REVIEW ARTICLE

MEDICAL PROGRESS

Opioid Therapy for Chronic Pain

Jane C. Ballantyne, M.D., and Jianren Mao, M.D., Ph.D.

From the Pain Center, Department of Anesthesia and Critical Care, Massachusetts General Hospital and Harvard Medical School — both in Boston. Address reprint requests to Dr. Ballantyne at the Massachusetts General Hospital Pain Center, 15 Parkman St., WACC 333, Boston, MA 02114, or at jballantyne@partners.org.

N Engl J Med 2003;349:1943-53.

OPIUM IS A BITTER, BROWN, GRANULAR POWDER DERIVED FROM THE seedpod of the poppy (*Papaver somniferum*). People have used opium for the relief of pain and suffering for thousands of years. Before the 19th century, opium was cultivated and used chiefly in the Middle East, whereas in Europe and the United States it was a luxury available mainly to the elite. During the 19th century, several historical events conspired to make opium and other opioids more readily available. The production of opium increased rapidly, and after the morphine alkaloid was identified in 1806 pharmacologic production of opioid drugs began. Use of morphine-containing tinctures such as laudanum became commonplace, especially in the treatment of the "travails" and "boredom" of Victorian women. Morphine-containing cures for colic, diarrhea, dysmenorrhea, and other painful conditions were widely available and could be bought from doctors and pharmacists.

With the rise of the "street use" of opium and heroin, legal controls were introduced. In the United States, the first attempts to control the abuse of narcotics came at the end of the 19th century, when a few states instituted limited controls. By the 1940s, opioids were so tightly restricted that they could be used legally only when they were prescribed by physicians according to strict regulatory controls. The legal use of opioids was thus placed entirely in the hands of physicians, who were, and still are, liable to lose their medical licenses and risk criminal prosecution if they prescribe these drugs inappropriately. The immediate effect of such strict regulatory control was that physicians became reluctant to prescribe opioids, and as a result pain was woefully undertreated.[1] Through the efforts of advocates of pain control, toward the end of the 20th century opioid therapy was reestablished as an invaluable and accepted treatment for acute pain, pain due to cancer, and pain caused by a terminal disease. The most difficult issue now facing physicians who treat patients with chronic pain probably is whether and how to prescribe opioid therapy for chronic pain that is not associated with terminal disease, including pain experienced by the increasing number of patients with cancer in remission who need long-term opioid therapy. Many of the issues involved in the treatment of patients with pain due to cancer in remission are the same as those in the treatment of patients with chronic pain that is unrelated to malignant conditions. Our review addresses specific questions about dose and toxicity in the light of recent studies that suggest a need to modify current practices in the use of opioid therapy for chronic pain.

CURRENT PRACTICE

The recognition that opioid therapy can relieve pain and improve mood and functioning in many patients with chronic pain has led experts on pain to recommend that such patients not be denied opioids.[2,3] Despite this recommendation, many physicians remain uncertain about prescribing opioids to treat chronic pain and do not prescribe them.[4] Some physicians argue that opioids are only marginally useful in the treatment of chronic pain, have a minimal effect on functioning, and may even worsen the out-

come.[5-10] However, this seems to be a minority view. Key organizations that strongly support the use of opioids to treat chronic pain have published consensus statements to guide physicians in prescribing these drugs.[11,12] These consensus statements emphasize the importance of a standardized approach.

Such an approach should include an initial, comprehensive medical history and physical examination, establish firmly that nonopioid therapy has failed, establish agreed-on goals for treatment, develop an understanding between physician and patient of the true benefits and pitfalls of the long-term use of opioids, involve a single physician and pharmacy whenever possible, and ensure comprehensive follow-up. The follow-up should comprise regular assessment of whether the goals are being achieved, careful monitoring for signs of opioid abuse (including toxicologic screening in some cases), the use of adjunctive treatments whenever possible, and a willingness to end opioid treatment if the goals are not met. This necessarily elaborate process should be fully documented. More detail is provided in the consensus documents and in the standard references.[11-14]

CLINICAL STUDIES

Most of the literature on opioid therapy consists of reports of surveys and uncontrolled case series.[2,15-24] The general finding is that patients with chronic pain not associated with a terminal disease can achieve satisfactory analgesia by using a stable (nonescalating) dose of opioids, with a minimal risk of addiction. The reported length of treatment is up to six years. In most cases, doses are in a moderate range (up to 195 mg of morphine or morphine equivalent per day). In two reports, higher doses were used (up to 360 mg in 52 patients,[16] and up to 2 g in 23 patients[18]). Some studies have also assessed functioning on the basis of patients' own reports, with most patients reporting improvement.[16,18,22] Studies have shown that cognitive function, including the ability to drive and operate machinery, is preserved in patients taking stable, moderate doses of opioids for chronic pain.[25-28] However, cognitive function may be impaired for up to seven days after an increase in the dose.[25] The effect of high doses of opioids on cognitive function is unknown.

Several controlled studies involving the use of single doses or short intravenous infusions of opioids confirm the responsiveness of various pain syndromes, including neuropathic pain, to opioid therapy.[29-31] Neuropathic pain, defined as pain due to nerve injury, neurologic disease, or the involvement of nerves by other disease processes, has traditionally been considered opioid-resistant. However, in recent clinical studies opioids were shown to be effective in the treatment of neuropathic pain, provided an adequate dose can be reached that provides analgesia without excess side effects.[30-35] Furthermore, studies in animals indicate that the resistance of neuropathic pain to opioids is relative, not absolute.[36,37] Other controlled studies have assessed the usefulness of long-term oral opioid therapy for chronic pain.[28,34,38-51]

An overview of these studies is provided in Supplementary Appendix 1 (available with the full text of this article at www.nejm.org). The majority (15 of 16) showed significant analgesic efficacy of opioids in the treatment of chronic pain, including neuropathic pain,[28,34,43,50,51] although the evidence of their effect on functioning is mixed. In a few of these studies, pain relief was achieved without functional improvement.[34,39,46,49,51] Pain relief is the expected end point of opioid therapy, but there is no consensus on whether pain relief without other benefits is a reasonable outcome of treatment for chronic pain or on what constitutes an acceptable outcome of opioid therapy for chronic pain. The doses of opioids used in controlled studies are generally in the moderate range (up to 180 mg of morphine or a morphine equivalent per day); in two studies a few patients received higher doses.[28,51] In 14 of the 16 studies, the duration of opioid therapy was less than 32 weeks.

PROLONGED, HIGH-DOSE OPIOID THERAPY

The published trials leave two important questions unanswered: Is opioid therapy beneficial in the long term (over a period of years rather than months)? Does the dose have an effect on the efficacy and the safety of long-term therapy? One of the fundamental principles of pain management is that the dose of an opioid should be increased until maximal analgesia is achieved with minimal side effects. Experts advise that in the treatment of chronic pain the initial dose increases should be achieved within weeks, doses should be moderate, and further increases in the dose should be introduced with extreme caution.[15] However, our clinical experience suggests that many physicians take a much more liberal approach to dose increases. Some patients with chronic pain receive doses as high as 1 g or more of morphine (or a morphine equivalent) per day, which may be five or more times the doses validated by the literature

(see Supplementary Appendix 1). Anecdotal evidence suggests that patients receiving opioid doses of this magnitude rarely report satisfactory analgesia or improved function. Although the clinical trials carried out to date have not examined the efficacy and safety of prolonged, high-dose opioid therapy, evidence is rapidly accumulating that, in the treatment of patients with chronic pain, opioid doses should be limited in order to maintain both efficacy and safety.

MECHANISMS OF FAILED ANALGESIA AND ADVERSE OUTCOMES

Over the past decade, much progress has been made in the search for the neuromodulatory, cellular, and molecular mechanisms that underlie clinical issues in the treatment of pain and addiction. Compelling evidence has been accumulated with potential implications for prolonged opioid therapy. For historical and other reasons, the effect of long-term opioid use has been studied more extensively in opioid addicts than in patients with chronic pain. Findings in the study of opioid addicts have often triggered basic science research that has improved our understanding of how opioids act. For example, the search for endogenous opioid systems was based on the proposed existence of endogenous opioid receptors that arose out of research on addiction. Some findings in the study of addicts and former addicts that are important in the context of scientific research are presented here, despite the obvious differences between addicts and patients with chronic pain.

OPIOID TOLERANCE

Opioid tolerance is a pharmacologic phenomenon that develops with the repeated use of opioids and brings about the need to increase the dose to maintain equipotent analgesic effects; it reduces the efficacy of opioids and may be a reason for dose escalation (Fig. 1). Associative (learned) tolerance can be distinguished from nonassociative (adaptive) tolerance, and the two types of tolerance appear to involve different neurotransmitter mechanisms.[52,53] Associative tolerance is linked to environmental clues and involves psychological factors. Clinically, associative tolerance may be noted in addicts admitted to a hospital who exhibit a marked reduction in opioid tolerance when the use of opioids is no longer associated with procurement. Nonassociative tolerance is an adaptive process at the cellular level that involves down-regulation (a reduction in the turnover rate and number of opioid receptors) or desensitization of opioid receptors, or both.[54-56] Several mechanisms are linked to the desensitization of opioid receptors, many of which are involved in the N-methyl-D-aspartate (NMDA)–receptor cascade.[57-62] In patients receiving prolonged opioid therapy, increased expression of the endogenous opioid dynorphin has been noted in the spinal cord dorsal horn that is associated with enhanced pain sensitivity. The precise mechanism of this effect is unclear, but electrophysiological evidence suggests that the NMDA receptor is involved.[36,37] Although the exact mechanisms of NMDA-receptor–mediated opioid tolerance have not yet been elucidated, this line of research has provided insights into several issues related to prolonged opioid therapy.

OPIOID-INDUCED ABNORMAL PAIN SENSITIVITY

Abnormal pain sensitivity occurs in neuropathic pain states and during the inflammatory phase of nerve injury. It is manifested as increased pain (perceived as tenderness) from noxious stimuli (hyperalgesia) and as pain from previously innocuous stimuli (allodynia). Long-term use of opioids may also be associated with the development of abnormal sensitivity to pain, and both preclinical and clinical studies suggest that opioid-induced abnormal pain sensitivity has much in common with the cellular mechanisms of neuropathic pain.[36,61] Opioid-induced abnormal pain sensitivity has been observed in patients treated for both pain and addiction.[63-66] In animals, NMDA-receptor–mediated changes that cause abnormal pain sensitivity occur in spinal cord dorsal-horn cells after repeated exposure to opioids, and similar changes have been observed in the spinal cord in animal models of neuropathic pain.[67] Animal models have also shown that NMDA-receptor–mediated cellular mechanisms mediate irreversible neurotoxic changes, including apoptosis.[68-70] Interactions between neural mechanisms of opioid tolerance and neuropathic pain involving spinal and supraspinal neural circuits may have important clinical implications.[36,71]

Repeated administration of opioids not only results in the development of tolerance (a desensitization process) but also leads to a pro-nociceptive (sensitization) process. Although the relative contribution of each process is not yet clear from either animal or human studies, sensitization may exacerbate and confuse the clinical picture of pharmacologic tolerance. Together, desensitization and sensitization arising during prolonged opioid therapy may contribute to an apparent decrease in analge-

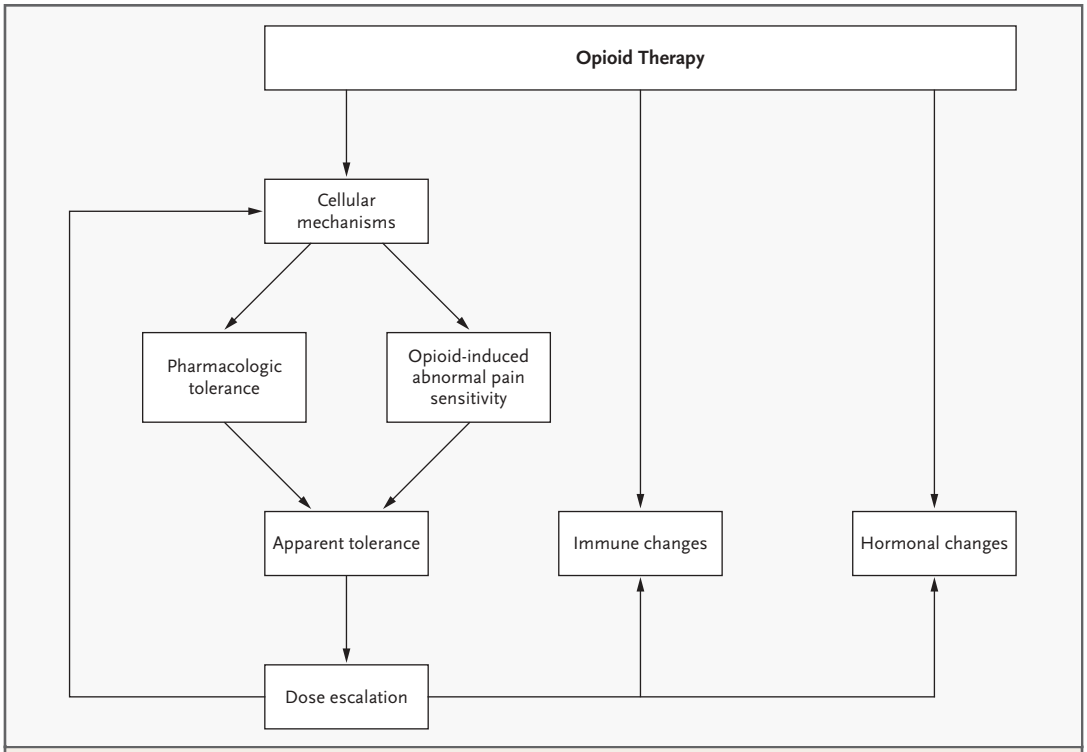

Figure 1. Possible Adverse Effects of Prolonged Opioid Therapy.

Prolonged opioid therapy can lead to cellular and intracellular changes, including activation of *N*-methyl-D-aspartate receptors. Such changes may contribute to pharmacologic opioid tolerance, increased sensitivity to pain (manifested as "apparent" opioid tolerance), or both and the need for dose escalation. Prolonged opioid treatment may also result in hormonal changes and may alter immune function. These effects may be exacerbated by dose escalation in some circumstances.

sic efficacy, regardless of the progression of the pain.[72] Thus, the need for dose escalation during opioid therapy — that is, the development of "apparent" opioid tolerance — may be the result of pharmacologic opioid tolerance, opioid-induced abnormal pain sensitivity, or disease progression. The possible use of NMDA antagonists in the treatment of neuropathic pain, opioid tolerance, and opioid-induced abnormal pain sensitivity is being investigated.

OPIOID-INDUCED HORMONAL CHANGES

Opioids influence at least two major hormonal systems, the hypothalamic–pituitary–adrenal axis and the hypothalamic–pituitary–gonadal axis. Morphine has been reported to cause a strong, progressive decline in the plasma cortisol level in adults,[73] and a similar effect has also been observed in laboratory animals.[74-76] The main effects of opioids on the hypothalamic–pituitary–gonadal axis involve the modulation of hormonal release, including an increase in prolactin and a decrease in luteinizing hormone, follicle-stimulating hormone, testosterone, and estrogen.[77] Testosterone depletion has been demonstrated in heroin addicts and in patients receiving methadone maintenance therapy.[78-80] In heroin addicts, the collective effects of the hormonal changes may lead to decreased libido, aggression, and drive; amenorrhea or irregular menses; and galactorrhea.[81] Clinically relevant testosterone depletion develops in the majority of men receiving intrathecal opioid therapy for chronic pain, and they benefit from testosterone-replacement therapy.[82,83] The high opioid level in the cerebrospinal fluid in these patients suggests a dose-related effect. Studies are needed to address this issue in patients with chronic pain treated with systemic opioids.

OPIOID-INDUCED IMMUNE MODULATION

Exogenous opioids may affect immunity through their neuroendocrine effects, or through direct effects on the immune system. Preclinical evidence in-

dicates overwhelmingly that opioids alter the development, differentiation, and function of immune cells, and that both innate and adaptive systems are affected.[84,85] Bone marrow progenitor cells, macrophages, natural killer cells, immature thymocytes and T cells, and B cells are all involved. The relatively recent identification of opioid-related receptors on immune cells makes it even more likely that opioids have direct effects on the immune system.[86] On the basis of studies in animals, prolonged exposure to opioids appears to be more likely to suppress immune function than short-term exposure, and abrupt withdrawal of opioids may also induce immunosuppression.[87]

Different opioids appear to act differently on the immune system.[88] For example, methadone may be less immunosuppressive than morphine.[89] Although evidence of immune modulation in humans is limited, opioids have been shown to exacerbate immunosuppression in persons infected with the human immunodeficiency virus and may increase the viral load, which suggests that prolonged opioid use may affect the immune system, at least in immunocompromised persons.[90] Studies of immune function in patients receiving long-term opioid therapy for chronic pain are notably lacking, but the direct evidence that opioids impair immune function has aroused concern, particularly in the case of susceptible persons. However, pain itself can impair immune function,[91] so the greatest concern is likely to pertain to patients receiving high doses of opioids who do not obtain satisfactory pain relief.

CLINICAL IMPLICATIONS

Two important concepts arise from our improved understanding of how opioids act: first, that apparent opioid tolerance does not equal pharmacologic opioid tolerance; and, second, that prolonged, high-dose opioid therapy may have serious adverse consequences.

RELATION OF APPARENT TOLERANCE TO PHARMACOLOGIC TOLERANCE

Pharmacologic tolerance to opioids has defined cellular mechanisms. The clinical hallmark of pharmacologic tolerance is the need for increasing doses to maintain the same level of analgesia. However, there is evidence that opioids can induce abnormal pain sensitivity or hyperalgesia, which is also manifested clinically as the need for increasing doses of opioids to maintain the same level of analgesia. Although sophisticated testing can identify hyperalgesia (to distinguish it from pharmacologic tolerance), it may not distinguish the hyperalgesia due to opioid treatment from the hyperalgesia due to worsening neuropathic pain. Furthermore, in everyday clinical practice (without testing), it is impossible to distinguish between pharmacologic tolerance and abnormal pain sensitivity. Whether opioid-induced abnormal pain sensitivity is related to the dose, the particular opioid, the route of administration, the duration of use, or other factors remains unclear. Nevertheless, abnormal pain sensitivity may, at least in part, explain the failure to relieve pain in some patients, despite increases in the opioid dose. Thus, in some instances, treating increasing pain with increasing doses of opioids may be futile.

ADVERSE CONSEQUENCES OF PROLONGED, HIGH-DOSE OPIOID THERAPY

Clinical and preclinical studies indicate that prolonged use of opioids may have adverse consequences, including opioid tolerance with the need for dose escalation, and opioid-induced abnormal pain sensitivity. Prolonged opioid use may have hormonal effects that result in reduced fertility, libido, and drive. Prolonged use may also result in immunosuppression, especially in susceptible persons. We do not yet know to what extent these effects are clinically relevant. However, prolonged use of high doses of opioids is likely to be more toxic than short-term use of low doses, so hormonal effects are most likely to occur in patients with chronic pain who receive high-dose opioid therapy. The aim of current guidelines is to protect patients from the adverse effects of opioid therapy and to ensure careful follow-up and cessation of therapy if the treatment goals are not being met.[11-13]

Although it is relatively easy for physicians to follow these guidelines when patients have a good response to stable doses of opioids, it is harder when the problems are complex and patients therefore do not have a good response. Often, time or resources are insufficient to offer a truly comprehensive and careful approach to complex pain problems, which sometimes become even more complex when opioid treatment is added. Paradoxically, opioid treatment may be offered in an attempt to improve pain and functioning, and thereby reduce the burden of care, but the treatment may actually increase the burden of care, because the management of opioid therapy in patients with complex problems is time-consuming and difficult. When the necessary resources of time, personnel, and multidisciplinary rehabilitation are not available, physicians tend to

bypass the principles outlined in the guidelines and comply with patients' demands for increased opioid doses, even when the treatment goals are not achieved. Efforts to limit the opioid dose may be helpful to these patients particularly, for whom the principle of increasing the opioid dose until adequate analgesia is achieved may not be appropriate.

Figure 2 (facing page). Suggested Protocol for Opioid Therapy.

Before starting opioid therapy it is important to ensure, so far as possible, that its benefit will exceed its risk. The potential benefit will depend on the extent to which pain interferes with a patient's life and well-being. Side effects other than constipation usually subside during prolonged treatment but occasionally persist. Other adverse effects include addiction and complex problems in functioning or quality of life. There are no accepted or validated risk factors for these effects, but it is widely acknowledged that there is a link between previous drug or alcohol abuse and addiction to opioids prescribed for pain. Deterioration in functioning or quality of life appears to be closely associated with lack of motivation to improve; young adults are the most susceptible to this type of deterioration.

The joint consensus statement of the American Academy of Pain Medicine, American Pain Society, and American Society of Addiction Medicine defines addiction as a primary, chronic, neurobiologic disease, the development and manifestations of which are influenced by genetic, psychosocial, and environmental factors, and as characterized by one or more of the following types of behavior: impaired control over drug use, compulsive use, continued use despite harm, or craving.[93] A more comprehensive definition in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition,[94] emphasizes the destructive features of addictive behavior. Which definition is more appropriate in the case of patients treated with opioids for pain is unclear, and the diagnosis of addiction remains a matter for individual clinical judgment.

LIMITING THE OPIOID DOSE

The concept of a ceiling dose of opioids in the treatment of chronic pain is growing, yet it is difficult to define a dose that could be recommended as a ceiling. Daily doses above 180 mg of morphine or a morphine equivalent have not been validated in clinical trials involving patients with chronic pain and might be considered excessive. However, ceiling doses probably vary among patients, given the known differences in patients' responses to opioids.[92] More important than the dose itself, however, may be the need for frequent dose escalation beyond the time when establishing a stable dose during the dose-adjustment phase (e.g., up to eight weeks) would be reasonable. Figure 2 outlines a management approach that combines the established principles from consensus statements[11,12] with strategies for controlling dose escalation. The goal of these strategies is to maintain opioid efficacy while avoiding an adverse outcome.

Drug Formulation

The opioid formulations most commonly used in the treatment of chronic pain are listed in Table 1. Because there is no evidence that the dosing regimen influences the development of tolerance, the formulation and regimen should be tailored to the patient's pain pattern, lifestyle, and preference. The usefulness of combination formulations that include acetaminophen or aspirin is limited, because the doses cannot be increased without a risk of dangerous adverse effects in a prolonged treatment regimen. Long-acting formulations are useful for patients whose pain is frequent or constant.

Some authorities recommend the use of methadone, which has an intrinsically long half-life, as an alternative to slow-release formulations. Methadone is inexpensive, and its low street value makes it less likely to be diverted for profit. In addition, because of its NMDA-receptor–antagonist activity, which has been demonstrated in animals,[96,97] methadone may be a good choice for the treatment of neuropathic pain and may minimize tolerance, although the clinical relevance of these effects is still unclear. The chief drawback of methadone is its prolonged and unpredictable half-life, which may extend beyond the average of 12 to 16 hours. When methadone is taken more than once per day, as is commonly the case when it is used for pain, the drug may accumulate, resulting in dangerously high plasma levels.[98] According to a consensus document recently published by the American Society of Anesthesiologists, slow-release formulations (morphine and oxycodone) are preferable to methadone for outpatient pain management because of the risk of respiratory depression due to methadone accumulation.[99] Methadone is less likely to cause respiratory depression in patients who are already opioid tolerant, and it may be particularly useful in opioid rotation.

Opioid Rotation

The diversity of opioid receptors as a result of the existence of different splice variants of μ-opioid receptors[100] suggests that incomplete cross-tolerance may occur among different opioid agonists acting at

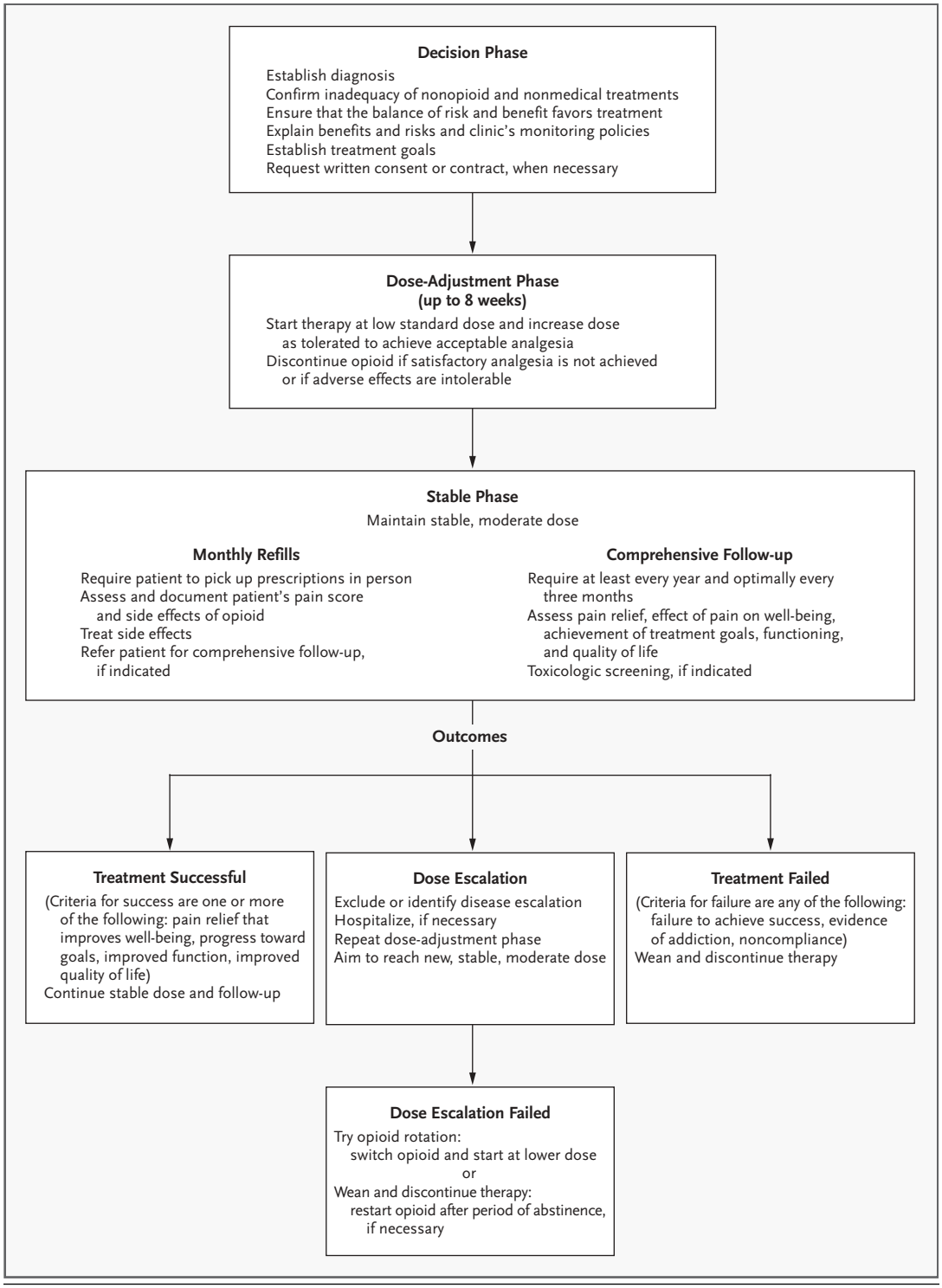

Table 1. Standard Doses of Commonly Used Opioids.*

Generic Name (Trade Name)	Analgesic Dose	Typical First Dose
Codeine		
Oral	30 mg every 3–4 hr	30 mg every 3–4 hr
Parenteral	10 mg every 3–4 hr	10 mg every 3–4 hr
Fentanyl (Duragesic)†		
Patch	25-μg-per-hr patch every 72 hr*	25-μg-per-hr patch every 72 hr†
Hydrocodone (Vicodin, Lorcet‡)		
Oral	NA	10 mg every 3–4 hr
Parenteral	NA	NA
Hydromorphone (Dilaudid)		
Oral	7.5 mg every 3–4 hr	2–4 mg every 3–4 hr
Parenteral	1.5 mg every 3–4 hr	1.5 mg every 3–4 hr
Levorphanol (Levo-Dromoran)		
Oral	4 mg every 6–8 hr	4 mg every 6–8 hr
Parenteral	2 mg every 6–8 hr	2 mg every 6–8 hr
Meperidine (Demerol)		
Oral	300 mg every 2–3 hr	100 mg every 3 hr
Parenteral	100 mg every 3 hr	100 mg every 3 hr
Methadone (Dolophine)		
Oral	20 mg every 6–8 hr	5 mg every 8–12 hr
Parenteral	10 mg every 6–8 hr	5 mg every 8–12 hr
Morphine		
Oral	30 mg every 3–4 hr	15 mg every 3–4 hr
Parenteral	10 mg every 3–4 hr	10 mg every 3–4 hr
Morphine SR (MSContin)		
Oral	NA	15 mg every 8–12 hr
Parenteral	NA	NA
Oxycodone (Percocet, Percodan‡)		
Oral	NA	5 mg every 3–4 hr
Parenteral	NA	NA
Oxycodone CR (OxyContin)		
Oral	NA	10 mg every 8–12 hr
Parenteral	NA	NA

* The information is adapted from *The Massachusetts General Hospital Handbook of Pain Management*.[95] Equivalent doses of opioids vary markedly according to source. A low dose of an opioid should be used to start and gradually increased until a dose is established that combines maximal analgesia with minimal adverse effects. A short-acting opioid should be used when the patient's pain is occasional, and a long-acting opioid when the pain is constant or frequent. A short-acting opioid can be added to a long-acting opioid to treat breakthrough or incidental pain, but in the treatment of chronic pain the use of nonmedical strategies to treat breakthrough pain is preferable. Rapid or frequent increases in dose should be avoided. Opioid rotation may be useful when dose escalation fails. The new opioid can be started at one half to one quarter of the calculated equivalent dose of the previously prescribed opioid. NA denotes not applicable.

† This is the lowest available dose. There is a risk of overdose in patients unaccustomed to opioid therapy.

‡ These are combination formulations (with acetaminophen or aspirin), which have limited usefulness in the treatment of chronic pain.

μ- or κ-opioid receptors. This observation provides the rationale for switching to another opioid as a means of restoring analgesic efficacy when the first opioid is not working, as shown by the failure of dose escalation (Fig. 2). The second opioid can be started at half the dose equivalent of the first, because the patient's tolerance to the second opioid will be lower. For reasons that are not fully clear, methadone works particularly well in opioid rotation and can be started at less than half the dose equivalent of the first opioid. The second opioid can be increased if necessary. Table 1 lists dose equivalents for some commonly used opioids. Opioid rotation has been used in the treatment of pain due to cancer when the adverse consequences of high-dose opioid therapy, most commonly excessive sedation or painful myoclonus, are uncontrollable.[101] The use of opioid rotation in the treatment of chronic pain is promising but needs validation.

Failure to Control the Dose

Despite these strategies, attempts to limit the escalation of the opioid dose sometimes fail. If dose escalation is unsuccessful, it is crucial to ask whether the opioid used is effective in treating the patient's chronic pain. Sometimes the only way to answer this question is to reassess the management approach after weaning the patient from the opioid. Two to three months or longer without opioid therapy may be needed in order to make a true assessment. Nonopioid and nonmedical treatments can be used more intensely during the period of opioid detoxification, if necessary. Some patients find that after they have overcome the fear of living without opioids, they prefer not to receive opioid treatment.[64] Some even experience a reduction in pain.[63,65] For patients who do not have an improvement without opioids, therapy can be restarted, but at much lower doses of opioids than previously prescribed.

Aberrant opioid-seeking behavior may complicate the clinical picture of failed opioid therapy. Although occasionally aberrant behavior is a manifestation of inadequate analgesia and will revert to normal behavior when pain is adequately treated, more commonly it is a manifestation of addiction or noncompliance (Table 2). The relation between addiction and noncompliance is complex and poorly understood. Noncompliance shares many features with addictive behavior and may or may not indicate addiction. Sometimes diversion (selling prescribed opioids or passing them on to others), rather than addiction, drives abnormal opioid-seeking behavior. In general, noncompliance should arouse the physician's concern about possible addiction or diversion and prompt careful control and monitoring of opioid therapy. Opioid therapy should be discontinued if the behavior persists. Addiction can be

masked when physicians comply with the patient's unreasonable demands for opioids. In this case, the addictive behavior is, instead, not attributed to the patient but authenticated by the physician.

CONCLUSIONS

Although opioid drugs have been used in the treatment of pain for thousands of years, it is only in the past 60 years that they have been regulated, with legitimate use placed entirely in the hands of licensed practitioners. Also during this period, scientific research has led to a better understanding of the actions of opioids. Physicians are in a better position now to control opioid use so that it helps, rather than harms, patients. Current guidelines recommend a cautious approach to dose escalation and the discontinuation of opioids if treatment goals are not met. However, in busy practice settings, the reality of dealing with patients who have complex problems often forces physicians to compromise. As a consequence, very large doses of opioids are prescribed for patients with chronic pain that is not associated with terminal disease, often in the absence of any real improvement in the patient's pain or level of functioning. Whereas it was previously thought that unlimited dose escalation was at least safe, evidence now suggests that prolonged, high-dose opioid therapy may be neither safe nor effective. It is therefore important that physicians make every effort to control indiscriminate prescribing, even when they are under pressure by patients to increase the dose of opioids.

Table 2. Typical Features of Noncompliance with Opioid Therapy.

Unexpected results on toxicologic screening
Frequent requests for dose increases
Concurrent use of nonprescribed psychoactive substances
Failure to follow the dosage schedule
Failure to adhere to concurrently recommended treatments
Frequently reported loss of prescriptions or medications
Frequent visits to the emergency room for opioid therapy
Missed follow-up visits
Frequent extra appointments at the clinic or office
Prescriptions obtained from a second provider
Tampering with prescriptions

Supported in part by a grant (RO1DA08835) from the Public Health Service.

REFERENCES

1. Hill CS Jr. Government regulatory influences on opioid prescribing and their impact on the treatment of pain of nonmalignant origin. J Pain Symptom Manage 1996; 11:287-98.
2. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain 1986;25:171-86.
3. McQuay H. Opioids in pain management. Lancet 1999;353:2229-32.
4. Turk DC, Brody MC, Okifuji EA. Physicians' attitudes and practices regarding the long-term prescribing of opioids for noncancer pain. Pain 1994;59:201-8.
5. Ready LB, Sarkis E, Turner JA. Self-reported vs. actual use of medications in chronic pain patients. Pain 1982;12:285-94.
6. Turner JA, Calsyn DA, Fordyce WE, Ready LB. Drug utilization pattern in chronic pain patients. Pain 1982;12:357-63.
7. McNairy SL, Maruta T, Ivnik RJ, Swanson DW, Ilstrup DM. Prescription medication dependence and neuropsychologic function. Pain 1984;18:169-77.
8. Buckley FP, Sizemore WA, Charlton JE. Medication management in patients with chronic non-malignant pain: a review of the use of a drug withdrawal protocol. Pain 1986; 26:153-65.
9. Finlayson RE, Maruta T, Morse RM, Martin MA. Substance dependence and chronic pain: experience with treatment and follow-up results. Pain 1986;26:175-80.
10. Schofferman J. Long-term use of opioid analgesics for the treatment of chronic pain of nonmalignant origin. J Pain Symptom Manage 1993;8:279-88.
11. The use of opioids for the treatment of chronic pain: a consensus statement from the American Academy of Pain Medicine and the American Pain Society. Glenview, Ill.: American Academy of Pain Medicine and American Pain Society, 1997.
12. Model guidelines for the use of controlled substances for the treatment of pain: a policy document of the Federation of State Medical Boards of the United States Inc. Dallas: Federation of State Medical Boards of the United States, 1998.
13. Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage 1996;11: 203-17.
14. Fishman SM, Mao J. Opioid therapy in chronic nonmalignant pain. In: Ballantyne JC, ed. The Massachusetts General Hospital handbook of pain management. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2002.
15. Urban BJ, France RD, Steinberger EK, Scott DL, Maltbie AA. Long-term use of narcotic/antidepressant medication in the management of phantom limb pain. Pain 1986; 24:191-6.
16. Tennant FS Jr, Uelmen GF. Narcotic maintenance for chronic pain: medical and legal guidelines. Postgrad Med 1983;73: 81-3, 86-8, 91-4.
17. Bouckoms AJ, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic nonmalignant pain treatment with long term analgesics. Ann Clin Psychiatry 1992;4:185-92.
18. Zenz M, Strumpf M, Tryba M. Long-term opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage 1992;7:69-77.
19. Pappagallo M, Raja SN, Haythornthwaite JA, Clark M, Campbell JN. Oral opioids in the management of postherpetic neuralgia: a prospective survey. Analgesia 1994;1:S1-S5.
20. Gardner-Nix JS. Oral methadone for managing chronic nonmalignant pain. J Symptom Pain Manage 1996;11:321-8.
21. Lorenz J, Beck H, Bromm B. Cognitive performance, mood and experimental pain before and during morphine-induced analgesia in patients with chronic non-malignant pain. Pain 1997;73:369-75.

22. Simpson RK Jr, Edmondson EA, Constant CF, Collier C. Transdermal fentanyl for chronic low back pain. J Pain Symptom Manage 1997;14:218-24.
23. Ytterberg SR, Mahowald ML, Woods SR. Codeine and oxycodone use in patients with chronic rheumatic disease pain. Arthritis Rheum 1998;41:1603-12.
24. Altier N, Dion D, Boulanger A, Choiniere M. Successful use of methadone in the treatment of chronic neuropathic pain arising from burn injuries: a case-study. Burns 2001; 27:771-5.
25. Bruera E, Macmillan K, Hanson J, MacDonald RN. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. Pain 1989;39:13-6.
26. Vainio A, Ollila J, Matikainen E, Rosenberg P, Kalso E. Driving ability in cancer patients receiving long-term morphine analgesia. Lancet 1995;346:667-70.
27. Galski T, Willimas JB, Ehle HT. Effects of opioids on driving ability. J Pain Symptom Manage 2000;19:200-8.
28. Haythornthwaite JA, Menefee LA, Quatrano-Piacentini AL, Pappagallo M. Outcome of chronic opioid therapy for non-cancer pain. J Pain Symptom Manage 1998;15:185-94.
29. Max J, Price DD, Mayer DH. Association of pain relief with drug side-effects in postherpetic neuralgia: a single dose study of clonidine, codeine, ibuprofen and placebo. Clin Pharmacol Ther 1988;43:363-71.
30. Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. Neurology 1991;41:1024-8.
31. Dellemijn PL, Vanneste JA. Randomised double-blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. Lancet 1997;349:753-8.
32. Portenoy RK, Foley KM, Inturrisi CE. The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions. Pain 1990;43:273-86.
33. Jadad AR, Carroll D, Glynn CJ, Moore RA, McQuay HJ. Morphine responsiveness of chronic pain: double-blind randomised crossover study with patient-controlled analgesia. Lancet 1992;339:1367-71.
34. Rowbotham MC, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med 2003;348: 1223-32.
35. Foley KM. Opioids and chronic neuropathic pain. N Engl J Med 2003;348:1279-81.
36. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and opiate tolerance: a current view of their possible interactions. Pain 1995;62:259-74.
37. Bian D, Ossipov MH, Ibrahim M, et al. Loss of antiallodynic and antinociceptive spinal/supraspinal morphine synergy in nerve-injured rats: restoration by MK-801 or dynorphine antiserum. Brain Res 1999;831: 55-63.
38. Kjaersgaard-Andersen P, Nafei A, Skov O, et al. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip: a randomised, double-blind, multi-centre study. Pain 1990;43:309-18.
39. Moran C. MST continuous tablets and pain control in severe rheumatoid arthritis. Br J Clin Res 1991;2:1-12.
40. Arkinstall W, Sandler A, Goughnour B, Babul N, Harsanyi Z, Darke AC. Efficacy of controlled-release codeine in chronic nonmalignant pain: a randomized, placebo-controlled clinical trial. Pain 1995;62:169-78.
41. Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain: a randomized prospective study. Spine 1998;23:2591-600.
42. Sheather-Reid RB, Cohen M. Efficacy of analgesics in chronic pain: a series of N-of-1 studies. J Pain Symptom Manage 1998;15: 244-52.
43. Watson CPN, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology 1998;50:1837-41.
44. Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. J Rheumatol 1999;26: 862-9.
45. Schofferman J. Long-term opioid analgesic therapy for severe refractory lumbar spine pain. Clin J Pain 1999;15:136-40.
46. Moulin DE, Iezzi A, Amireh R, Sharpe WK, Boyd D, Merskey H. Randomised trial of oral morphine for chronic non-cancer pain. Lancet 1996;347:143-7.
47. Peloso PM, Bellamy N, Bensen W, et al. Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. J Rheumatol 2000;19:764-71.
48. Roth SH, Fleischmann RM, Burch RX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. Arch Intern Med 2000;160:853-60.
49. Caldwell JR, Rapoport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. J Pain Symptom Manage 2002;23:278-91.
50. Maier C, Hildebrandt J, Klinger R, Henrich-Eberl C, Lindena G. Morphine responsiveness, efficacy and tolerability in patients with chronic non-tumor associated pain — results of a double-blind placebo-controlled trial (MONTAS). Pain 2002;97:223-33.
51. Raja SN, Haythornthwaite JA, Pappagallo, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2002;59: 1015-21.
52. Grisel JE, Watkins LR, Maier SF. Associative and non-associative mechanisms of morphine analgesic tolerance are neurochemically distinct in the rat spinal cord. Psychopharmacology (Berl) 1996;128:248-55.
53. Mitchell JM, Basbaum AI, Fields HL. A locus and mechanism of action for associative morphine tolerance. Nat Neurosci 2000;3:47-53.
54. Alvarez V, Arttamangkul S, Williams JT. A RAVE about opioid withdrawal. Neuron 2001;32:761-3.
55. Finn AK, Whistler JL. Endocytosis of the mu opioid receptor reduces tolerance and a cellular hallmark of opiate withdrawal. Neuron 2001;32:829-39.
56. South SM, Smith MT. Analgesic tolerance to opioids. Pain Clinical Updates. December 2001:1-4.
57. Trujillo KA, Akil H. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science 1991;251:85-7.
58. Marek P, Ben-Eliyahu S, Vaccarino AL, Liebeskind JC. Delayed application of MK-801 attenuates development of morphine tolerance in rats. Brain Res 1991;558: 163-5.
59. Tiseo PJ, Inturrisi CE. Attenuation and reversal of morphine tolerance by the competitive N-methyl-D-aspartate receptor antagonist, LY274614. J Pharmacol Exp Ther 1993;264:1090-6.
60. Elliott K, Minami N, Kolesnikov YA, Pasternak GW, Inturrisi CE. The NMDA receptor antagonists, LY274614 and MK-801, and the nitric oxide synthase inhibitor, NG-nitro-L-arginine, attenuate analgesic tolerance to the mu-opioid morphine but not to kappa opioids. Pain 1994;56:69-75.
61. Mao J, Price DD, Mayer DJ. Thermal hyperalgesia in association with the development of morphine tolerance in rats: roles of excitatory amino acid receptors and protein kinase C. J Neurosci 1994;14:2301-12.
62. Manning BH, Mao J, Frenk H, Price DD, Mayer DJ. Continuous co-administration of dextromethorphan or MK-801 with morphine: attenuation of morphine dependence and naloxone-reversible attenuation of morphine tolerance. Pain 1996;67:79-86.
63. Brodner RA, Taub A. Chronic pain exacerbated by long-term narcotic use in patients with non-malignant disease: clinical syndrome and treatment. Mt Sinai J Med 1978;45:233-7.
64. Taylor CB, Zlutnick SI, Corley MJ, Flora J. The effects of detoxification, relaxation, and brief supportive therapy on chronic pain. Pain 1980;8:319-29.
65. Savage SR. Long-term opioid therapy: assessment of consequences and risks. J Pain Symptom Manage 1996;11:274-86.
66. Compton MA. Cold-pressor pain tolerance in opiate and cocaine abusers: correlates of drug type and use status. J Pain Symptom Manage 1994;9:462-73.

67. Mao J, Price DD, Mayer DJ. Experimental mononeuropathy reduces the antinociceptive effects of morphine: implications for common intracellular mechanisms involved in morphine tolerance and neuropathic pain. Pain 1995;61:353-64.
68. Mao J, Sung B, Ji RR, Lim G. Neuronal apoptosis associated with morphine tolerance: evidence for an opioid-induced neurotoxic mechanism. J Neurosci 2002;22:7650-61.
69. Chaney MA. Side effects of intrathecal and epidural opioids. Can J Anaesth 1995; 42:891-903.
70. Giffard RG, Morgan RL. Cell death in the central nervous system: therapeutic possibilities? Reg Anesth Pain Med 2000;25: 22-5.
71. Mao J, Sung B, Ji RR, Lim G. Chronic morphine induces downregulation of spinal glutamate transporters: implications in morphine tolerance and abnormal pain sensitivity. J Neurosci 2002;22:8312-23.
72. Mao J. Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy. Pain 2002;100:213-7.
73. Banki CM, Arato M. Multiple hormonal responses to morphine: relationship to diagnosis and dexamethasone suppression. Psychoneuroendocrinology 1987;12:3-11.
74. Collu R, Clermont MJ, Ducharme JR. Effects of thyrotropin-releasing hormone on prolactin, growth hormone and corticosterone secretions in adult male rats treated with pentobarbital or morphine. Eur J Pharmacol 1976;37:133-40.
75. Bartolome MB, Kuhn CM. Endocrine effects of methadone in rats: acute effects in adults. Eur J Pharmacol 1983;95:231-8.
76. Rolandi E, Marabini A, Franceschini R, Messina V, Bongera P, Barreca T. Changes in pituitary secretion induced by an agonist-antagonist opioid drug, buprenorphine. Acta Endocrinol (Copenh) 1983;104:257-60.
77. Malaivijitnond S, Varavudhi P. Evidence for morphine-induced galactorrhea in male cynomolgus monkeys. J Med Primatol 1998; 27:1-9.
78. Mendelson JH, Mendelson JE, Patch VD. Plasma testosterone levels in heroin addiction and during methadone maintenance. J Pharmacol Exp Ther 1975;192:211-7.
79. Mendelson JH, Meyer RE, Ellingboe J, Mirin SM, McDougle M. Effects of heroin and methadone on plasma cortisol and testosterone. J Pharmacol Exp Ther 1975;195: 296-302.
80. Rasheed A, Tareen IA. Effects of heroin on thyroid function, cortisol and testosterone level in addicts. Pol J Pharmacol 1995; 47:441-4.
81. Malik SA, Khan C, Jabbar A, Iqbal A. Heroin addiction and sex hormones in males. J Pak Med Assoc 1992;42:210-2.
82. Abs R, Verhelst J, Maeyaert J, et al. Endocrine consequences of long-term intrathecal administration of opioids. J Clin Endocrinol Metab 2000;85:2215-22.
83. Finch PM, Roberts LJ, Price L, Hadlow NC, Pullan PT. Hypogonadism in patients treated with intrathecal morphine. Clin J Pain 2000;16:251-4.
84. Roy S, Loh HH. Effects of opioids on the immune system. Neurochem Res 1996;21: 1375-86.
85. Risdahl JM, Khanna KV, Peterson PK, Molitor TW. Opiates and infection. J Neuroimmunol 1998;83:4-18.
86. Makman MH. Morphine receptors in immunocytes and neurons. Adv Neuroimmunol 1994;4:69-82.
87. Rahim RT, Adler MW, Meissler JJ Jr, et al. Abrupt or precipitated withdrawal from morphine induces immunosuppression. J Neuroimmunol 2002;127:88-95.
88. Sacerdote P, Manfredi B, Mantegazza P, Panerai AE. Antinociceptive and immunosuppressive effects of opiate drugs: a structure-related activity study. Br J Pharmacol 1997;121:834-40.
89. De Waal EJ, Van Der Laan JW, Van Loveren H. Effects of prolonged exposure to morphine and methadone on in vivo parameters of immune function in rats. Toxicology 1998;129:201-10.
90. Peterson PK, Sharp BM, Gekker G, Portoghese PS, Sannerud K, Balfour HH Jr. Morphine promotes the growth of HIV-1 in human peripheral blood mononuclear cell cocultures. AIDS 1990;4:869-73.
91. Kusnecov AW, Rabin BS. Stressor-induced alterations of immune function: mechanisms and issues. Int Arch Allergy Immunol 1994;105:107-21.
92. Galer BS, Coyle N, Pasternak GW, Portenoy RK. Individual variability in the response to different opioids: report of five cases. Pain 1992;49:87-91.
93. Definitions related to the use of opioids for the treatment of pain: a consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. Glenview, Ill.: American Academy of Pain Medicine, 2001.
94. Frances A, Pincus HA, First MB, et al. Substance related disorders. In: Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association, 2000:191-295.
95. Ballantyne J, ed. The Massachusetts General Hospital handbook of pain management. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2002:562.
96. Bulka A, Plesan A, Xu XJ, Wiesenfeld-Hallin Z. Reduced tolerance to the antihyperalgesic effect of methadone in comparison to morphine in a rat model of mononeuropathy. Pain 2002;95:103-9.
97. Davis AM, Inturrisi CE. d-Methadone blocks morphine tolerance and N-methyl-D-aspartate-induced hyperalgesia. J Pharmacol Exp Ther 1999;289:1048-53.
98. Fishman SM, Wilsey B, Mahajan G, Molina P. Methadone reincarnated: novel clinical applications with related concerns. Pain Med 2002;3:339-48.
99. Wilson PR. Opioid use and diversion: report on recent hearing by FDA and DEA. ASA statement to FDA committee. ASA Newslett 2002;66(10):9-10.
100. Pasternak GW. The pharmacology of mu analgesics: from patients to genes. Neuroscientist 2001;7:220-31.
101. Mercadante S. Opioid rotation for cancer pain: rationale and clinical aspects. Cancer 1999;86:1856-66.