appropriate medication as required.

Neuraxial Analgesia for Postoperative Pain. Neuraxial administration of opioids offers a more efficient method of providing postsurgical analgesia than parenteral or oral opioids.[93–96] Intrathecal and epidural doses of morphine are roughly 100 times and 10 times more efficacious, respectively, than the same dose of morphine given parenterally.[94] Therefore, significantly greater levels of analgesia can be delivered to those patients recovering from more extensive procedures where postsurgical parenteral opioid doses would be expected to be very high.

There have been few evaluations of neuraxial analgesia in opioid-dependent patients.[3,5,19,92,95,96] In contrast to local anesthetic blockade,[94] neuraxial opioid analgesia is influenced by down-regulation of spinal opiate receptors,[16,18] and epidural and intrathecal dose requirements are increased proportionally.[18,95,96] Indirect scientific support for this comes from the landmark study of Wang *et al.*,[95] who noted that patients with terminal pelvic cancer and dependent on high doses of parenteral morphine (5–20 mg every 2 h) required relatively large amounts of intrathecal morphine (1 mg as often as every 4 h) to achieve effective pain relief. This dose of intrathecal morphine, although 2–3 times higher than amounts used for postoperative analgesia in opioid-naive patients, did not result in excessive sedation, nausea/vomiting, or delayed respiratory depression.

The opioid dose is generally a small fraction of the patient's baseline oral requirement with intrathecal administration. Despite the fact that patients experience effective pain relief, plasma concentrations and supraspinal receptor binding may decline to the point that acute withdrawal is precipitated, unless supplementary opioids are given.[19,96] For this reason, it is important to maintain baseline opioid requirements either orally or by intravenous PCA. Monitoring for complications such as excessive sedation and respiratory depression is mandatory when administering opioids in higher dose and *via*

different routes of administration. Caregivers on postsurgical units should be instructed about the high opioid dose requirements of highly tolerant patients, as well as the potential for overdose when parenteral and neuraxial opioids are administered concomitantly.

Increasing the concentration of epidurally administered opioids may compensate for spinal receptor down-regulation. An epidural opioid loading dose greater than that used in naive patients, followed by a more concentrated infusion, may improve pain control in highly tolerant patients. Patient-controlled epidural boluses may be added to complement the basal epidural infusion. Local anesthetics such as 0.1% bupivacaine, 0.1% levobupivacaine, or 0.2% ropivacaine may be added to the epidural infusate to provide selective neural blockade and augment opioid-mediated analgesia.[94,96] Rescue doses of parenteral and possibly oral opioids should be administered to gain supraspinal analgesic effects and to prevent withdrawal symptoms. In patients ordered to take nothing by mouth, epidural analgesia is used for postsurgical pain while baseline requirements are maintained with intravenous PCA, intravenous boluses of opioids, or "sip and swallow" doses of methadone.

Switching to an opioid that has high intrinsic potency has been previously advocated.[18,19,96,97] de Leon-Casasola and Lema[96] presented a case in which a patient with high-grade opioid tolerance recovering from pelvic surgery experienced ineffective pain control despite treatment with relatively high doses of epidural morphine (30 mg/h). After an epidural bolus of sufentanil (50 μg), her pain was substantially reduced. An epidural infusion containing 2 μg/ml sufentanil and 0.1% bupivacaine maintained excellent pain control for 19 days after surgery. After this interval, the medication was changed to oral methadone. Although this patient clearly benefited by switching to a more potent opioid agonist, it is conceivable that improved pain control could also have been achieved by increasing the dose of epidural morphine to 50–60 mg/h.

A final method that may be used to improve neuraxial analgesic efficacy is to administer opioids directly into the subarachnoid space.[94,95] Subarachnoid dosing markedly increases the concentration of molecules available to bind spinal opioid receptors. Placement of subarachnoid catheters and administration of intrathecal opioids, although rarely used for acute pain management in opioid-naive patients, may provide effective analgesia in opioid-dependent patients (refer to intrathecal dosing guidelines outlined in appendix) although no scientific literature is available.

Regional Analgesia for Postoperative Pain. Expert opinion suggests that, whenever possible, opioid-tolerant patients should be offered regional anesthesia or analgesia, particularly for procedures performed on the extremities.[5,7,41,72] Techniques that may be considered include tissue infiltration and nerve and plexus block-

ade. Advantages of a regional anesthetic/analgesic approach include reduction in parenteral/oral opioid requirements and improvement in distal perfusion as a result of sympathetic blockade. Regional blockade may offer a useful anesthetic alternative for most peripheral vascular and reimplantation surgeries and for other procedures requiring graft revision or replacement. Neural blockade may be initiated with bupivacaine or levobupivacaine in standard doses, and a continuous infusion may be continued postoperatively. Patients may be discharged home with indwelling brachial plexus catheters and local anesthetic infused for up to 48 h *via* disposable pumps. Other interventions include injection of local anesthetics and opioids into the knee and other articular joints and injections of local anesthetics into disc spaces or the iliac crest for spinal surgery. The goal is to minimize pain perception and reduce, although not completely eliminate, the use of oral or parenteral opioids for baseline requirements in dependent patients.[7,72]

Dose Tapering. Baseline requirements for oral opioids after ambulatory surgery generally must be supplemented with additional medication (generally 20–50% increases above baseline) to accommodate pain associated with surgical injury.[72] Oral opioids should then be down-titrated slowly over 3–7 days to presurgical amounts as the intensity of acute pain diminishes.

Opioid analgesics should never be withheld from dependent patients, but some caregivers cautiously underestimate theoretical intravenous dose equivalencies in patients requiring extremely high baseline doses of oral or transdermal opioids.[72,73] This is especially true in patients recovering from surgical procedures performed to reduce baseline chronic pain.[7,72,86] For example, only 50% of an intravenous equivalent may need to be given to patients requiring oxycodone doses greater than 200 mg/day, morphine doses greater than 300 mg/day, or transdermal fentanyl doses greater than 150 μg/h. Opioid dosing may be increased as needed if patients do not experience adequate pain control. Baseline opioid dosing should be gradually tapered rather than abruptly stopped to avoid withdrawal when pain is markedly reduced after successful spine surgery, neurolysis, or cordotomy.[7,41,72,97] In this setting, baseline dose may be reduced by 50% the day after surgery and then tapered 25% every 24–48 h, depending on the opioid administered. When the dose has been decreased to 10–15 mg morphine equivalent per 24 h, it may be discontinued.[72]

Alternatively, patients can be switched to an equianalgesic dose of methadone, which can then be slowly tapered.[7,60,84] Transdermal fentanyl patches are easily maintained and replaced. Surgical improvement in analgesia may allow fentanyl dose tapering of 25% within 24–48 h in patients recovering from back procedures. Further tapering may continue every 48–72 h as tolerated by the patient. Application of a 0.1–0.2 mg/h clonidine transdermal patch may help to minimize some

of the autonomic aspects of opioid withdrawal if symptoms should become distressing.[21]

After hospital discharge, opioid-dependent patients should be scheduled for a follow-up visit with a pain specialist, who can optimize pain management during rehabilitation and facilitate opioid dose tapering. Some patients may require the expertise of an addictionologist. Suggested guidelines for perioperative pain management in opioid-tolerant patients are provided in table 7 and the appendix.

Future Directions in Management

Several newer agents have been shown to enhance postoperative analgesia or chronic pain control and may serve as useful analgesic adjuncts in opioid-dependent patients. These include the α_2-adrenergic receptor agonist dexmedetomidine,[98] the NMDA receptor antagonist dextromethorphan,[99] the anticonvulsant gabapentin,[100] and the second-generation parenteral cyclooxygenase inhibitors etoricoxib and parecoxib.[101] Dextromethorphan, a common over-the-counter antitussive, has been shown to have a postoperative opioid-sparing effect in patients with bone malignancy[102] and in patients under-

Table 7. Guidelines for Perioperative Pain Management in Opioid-tolerant Patients

Preoperative
1. Evaluation: Evaluation should include early recognition and high index of suspicion.
2. Identification: Identify factors such as total opioid dose requirement and previous surgery/trauma resulting in undermedication, inadequate analgesia, or relapse episodes.
3. Consultation: Meet with addiction specialists and pain specialists with regard to perioperative planning.
4. Reassurance: Discuss patient concerns related to pain control, anxiety, and risk of relapse.
5. Medication: Calculate opioid dose requirement and modes of administration; provide anxiolytics or other medications as clinically indicated.

Intraoperative
1. Maintain baseline opioids (oral, transdermal, intravenous).
2. Increase intraoperative and postoperative opioid dose to compensate for tolerance.
3. Provide peripheral neural or plexus blockade; consider neuraxial analgesic techniques when clinically indicated.
4. Use nonopioids as analgesic adjuncts.

Postoperative
1. Plan preoperatively for postoperative analgesia; formulate primary strategy as well as suitable alternatives.
2. Maintain baseline opioids.
3. Use multimodal analgesic techniques.
4. Patient-controlled analgesia: Use as primary therapy or as supplementation for epidural or regional techniques.
5. Continue neuraxial opioids: intrathecal or epidural analgesia.
6. Continue continuous neural blockade.

After discharge
7. If surgery provides complete pain relief, opioids should be slowly tapered, rather than abruptly discontinued.
8. Develop a pain management plan before hospital discharge. Provide adequate doses of opioid and nonopioid analgesics.
9. Arrange for a timely outpatient pain clinic follow-up or a visit with the patient's addictionologist.

going general surgery during epidural or general anesthesia.[103,104] Well-controlled phase III clinical evaluations of combined opioid agonist–dextromethorphan analgesics for postsurgical pain are in progress.#

Gabapentin has been shown to reduce postoperative morphine requirement in patients undergoing radical mastectomy[101] and also to enhance morphine analgesia in healthy volunteers.[105] There are no published reports of efficacy of this drug in opioid-dependent patient groups, but it may compliment standard measures outlined above.

Another promising line of research and potential therapy concerns the development of agents targeted to reduce opioid tolerance and increase intrinsic efficacy, thus obviating the need for dose escalation. Production of nitric oxide, possibly influenced by NMDA receptor activation, has been implicated in tolerance development; however, its exact role remains unclear. Inhibition of nitric oxide synthase has been shown to reduce morphine tolerance.[106] In contrast, Lauretti *et al.*[107] recently showed that transdermal nitroglycerine (which increases *in vivo* concentrations of nitric oxide) provides a measurable opioid-sparing effect in patients with cancer pain. Dextromethorphan has been shown in animal studies to attenuate the development of and reverse established opioid tolerance.[108] Finally, Basile *et al.*[109] recently demonstrated the role of M5 muscarinic acetylcholine receptors in mediating the reward and withdrawal-related properties of opioids. The analgesic efficacy of morphine and the development of tolerance remain unaltered by the lack of M5 receptors. One possible implication of this research is that if the M5 receptor is blocked, opioid analgesia might remain unimpaired, whereas opioid tolerance and addiction may not develop. This may ultimately have significant clinical implications in treating opioid-dependent patients.

Conclusion

Opioid-dependent patients have special needs in the perioperative period. There is lack of scientifically rigorous studies in this important area, and most of the information must be derived from anecdotal reports and personal experience of anesthesiologists working in this field. This review has highlighted the need to conduct such studies in the future.

The anesthesiologist plays the key role in maintaining baseline opioid requirements, administering supplemental intraoperative and postoperative opioids, and providing nonopioid analgesics and neural blockade. To prevent undermedication, the anesthesiologist and pain specialist may be required to titrate doses of opioid that would clearly result in overdose in opioid-naive patients. Nevertheless, undermedicating these patients must be avoided. The dependent patient experiencing opioid overdosage is rare. However, delivering a patient to the PACU who has severe pain is an unacceptable practice and often results in an extremely difficult and time-consuming management issue. Awareness and administration of appropriate doses of analgesics as well as continuous clinical monitoring remain the keys to successful perioperative pain management in this special group of patients.

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Appendix: Dosing Recommendations for Perioperative Analgesia**

1. Day of Surgery

The patient should be instructed to take his or her morning dose of oral opioid before leaving for the hospital. The patient should not remove transdermal fentanyl patches but can replace them. Patients who are unable to take baseline opioids (heroin addicts, accident victims, or patients who forget to take prescribed analgesics) may be provided equianalgesic loading with intravenous doses of morphine, hydromorphone, or methadone.

2. Preinduction Period

After placement of a peripheral intravenous line, parenteral doses of fentanyl, morphine, or hydromorphone 25–50% higher than typically used in opioid-naive patients may be administered for sedation before induction of general or regional anesthesia. Intravenous methadone

may be considered for heroin addicts and methadone-maintained patients. A methadone loading dose that approaches the patient's daily baseline dose or a minimum of 0.3 mg/kg may be given either before or during induction of anesthesia.

3. Intraoperative Period

After induction of general anesthesia, supplemental intravenous doses of fentanyl, hydromorphone, or morphine are titrated as needed to augment intraoperative anesthesia and to treat surgical pain. The total intraoperative dose is liberal, generally 30–100% greater than that administered to naive patients. Patients treated with methadone may be given additional intraoperative doses (0.1 mg/kg) titrated in response to hemodynamic and pupillary responses.

4. Intravenous PCA

Before initiating intravenous PCA, an additional loading dose of opioid may be required. Typical loading doses include morphine (5–20 mg), hydromorphone (2–5 mg), oxymorphone (1–2 mg), fentanyl (100–250 μg), or sufentanil (25–75 μg). The PCA device may be programmed to administer intermittent bolus doses of 3–5 mg morphine, 0.5–1 mg hydromorphone, 50–100 μg fentanyl, or 10–20 μg sufentanil, with a lockout interval ranging from 6 to 10 min. A basal opioid infusion is added to cover baseline requirements in patients who cannot take their daily dose of oral opioid. A baseline oral opioid dose is converted to an equianalgesic intravenous dose, which is then administered as a basal infusion hourly over a 24-h period. For example, if the patient's daily requirement for morphine is 60 mg, that dose is divided by 3 to compensate for the higher bioavailability of intravenous morphine, and the resulting 20 mg is administered as a basal morphine infusion of 0.8 mg/h.

5. Epidural Analgesia

Patients receiving epidural infusions or patient-controlled epidural analgesia may be given an opioid loading dose of 50–75 μg sufentanil, 100–200 μg fentanyl, 2–3 mg hydromorphone, or 8–12 mg morphine. In our practice, loading doses are mixed with local anesthetic (0.25–0.5% bupivacaine or 0.25–0.75% levobupivacaine) and generally administered before surgical incision. An epidural infusion is then initiated either in the operating room or in the PACU. Infusate concentrations for morphine range from 75 to 150 μg/ml or higher, depending on the magnitude of opioid tolerance. Concentrations for other opioids range as follows: hydromorphone, 20–60 μg/ml; fentanyl, 10–30 μg/ml; and sufentanil, 5–10 μg/ml. Epidural infusion rates, bolus dose, and lockout intervals for patient-controlled epidural analgesia vary at different institutions; however, the following settings may be considered: infusion rates ranging from 6 to 12 ml/h, and patient and controlled bolus doses ranging from 2 to 4 ml every 15 min for morphine, every 6–12 min for hydromorphone, and every 6–8 min for fentanyl and sufentanil. Unless contraindicated, local anesthetics, including 0.05–0.1% bupivacaine, 0.05–0.1% levobupivacaine, and 0.1–0.2% ropivacaine, may be added to the epidural infusate to augment opioid-based analgesia.

6. Intrathecal Analgesia Dosing

Single-dose intrathecal analgesia may be accomplished by administering preservative-free morphine (0.5–2 mg Duramorph [Elkins-Sinn, Cherry Hill, NJ]) either alone or added to the spinal local anesthetic. Most patients experience 8–20 h of effective pain relief and are less likely than opioid-naive patients to experience clinically significant respiratory depression or severe itching or nausea and vomiting.

For patients receiving continuous intrathecal analgesia, a standard 20-gauge epidural catheter or those developed for subarachnoid use is inserted 2 cm beyond the dura. A local anesthetic (0.1% bupivacaine) and an opioid analgesic (up to 10–30 μg/ml fentanyl or 50–100 μg/ml morphine) are infused intrathecally at a rate of 2–3 ml/h. Intravenous and oral

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** Summarizing information gathered from case reports, reviews, suggestions provided by pain management specialists at major medical centers, and our experience caring for opioid dependent patients.

opioids are coadministered for breakthrough surgical pain and to maintain baseline plasma concentrations of opioid. It is preferable to tunnel all subarachnoid catheters to minimize the risk of infection. The potential for spinal headache exists; however, many such patients remain in bed for a longer period of time and are not troubled by this adverse effect.

8. Neural Blockade

For patients recovering from regional anesthesia with indwelling 20-gauge polyethylene catheters, a continuous neural infusion is initiated in the PACU with 0.125–0.25% bupivacaine. The initial anesthetic block is allowed to regress to the point that motor or position sense returns but never to the point that the patient experiences discomfort. Intravenous PCA is also initiated in the PACU for breakthrough pain. Again, PCA doses of morphine or hydromorphone are generally one to three times higher than amounts used for nondependent patients.

9. Adjunctive Analgesics

Nonopioid analgesics may be administered to augment postoperative analgesia and reduce opioid dose requirements. Intraoperative doses of 0.05 mg/kg ketamine provide NMDA receptor blockade and postoperative opioid sparing. Nonselective nonsteroidal antiinflammatory drugs and cyclooxygenase-2 inhibitors (50 mg oral rofecoxib solution daily or 400 mg celecoxib followed by 200 mg daily) offer safe antiinflammatory, analgesic, and opioid-sparing effects and may be used to supplement intravenous and epidural PCA and regional analgesia. Additional analgesic augmentation may be gained by applying transdermal clonidine patch (0.1 mg/h). Patients with neuropathic pain may experience a reduction in symptoms and opioid sparing after administration of 300–900 mg gabapentin three times daily and tricyclic antidepressants such as 25 mg desipramine or 25–50 mg trazodone taken at bedtime.