

## REVIEW ARTICLE

## MEDICAL PROGRESS

## Opioid Therapy for Chronic Pain

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OPPIUM 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.<sup>1</sup> 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.<sup>2,3</sup> Despite this recommendation, many physicians remain uncertain about prescribing opioids to treat chronic pain and do not prescribe them.<sup>4</sup> 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-

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come.<sup>5-10</sup> 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.<sup>11,12</sup> 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.<sup>11-14</sup>

#### CLINICAL STUDIES

Most of the literature on opioid therapy consists of reports of surveys and uncontrolled case series.<sup>2,15-24</sup> 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,<sup>16</sup> and up to 2 g in 23 patients<sup>18</sup>). Some studies have also assessed functioning on the basis of patients' own reports, with most patients reporting improvement.<sup>16,18,22</sup> 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.<sup>25-28</sup> However, cognitive function may be impaired for up to seven days after an increase in the dose.<sup>25</sup> 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 ther-

apy.<sup>29-31</sup> 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.<sup>30-35</sup> Furthermore, studies in animals indicate that the resistance of neuropathic pain to opioids is relative, not absolute.<sup>36,37</sup> Other controlled studies have assessed the usefulness of long-term oral opioid therapy for chronic pain.<sup>28,34,38-51</sup>

An overview of these studies is provided in Supplementary Appendix 1 (available with the full text of this article at [www.nejm.org](http://www.nejm.org)). The majority (15 of 16) showed significant analgesic efficacy of opioids in the treatment of chronic pain, including neuropathic pain,<sup>28,34,43,50,51</sup> although the evidence of their effect on functioning is mixed. In a few of these studies, pain relief was achieved without functional improvement.<sup>34,39,46,49,51</sup> 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.<sup>28,51</sup> 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.<sup>15</sup> 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.

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#### MECHANISMS OF FAILED ANALGESIA AND ADVERSE OUTCOMES

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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

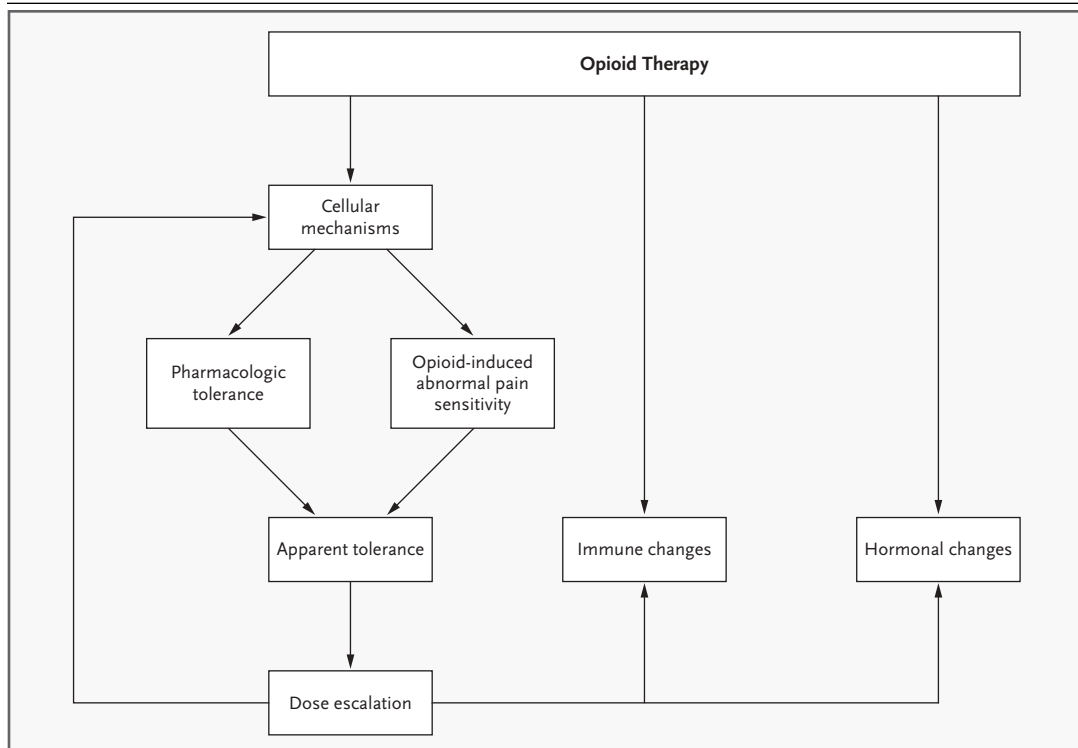
Opioid tolerance is a pharmacologic phenomenon that develops with the repeated use of opioids and brings about the need to increase the dose to maintain equipotent analgesic effects; it reduces the efficacy of opioids and may be a reason for dose escalation (Fig. 1). Associative (learned) tolerance can be distinguished from nonassociative (adaptive) tolerance, and the two types of tolerance appear to involve different neurotransmitter mechanisms.<sup>52,53</sup> 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 turn-

over rate and number of opioid receptors) or desensitization of opioid receptors, or both.<sup>54-56</sup> Several mechanisms are linked to the desensitization of opioid receptors, many of which are involved in the N-methyl-D-aspartate (NMDA)-receptor cascade.<sup>57-62</sup> 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.<sup>36,37</sup> 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.<sup>36,61</sup> Opioid-induced abnormal pain sensitivity has been observed in patients treated for both pain and addiction.<sup>63-66</sup> 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.<sup>67</sup> Animal models have also shown that NMDA-receptor-mediated cellular mechanisms mediate irreversible neurotoxic changes, including apoptosis.<sup>68-70</sup> Interactions between neural mechanisms of opioid tolerance and neuropathic pain involving spinal and supraspinal neural circuits may have important clinical implications.<sup>36,71</sup>

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.<sup>72</sup> 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,<sup>73</sup> and a similar effect has also been observed in laboratory animals.<sup>74-76</sup> 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.<sup>77</sup> Testosterone depletion has been demonstrated in heroin addicts and in patients receiving methadone maintenance therapy.<sup>78-80</sup> In heroin addicts, the collective effects of the hormonal changes may lead to decreased libido, aggression, and drive; amenorrhea or irregular menses; and galactorrhea.<sup>81</sup> Clinically relevant testosterone depletion develops in the majority of men receiving intrathecal opioid therapy for chronic pain, and they benefit from testosterone-replacement therapy.<sup>82,83</sup> 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.<sup>84,85</sup> 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.<sup>86</sup> 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.<sup>87</sup>

Different opioids appear to act differently on the immune system.<sup>88</sup> For example, methadone may be less immunosuppressive than morphine.<sup>89</sup> 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.<sup>90</sup> 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,<sup>91</sup> so the greatest concern is likely to pertain to patients receiving high doses of opioids who do not obtain satisfactory pain relief.

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#### CLINICAL IMPLICATIONS

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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 hyperal-

gesia (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.<sup>11-13</sup>

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.

#### 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.<sup>92</sup> 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<sup>11,12</sup> 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,<sup>96,97</sup> 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

#### 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.

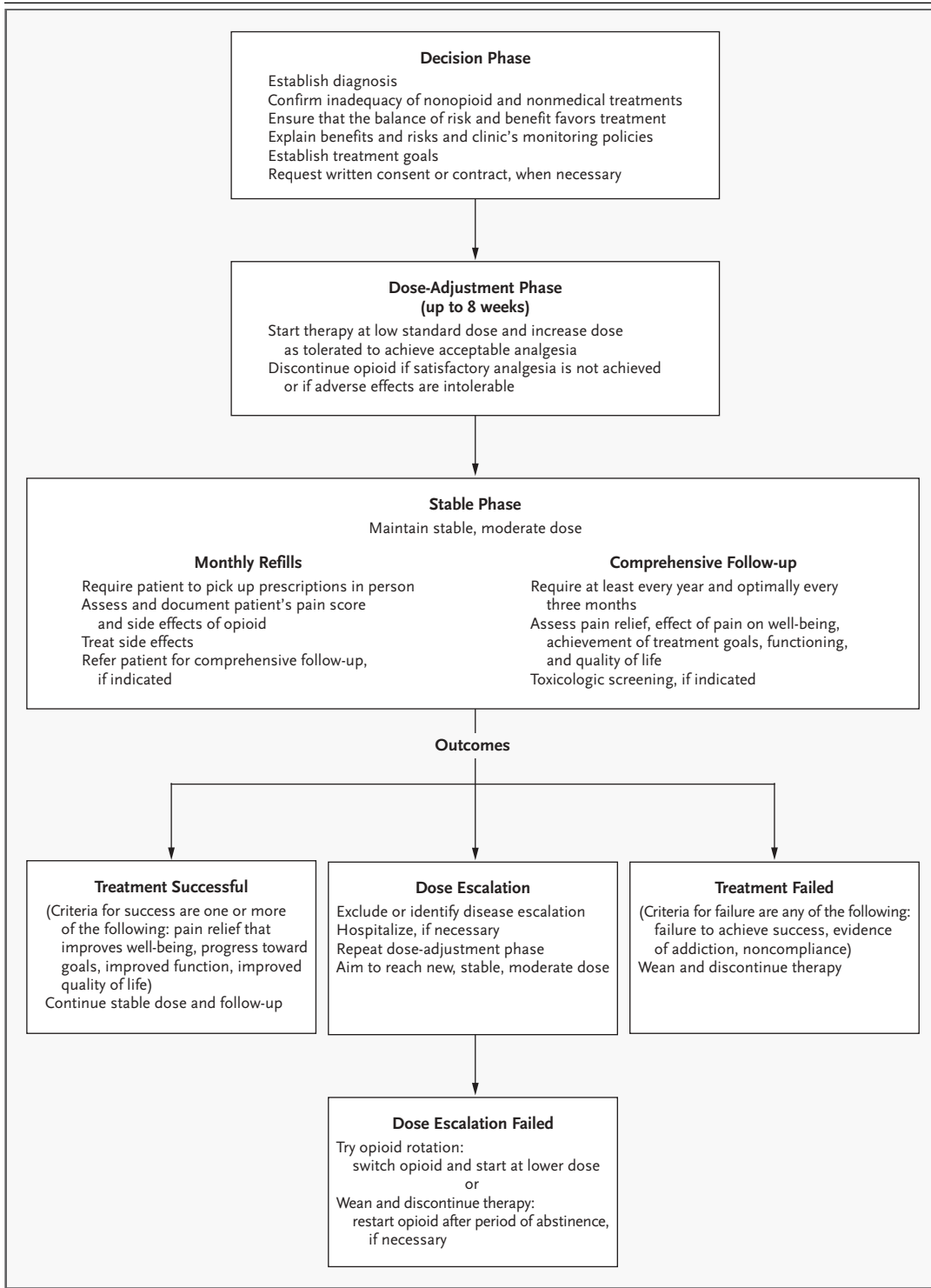
The joint consensus statement of the American Academy of Pain Medicine, American Pain Society, and American Society of Addiction Medicine defines addiction as a primary, chronic, neurobiologic disease, the development and manifestations of which are influenced by genetic, psychosocial, and environmental 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.<sup>93</sup> A more comprehensive definition in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition,<sup>94</sup> 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.

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.<sup>98</sup> 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.<sup>99</sup> 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  $\mu$ -opioid receptors<sup>100</sup> suggests that incomplete cross-tolerance may occur among different opioid agonists acting at

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**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) †	25- $\mu$ g-per-hr patch every 72 hr*	25- $\mu$ g-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*.<sup>95</sup> 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.

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.<sup>101</sup> 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. Non-opioid 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.<sup>64</sup> Some even experience a reduction in pain.<sup>63,65</sup> 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

$\mu$ - or  $\kappa$ -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



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

**Table 2. Typical Features of Noncompliance with Opioid Therapy.**

<p>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</p>
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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.

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