

Opioid Therapy for Chronic Nonmalignant Pain: Clinicians' Perspective

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During the past decade, debate has intensified about the role of long-term opioid therapy in the management of chronic nonmalignant pain. Specialists in pain management have discussed the issues extensively¹ and now generally agree that a selected population of patients with chronic pain can attain sustained analgesia without significant adverse consequences. This perspective, however, is not uniformly accepted by pain specialists and has not been widely disseminated to other disciplines or the public. Rather, the more traditional perspective, which ascribes both transitory benefit and substantial cumulative risk to long-term opioid therapy, continues to predominate. According to this perspective, the inevitability of tolerance limits the possibility of sustained efficacy, and other pharmacological properties increase the likelihood of adverse outcomes, including persistent side-effects, impairment in physical and psychosocial functioning, and addiction. If accurate, these outcomes would indeed justify the withholding of opioid therapy for all but the most extreme cases of chronic nonmalignant pain.

Two sets of observations have been the strongest impetus for a critical reexamination of the evidence supporting the traditional view of opioid therapy. First, experience gained during the management of cancer pain has demonstrated the potential for highly favorable outcomes from long-term opioid therapy. Second, evidence has accumulated that the laws and regulations intended to reduce illicit use and misuse may have unintended adverse effects on legitimate prescribing. These observations provide a context for further analysis of the controversy surrounding the use of opioids for nonmalignant pain.

Implications of opioid therapy for cancer pain

Experience in the cancer population contrasts starkly with the negative view of opioid drugs. Numerous surveys indicate that long-term opioid therapy provides adequate relief to 70 to 90 percent of patients with cancer pain.² Rather than contributing to distress or dysfunction, the relief of pain in this population is associated with an improved quality of life.³ On this basis, long-term treatment with opioid drugs has been strongly advocated by pain specialists and both national and international medical organizations.⁴

This experience in the treatment of cancer pain has produced observations that belie accepted dogma about opioid therapy. For example, patients rarely demonstrate euphoric responses to opioid drugs, and neither analgesic tolerance nor physical dependence is a significant clinical problem. Moreover, patients without concurrent brain pathology seldom experience persistent neuropsychological toxicity (such as somnolence or mental clouding). Most important perhaps, addiction is extremely rare among cancer patients with no prior history of substance abuse who are administered opioids for pain. These observations justify the need to examine conventional thinking about the role of these drugs overall, including their potential utility in chronic nonmalignant pain.

Implications of opioid regulation

The prescription of opioids is scrutinized by regulatory and law enforcement agencies, which are responsible for preventing drug diversion and eliminating inappropriate prescribing practices. In pursuing these functions, these agencies have no statutory or regulatory interest in impeding the legitimate use of opioids by physicians.⁵ Physicians understand the need to monitor and regulate controlled prescription drugs, and must be assured that prescribing behavior

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that is within the bounds of accepted medical practice will not lead to investigation or sanction. If a proper balance were struck between the intrusions necessary to regulate these potentially abusable drugs and protecting patients' access to them, there would be no need for concern.

Unfortunately, evidence indicates that this balance has not been achieved.⁶ Regulatory policies contribute to the undertreatment of pain both directly, by impeding access to controlled prescription drugs, and indirectly, by negatively influencing prescribing behavior. Impediments to access are exemplified by regulations in some states that limit the number of tablets that can be prescribed at one time. Such a regulation may force patients with a legitimate need for high opioid doses, most of whom have cancer pain, to obtain multiple prescriptions per week, which may be exhausting to both the patient and prescriber.

The adverse impact of regulation on legitimate prescribing is less concrete but probably far more widespread. In a recent survey, a majority of physicians admitted that concerns about regulatory scrutiny at least occasionally impel a change in the prescription of a controlled drug.⁷ Not surprisingly, the degree of concern about regulatory oversight was greatest with the drugs most often used in the management of severe pain, such as morphine.

Analysis of multiple copy prescription programs offers additional evidence of the influence of regulatory policies on physician prescribing. These programs, which monitor physician behavior through the use of a special prescription form for controlled drugs, offer point-of-sale data that are strongly favored by those in the regulatory and law enforcement communities.⁸ Every state that has initiated a multiple copy prescription program has recorded a greater than 50 percent reduction in the prescribing of the regulated drugs.⁹ Although proponents contend that this change reflects a lower rate of abuse, these claims have been disputed by pain specialists and others.¹⁰ Data from the federal Drug Abuse Warning Network have not confirmed that multiple copy prescription programs curtail prescription drug abuse,¹¹ and surveys in Texas and New York suggest that the increased awareness of regulatory oversight associated with these programs reduces legitimate prescribing of the regulated drug and increases prescribing of substitute drugs that may be less preferred for the indication in question.¹²

These observations indicate that clinicians may perceive some degree of personal risk in prescribing opioids, even if medical judgment supports this use. The reality of this perception has been buttressed by a nationwide survey of members of boards of medical examiners, which revealed that a substantial proportion of these regulators would potentially recommend investigation of a prescriber solely in response to the knowledge that an opioid had been administered to a patient with nonmalignant pain for more than six months.¹³

Decision making by physicians within the broad parameters of conventional medical practice should not be unduly influenced by federal or state laws, regulations, policies, or communications that restrict patient access to controlled prescription drugs or incite fear of inappropriate scrutiny or sanction by regulators or those in law enforcement. In an area of therapeutics that is continuing to evolve, like long-term opioid therapy, a clear need exists for dialogue between regulators and clinicians that can define the shifting parameters of conventional practice and continually reassure legitimate prescribers. This dialogue has not taken place and efforts are needed to support it. A critical reevaluation of the role of opioid therapy in the management of chronic nonmalignant pain can be a useful element in this process.

Published experience

Opioid therapy has been evaluated in a small number of controlled clinical trials that assess brief periods of dosing in specific populations with nonmalignant pain. Most of these trials evaluate one or two weeks of treatment in patients with arthritis. The results largely, but not uniformly, support the efficacy of the therapy, but their relevance to long-term management is dubious.¹⁴ None demonstrates the development of abuse behaviors during the brief treatment periods. One controlled trial had an open-label extension phase, during which treatment benefit was maintained.

The most relevant controlled trial published to date evaluated six weeks of morphine therapy in patients with chronic musculoskeletal pain.¹⁵ This study, which used a crossover design, compared the opioid against an active placebo (benztropine) to ensure blinding of the therapy and evaluated a broad range of outcomes related to subjective effects and function. The results demonstrated a significant reduction in pain during morphine therapy, without change in physical or psychological functioning, and without evidence of psychological dependence (measured on a "drug liking" scale) or aberrant drug-related behavior.

Numerous surveys have also been published during the past decade. Some have described the favorable experience of clinicians who have administered opioid drugs to selected patients with nonmalignant pain.¹⁶ One large survey, for example, described 100 patients with diverse pain syndromes who received dihydrocodeine, buprenorphine, or morphine for prolonged periods.¹⁷ More than half these patients maintained greater than 50 percent analgesia for at least one month and performance status increased overall, with the largest improvement observed among those with the greatest relief of pain. No incidents were reported of serious toxicity or drug-related behaviors suggestive of addiction or abuse.

In another survey, patients treated for sickle cell dis-

ease at a single university-based clinic were offered liberalized prescribing of opioids modeled on the treatment of cancer pain.¹⁸ During a two-year follow-up period, emergency room visits declined by 67 percent and hospital admissions decreased by 44 percent. No increase in opioid abuse was reported.

In contrast to these favorable surveys, others depict negative outcomes associated with long-term opioid therapy. These generally originate from multidisciplinary pain management programs and suggest that opioid use may predispose to heightened pain and functional impairment, neuropsychological toxicity, prevarication about drug use, and poor treatment response.¹⁹ Many of the patients described in these reports improve (at least functionally, and sometimes even in terms of pain) when opioids are tapered and discontinued within the context of a more comprehensive pain treatment program.

The limited number of controlled trials, combined with the disparities and inherent biases of the survey literature, preclude definitive conclusions about the risks and benefits of long-term opioid therapy. Nonetheless, it is reasonable to infer from these conflicting results that there is a spectrum of patient responses. On one end of this spectrum is a “successful” subpopulation that achieves sustained partial analgesia without the development of treatment-limiting toxicity, functional deterioration, or aberrant drug-related behaviors. Some of these patients achieve functional gains as pain declines. On the other end is a subpopulation that deteriorates during opioid therapy. This deterioration can be characterized by worsening pain and disability, the development of aberrant drug-related behaviors, or both.

Most pain specialists endorse this view of opioid therapy and, consequently, no longer debate the role of opioid therapy in absolute terms. For pain specialists, the issue is not whether opioid drugs should ever be used in the treatment of chronic pain, but when and how. Although this shift in consensus may not be shared by all specialists, and has certainly not disseminated widely to other professional disciplines, it is noteworthy, and suggests that the use of opioid therapy for chronic nonmalignant pain must now be evaluated as a potentially salutary therapeutic option for carefully selected patients. From this vantage, all those who might become involved in this therapy—clinicians, pharmacists, regulators, and patients—could benefit from a clear understanding of the evidence that defines its risks and benefits.

Opioid therapy for nonmalignant pain: critical issues

The risks and benefits of opioid therapy can be addressed by examining the diverse literature that relates to several critical issues, specifically efficacy, the potential for adverse pharmacological effects, and addiction liability.

Therapeutic efficacy

The efficacy of opioid therapy can be discussed in terms of the responsiveness of different patient subgroups, the durability of the response, and the appropriateness of therapy in the context of larger treatment goals.

Opioid responsiveness

Experience in the management of cancer pain has focused attention on the concept of *opioid responsiveness*.²⁰ Opioid responsiveness refers to the probability that “adequate” analgesia (that is, satisfactory relief without intolerable and unmanageable side-effects) can be attained during dose titration. After opioid therapy is initiated, most patients undergo gradual escalation of the dose until a favorable balance between analgesia and side-effects is reached, or treatment-limiting toxicity precludes further dose adjustments. The balance between analgesia and side-effects varies from patient to patient given the same opioid, and from opioid to opioid within the same individual.²¹

The large individual variability in the responsiveness to opioid drugs can be ascribed to a variety of patient-related and pain-related factors.²² The existence of one or more of these factors can relatively increase or decrease the likelihood that optimally administered opioid therapy will yield a favorable balance between analgesia and side-effects. No factor has ever been shown to impart complete resistance to opioid analgesia. For example, a neuropathic mechanism may reduce the overall responsiveness to opioid drugs,²³ but does not exclude a favorable response in any individual case.²⁴ No characteristic of the patient or pain syndrome can predict the overall benefit of opioid therapy.

These observations resonate well with clinical experience. They indicate that opioid therapy may or may not provide adequate pain relief to any individual patient. The only method for determining outcome is through a therapeutic trial. At present, the predictors of opioid response are not strong enough to exclude patients as candidates for treatment on the presumption of inefficacy.

Durability of response

Clinicians and patients alike commonly express concern that the inherent pharmacology of opioid drugs, specifically the potential for tolerance, limits the potential for long-term efficacy. *Tolerance* is a pharmacological property defined by the need for increasing doses to maintain effects. The term does not imply a specific mechanism or mechanisms, but does indicate that exposure to the drug is the driving force for the change in response.

Although tolerance can be readily demonstrated in animal models,²⁵ these models have limited relevance to the complex clinical setting.²⁶ During opioid therapy, tolerance to adverse effects, such as respiratory depression,

somnolence, and nausea, appears to occur routinely. This is a favorable outcome that allows dose escalation to levels associated with analgesia. In contrast, clinically significant tolerance to analgesic effects appears to be uncommon. Most patients who are receiving opioid drugs for chronic pain attain stable doses associated with a favorable balance between analgesia and side-effects for prolonged periods.²⁷ Dose escalation, when it is required, usually has an obvious alternative explanation, such as worsening of a painful lesion.

Analgesic tolerance, therefore, seldom compromises the efficacy of therapy. Fear of tolerance does not justify a decision to withhold or delay a therapeutic opioid trial.

Therapeutic appropriateness

The treatment of chronic nonmalignant pain is usually guided by the dual goals of enhanced comfort and improved physical and psychosocial functioning. Although conventional thinking assumes that opioid therapy compromises functional restoration, the surveys described previously present a more complex situation. Some patients with nonmalignant pain can receive opioids and apparently capitalize on improved comfort by increasing function, whereas others receive the same drugs and develop worsening disability.

This variability in the response to opioid therapy highlights the heterogeneity of patients with chronic pain. Reports from multidisciplinary pain management programs that suggest a high likelihood of opioid-related functional disturbances may reflect the population referred to such programs, which is characterized by higher levels of psychosocial distress and functional impairment than other patients with chronic pain.²⁸ The appropriateness of opioid therapy for all patients with chronic nonmalignant pain cannot be generalized from any selected population.

Furthermore, pain specialists do not advocate opioid therapy as a substitute for a comprehensive pain management approach that may incorporate psychological and rehabilitative treatments for appropriate patients. It is even possible that some patients who are candidates for multidisciplinary pain management programs could benefit from opioid therapy as a complementary treatment. Opioid treatment may also be an approach that could be implemented by the individual practitioner as part of a multimodality treatment strategy for patients who have disabling pain and are not candidates for specialized pain treatment programs, lack access to such programs or the resources to attend them, or continue to experience severe pain after completing such a program. Persistent pain is common following participation in a multidisciplinary pain management program, even if functional benefits are initially gained, and many patients continue to use opioid drugs.²⁹

Adverse pharmacological outcomes

The risk of adverse pharmacological outcomes can be evaluated in terms of major organ toxicity, persistent side-effects, and the potential problems posed by physical dependence.

Major organ toxicity

There is no evidence of major organ toxicity during long-term opioid therapy in either the cancer population or the methadone-maintenance population. Case reports have described the occurrence of pulmonary edema in dying cancer patients who received very high opioid doses,³⁰ but this clinical situation is extreme and the connection between the drug and the adverse event is unproven. Longitudinal studies in the methadone-maintenance population have demonstrated that the occurrence of liver disease relates to concurrent alcohol use or another medical disorder, rather than ingestion of the opioid.³¹

Recent studies in animal models have revealed the existence of opioid-related dysimmune effects.³² Human data relevant to this issue of immune alteration are very limited, and no worrisome clinical observations have been made in the cancer population or the methadone-maintenance population. Although the potential for adverse immune effects is a serious concern that awaits clinical evaluation, it would not be appropriate to consider any practical changes in the therapeutic use of opioid drugs in the absence of additional data.

Theoretically, continuous exposure to an exogenous opioid could produce long-lasting changes in central nervous system mechanisms that are mediated by endogenous opioids and their receptors. These mechanisms could involve the processing of nociceptive information or any of the other diverse homeostatic functions mediated by these compounds. It is even possible, of course, that exposure to an opioid drug at critical periods could change the vulnerability to the aberrant processes that underlie addiction. Future studies should continue to evaluate the possibility of such outcomes. To date, no clinical evidence indicates that these phenomena are occurring.

Persistent side-effects

Many of the diverse clinical effects produced by opioids could be manifest as morbid side-effects during pain treatment. Persistent constipation, somnolence, or cognitive impairment, for example, can become problematic and limit the utility of the therapy. Constipation is the only persistent side-effect that commonly occurs in the cancer population, but a few patients experience other adverse effects. In the methadone-maintenance population, approximately 10 to 20 percent of patients complain of persistent constipation, insomnia, and decreased sexual function; a somewhat higher percentage report persistent sweating.³³

The potential for cognitive impairment is particularly important in the use of opioids for chronic nonmalignant pain. Overt impairment could compromise rehabilitation efforts and place the patient at risk (for example, during driving). Conceivably, mild impairment could have the same effect and even go unrecognized by the patient or others.

Although cognitive impairment and disturbances in psychomotor functioning are commonly observed following acute administration of opioids to nontolerant patients or dose escalation in those on chronic therapy, these effects typically wane with stable long-term therapy.³⁴ In opioid-treated patients with cancer pain, small impairments in reaction time have been observed,³⁵ but the clinical significance of this finding is not clear. A recent study of cancer patients receiving long-term morphine therapy revealed only minimal effects on cognitive and psychomotor functions related to driving.³⁶ Another study of cancer patients suggested that tolerance to the adverse neuropsychological effects that occur immediately after opioid dose escalation develops within two weeks.³⁷

In patients without cancer, the data are more conflicting. Several surveys of patients admitted to pain programs and surveys of heroin addicts and methadone-maintenance patients have demonstrated clinically evident sedation or abnormalities on neuropsychological testing.³⁸ All these populations were subject to selection bias, however, and no survey controlled for the possible confounds of prior head injury or concurrent administration of other centrally acting drugs. Some studies of methadone-maintained patients have not observed cognitive impairment, and a small study that compared a group of chronic pain patients treated with opioids alone with a group treated with benzodiazepines noted significant cognitive effects only in the latter group.³⁹ Also reassuring, surveys of driving records performed in methadone-maintained populations have not revealed an increased rate of infractions or accidents.⁴⁰

Thus, the data cannot adequately characterize the risk of subtle neuropsychological impairment among patients with chronic nonmalignant pain. Additional investigations in this area are needed. In the cancer population, conventional clinical practice views long-term opioid use as fully compatible with normal function in most cases. Patients are encouraged to be active and there is no admonition to limit driving or other activities unless overt impairment is observed. Clinical experience in the methadone-maintenance population is similar. In the absence of definitive studies, however, clinicians who administer opioids to patients with nonmalignant pain must carefully assess the potential for subtle cognitive impairment over time. Occasionally, this may require formal neuropsychological testing.

Risk of addiction and abuse

The potential for iatrogenic addiction is a major issue in

the use of opioid drugs for the management of chronic nonmalignant pain. To assess this potential, the definitions of phenomena relevant to drug dependence must be clarified.

Definition and implications of physical dependence

Physical dependence is a physiological phenomenon defined solely by the development of an *abstinence syndrome* (opioid withdrawal) following abrupt discontinuation of therapy, substantial dose reduction, or administration of an antagonist drug.⁴¹ No studies have been conducted of physical dependence in patients who are receiving opioids for pain, and clinical observation suggests that the dose and duration of treatment required to produce the phenomenon vary remarkably across patients. To be prudent, clinicians generally assume that patients are physically dependent (that is, have the capacity for an abstinence syndrome) after a few days of repeated opioid doses.

Great confusion exists among clinicians about the differences between physical dependence and addiction. This continues despite the widespread acceptance among addiction specialists of the critical distinctions between these phenomena. Although physical dependence, like tolerance, has been suggested to be a component of addiction⁴² (specifically, the avoidance of withdrawal has been postulated to lead to drug-seeking behavior⁴³), the clinical experience gained in the population with chronic pain strongly affirms that addiction should be defined in a manner that fully distinguishes it from physical dependence. Physical dependence alone does not preclude the uncomplicated discontinuation of opioids in the medical setting, as amply demonstrated by the success of opioid detoxification by multidisciplinary pain programs and the routine cessation of opioids in cancer patients who become fully analgesic following a pain-relieving neurolytic procedure.⁴⁴ Indirect evidence for this distinction between physical dependence and addiction is even provided by animal models of opioid self-administration, which have demonstrated that persistent drug-taking behavior can be maintained in the absence of physical dependence.⁴⁵

The fundamental distinction between addiction and physical dependence implies that clinicians should never label patients who are presumed to be at risk for an abstinence syndrome (that is, physically dependent) as *addicted*. Such a description misrepresents reality and stigmatizes the patient. For the same reason, use of the imprecise general term *dependent* should be avoided. Clinicians should use *physically dependent* when this fits the intended meaning.

Physical dependence is often perceived to be clinically unimportant as long as an abstinence syndrome is avoided. It must be acknowledged, however, that the possibility of adverse effects, such as psychological and physical morbidity related to the syndrome of protracted abstinence or the potential for psychological distress driven by a fear of

withdrawal, has not been investigated. These possible outcomes require additional evaluation.

It has also been postulated that subtle abstinence syndrome phenomena could contribute to a “downhill spiral” in which pain is sustained or maladaptive behaviors are perpetuated as a result of opioid use.⁴⁶ Some type of similar process has also been suggested to explain “rebound” headache, a syndrome of refractory pain ascribed to frequent use of short-acting analgesics.⁴⁷ Although no systematic study has been done of this putative phenomenon, the problematic nature of opioid therapy in some patients is unquestionable, and, in these individuals, the impact of all possible outcomes related to treatment, including physical dependence, should be carefully assessed. In some cases, this assessment can only be performed if opioid therapy is discontinued for a period of weeks to months, so that patient responses independent of the drug can be monitored.

Definition of addiction

Standard definitions of addiction have been developed from experience with substance abusers, but are difficult to apply to patients who are receiving a prescribed therapy for an appropriate medical indication. The definition in a major

pharmacology text⁴⁸ incorporates “relapse after withdrawal” and the definition promulgated by the World Health Organization⁴⁹ includes a reference to physical dependence. These definitions could be applied to opioid-treated patients generally. Similarly, the definitions for psychoactive substance dependence in the third and fourth editions of *Diagnostic and Statistical Manual of Mental Disorders*⁵⁰ include criteria based on chronicity of use, physical dependence, and tolerance. Such criteria also fail to distinguish patients who receive chronic opioid therapy for pain from those who are addicted.⁵¹ The definition developed by a task force of the American Medical Association⁵² appears to be most relevant to patients (“compulsive use of a substance resulting in physical, psychological or social harm to the user and continued use despite that harm”), but requires additional detail to be useful.

In the clinical setting, *addiction* should be defined as a psychological and behavioral syndrome characterized by (1) loss of control over drug use, (2) compulsive drug use, and (3) continued use despite harm. These phenomena must be described in a manner appropriate to patients with chronic pain by reference to specific aberrant drug-related behaviors that may be encountered in practice (see Table 1). These behaviors are familiar to clinicians, but have not

been empirically studied. *A priori*, they can be placed along a spectrum, in which some (such as repeated visits to an emergency room against medical advice or the demand for a specific opioid) are worrisome, but less likely to indicate addiction than others (such as injection of an oral formulation or acquisition of illicit opioids to supplement prescribed drugs).⁵³

Although the diagnosis of addiction may be relatively straightforward in the patient who engages in highly aberrant behaviors, the more common situation, in which the patient occasionally demonstrates a less egregious behavior, is far more challenging to assess. In this circumstance, true addiction actually appears on a “differential diagnosis,” which must be resolved through a careful evaluation. This differential diagnosis includes *pseudoaddiction*, for example, which is a term that describes the development of aberrant behavior in cancer patients who are experiencing un-

Probably More Predictive

- Selling prescription drugs
- Prescription forgery
- Stealing or “borrowing” drugs from others
- Injecting oral formulations
- Obtaining prescription drugs from nonmedical sources
- Concurrent abuse of alcohol or illicit drugs
- Multiple dose escalations or other noncompliance with therapy despite warnings
- Multiple episodes of prescription “loss”
- Repeatedly seeking prescriptions from other clinicians or from emergency rooms without informing prescriber or after warnings to desist
- Evidence of deterioration in the ability to function at work, in the family, or socially that appears to be related to drug use
- Repeated resistance to changes in therapy despite clear evidence of adverse physical or psychological effects from the drug

Probably Less Predictive

- Aggressive complaining about needing more of the drug
- Drug hoarding during periods of reduced symptoms
- Requesting specific drugs
- Openly acquiring similar drugs from other medical sources
- Unsanctioned dose escalation or other noncompliance with therapy on one or two occasions
- Unapproved use of the drug to treat another symptom
- Reporting psychic effects not intended by the clinician
- Resistance to a change in therapy associated with “tolerable” adverse effects with expressions of anxiety related to the return of severe symptoms

Table 1: Aberrant Drug-Related Behaviors, Empirically Divided into Those Assumed to Be Relatively More Predictive and Those Assumed to Be Relatively Less Predictive of Addiction.

Reprinted with permission from R.K. Portenoy, “Opioid Therapy for Chronic Nonmalignant Pain: Current Status,” in H.L. Fields and J.C. Liebeskind, eds., *Progress in Pain Research and Management* (Seattle: IASP Press, Vol. 1, 1994): at 267.

relieved pain; with better analgesia, the behaviors cease.⁵⁴ Other diagnoses include specific psychiatric disorders, such as some personality disorders, that can be characterized by impulsive drug use. Occasionally, problematic behaviors reflect an encephalopathy with confusion about the therapeutic regimen. Irresponsible drug-related behavior rarely indicates criminal intent.

Given this complexity, the diagnosis of addiction can only be entertained following a careful assessment of specific drug-related behaviors. This assessment must first ascertain if the behaviors can be fairly labeled as aberrant. In some cases (for example, the patient who consumes less of the drug when pain spontaneously remits and consumes more than prescribed when pain flares), this may involve consideration of the instructions given to the patient.

If aberrant drug-related behavior has occurred, the clinician must explore its nature and implications. An episode volunteered by the patient and perceived to be transitory and impulsive, perhaps related to a period of unrelieved symptoms, does not warrant a diagnosis of addiction, whereas behaviors that have occurred repeatedly and suggest a more profound loss of control over drug use should be appropriately labeled as such. If the meaning of the behavior is not clear, some time may be required to assess the patient correctly and observe the reaction to additional requirements, such as frequent clinic visits or periodic drug screens.

Risk of addiction

If a true addiction syndrome were a common occurrence among patients who are administered opioids for nonmalignant pain, the approach could not be justified. Indeed, therapeutic decision making about this therapy should be influenced by the potential for any management problems, including those that could potentially be classified as pseudoaddiction. Unfortunately, published surveys have failed to report the prevalence of the various aberrant drug-related behaviors, and a critical evaluation of the current literature can only begin to clarify the occurrence of more severe disturbances consistent with addiction. Specific information about the prevalence and impact of all aberrant drug-related behaviors is needed.

Early surveys of individuals undergoing treatment for addiction yielded data that appeared to suggest a substantial risk of iatrogenic addiction during opioid therapy for pain. In one report, more than one-quarter of some addict groups stated that addiction began as a result of prescribed opioid treatment.⁵⁵ Combined with reports of high recidivism rates among detoxified addicts,⁵⁶ and theoretical writings that linked addiction to the pharmacological properties of tolerance and physical dependence,⁵⁷ these data supported the view that the mere exposure to an opioid could induce and sustain an addiction.

These surveys were unable to elucidate the risk of addiction during long-term opioid administration to patients without a known history of substance abuse, or patients with varying histories of abuse or addiction. Indeed, the biases inherent in these surveys limit the utility of the information they provide. Surveys of actual pain patients are more relevant, but these, too, are subject to the potential for selection bias and observer bias. The relatively high rate of aberrant drug use observed among patients referred to multidisciplinary pain management programs,⁵⁸ for example, is difficult to interpret due to variability in the definitions applied to drug-related outcomes in these settings and the highly selected nature of the populations.⁵⁹

In the absence of well-conducted longitudinal surveys of otherwise unselected populations with nonmalignant pain, other data have been adduced to clarify addiction liability during opioid therapy. For example, although it is widely believed that opioids produce the reinforcing experience of euphoria, surveys of cancer patients, postoperative patients, and normal volunteers indicate that elation is uncommon following administration of an opioid; dysphoria is observed more typically, especially in those who receive meperidine.⁶⁰ The rare occurrence of euphoria in patients without a history of abuse suggests that fundamental processes may predispose to addiction and are uncommon among patients who have not previously demonstrated abuse behaviors. It can be speculated that the lack of prior substance abuse, combined with the lack of a euphorigenic response to a therapeutic opioid, signals a particularly low risk of addiction.

Several patient surveys are also relevant. The Boston Collaborative Drug Surveillance Project, for example, identified only four cases of addiction among 11,882 hospitalized patients with no history of substance abuse who received at least one dose of an opioid.⁶¹ A nationwide survey of burn units found no cases of addiction in the information obtained about 10,000 patients treated for burn pain,⁶² and a survey of patients treated at a large headache center could only identify three problem cases among 2,369 patients who had access to opioid analgesics.⁶³ Recent studies of patients who were allowed to self-administer an opioid for a period of weeks to treat mucositis pain following bone marrow transplantation observed patterns of drug-taking behavior that were inconsistent with the diagnosis of addiction.⁶⁴ The latter finding is consistent with clinical experience, which indicates that addiction is an exceedingly rare outcome during long-term opioid treatment of cancer pain.

Although these surveys of patients with pain are reassuring, they, too, are limited by various sources of bias and a lack of generalizability to the diverse populations with chronic nonmalignant pain. Moreover, the interpretation of all survey data requires comparison to U.S. population prevalence rates for alcoholism (3 to 16 percent) and other

forms of substance abuse (5 to 6 percent).⁶⁵ Obviously, surveys of pain patients that demonstrate rates of substance abuse much lower than population base rates must be interpreted cautiously.

Overall, these surveys provide evidence that the outcomes of drug abuse and addiction do not commonly occur among patients with no history of abuse who receive opioids for medical indications. Other epidemiological data similarly contradict the notion that exposure to opioid drugs alone reliably leads to escalating use and recidivism after detoxification. The existence of so-called “chippers,” individuals who occasionally use heroin recreationally,⁶⁶ belies the inevitability of the full addiction syndrome even in those who consume the drugs for purposes other than pain control. More interesting, perhaps, is the evidence that a large proportion of soldiers who abused heroin in Vietnam stopped this activity abruptly on return to the United States and subsequently demonstrated a low rate of relapse.⁶⁷ This finding highlights the importance of situational factors in the pathogenesis of addiction.

Some direct evidence even indicates that a genetic factor may be important in the development of addiction.⁶⁸ A genetic predisposition has been demonstrated convincingly in alcoholism,⁶⁹ and it has been postulated that the development of alcoholism in a small minority of those who imbibe parallels the development of addiction in a small proportion of those exposed to opioids.⁷⁰

Together, these data suggest that the development of addiction cannot be ascribed solely to the reinforcing properties inherent in a drug. Rather, addiction requires predisposing psychological, social, and physiological (possibly genetic) factors, which presumably interact in some complex fashion during drug exposure. Based on the limited information available, it is highly unlikely that patients without a significant history of substance abuse will become addicted during long-term opioid treatment of chronic pain.

This risk should not be assumed to be nil, however, and assumptions concerning addiction should not be assumed to extend to all types of aberrant drug-related behavior. Indeed, it is probable that patients without prior abuse vary in the risk of aberrant behavior. For example, it can be speculated that the risk of aberrant behaviors (including those consistent with addiction) is probably greater among those with severe character pathology associated with impulsivity and among those who are relatively young. A brief, five-item screening tool has recently been validated and suggests that the number of alcoholic drinks per day, acknowledged use of cannabis, a history of smoking, and age may be important predictors of opioid abuse;⁷¹ further experience with this instrument is needed to determine its predictive validity, and hence its utility in clinical practice. Although the risk of problematic drug taking, and perhaps addiction, is probably higher among those with a known

history of substance abuse, it is likely that this risk also varies with the type and frequency of abuse, the history of substance abuse treatment, current psychosocial supports, and other factors. Additional studies are needed to confirm the low risk of addiction or abuse among those with no history of significant abuse and to clarify the predictive value of specific patient characteristics.

Conclusions

Pain specialists now generally agree that a subpopulation of patients with chronic nonmalignant pain can attain favorable outcomes for prolonged periods using opioid drugs. These outcomes are characterized by sustained analgesia, relatively stable doses, tolerable side-effects, functional gains (or at least no demonstrable functional decline), and highly responsible drug taking (that is, no evidence of significant aberrant drug-related behavior). These outcomes substantively mimic those observed in the typical cancer patient.

On the basis of clinical experience and the foregoing analysis, guidelines for the use of opioid therapy in nonmalignant pain have been proposed (see Table 2). These guidelines, which attempt to balance the potential for salutary effects and the possibility of serious morbidity, will likely evolve as additional data become available.

Given the evidence that opioid therapy can be discontinued without difficulty in virtually all patients, treatment can be initiated in the form of a therapeutic clinical trial. Prior to such a trial, the patient should be fully informed and consent to the therapy. As treatment is administered, close monitoring of the relevant outcomes (specifically pain relief, side-effects, physical and psychosocial functioning, and the development of aberrant drug-related behaviors) can clarify its benefit.

Once begun, opioid therapy requires a working knowledge of the pharmacological techniques described in the cancer pain literature.⁷² These guidelines optimize the likelihood of successful therapy by emphasizing individualization of therapy through a process of assessment and dose adjustment. Although some clinicians support specific approaches for all patients with nonmalignant pain, such as the use of long-acting drugs and no access to supplemental doses, these recommendations are derived solely from anecdotes and are better applied on a case-by-case basis.

Escalation of the opioid dose until satisfactory analgesia occurs, or intolerable and unmanageable side-effects supervene, is the standard for cancer pain management and would presumably optimize analgesic outcomes during the treatment of patients with nonmalignant pain as well. Adherence to this principle may pose a problem, however, if excessive focus on therapy limits rehabilitation, or increases the discomfort of the clinician who is managing a controversial therapy in a highly regulated environment. Previous experience also suggests that the need for repeated dose

- (1) Opioid therapy should be considered only after all other reasonable attempts at analgesia have failed.
- (2) The use of opioid therapy in an individual with a history of substance abuse is clinically complex and should be approached with great care. The inclusion of an individual experienced in addictions evaluation and treatment is recommended in such instances.
- (3) A single practitioner should take primary responsibility for treatment.
- (4) Patients should give informed consent before starting therapy; points to be covered include recognition of the low risk of true addiction as an outcome, potential for cognitive impairment with the drug alone and in combination with sedative/hypnotics, likelihood that physical dependence will occur (abstinence syndrome possible with acute discontinuation), and understanding by female patients that children born when the mother is on opioid therapy will likely be physically dependent at birth.
- (5) After drug selection, doses should be given around the clock; several weeks should be agreed on as the period of initial dose titration, and although improvement in function should be continually stressed, all should agree to at least partial analgesia as the appropriate goal of therapy.
- (6) Failure to achieve at least partial analgesia at relatively low initial doses in the nontolerant patient raises questions about the potential treatability of the pain syndrome with opioids.
- (7) Emphasis should be given to capitalizing on improved analgesia by gains in physical and social function; opioid therapy should be considered complementary to other analgesic and rehabilitative approaches.
- (8) In addition to the daily dose determined initially, patients should be permitted to escalate dose transiently on days of increased pain; two methods are acceptable: (a) prescription of an additional four to six "rescue doses" to be taken as needed during the month; or (b) instruction that one or two extra doses may be taken on any day, but must be followed by an equal reduction of dose on subsequent days.
- (9) Initially, patients must be seen and drugs prescribed at least monthly. When stable, less frequent visits may be acceptable.
- (10) Exacerbations of pain not effectively treated by transient, small increases in dose are best managed in the hospital, where dose escalation, if appropriate, can be observed closely and return-to-baseline doses can be accomplished in a controlled environment.
- (11) Evidence of drug hoarding, acquisition of drugs from other physicians, uncontrolled dose escalation, or other aberrant behaviors must be carefully assessed. In some cases, tapering and discontinuation of opioid therapy will be necessary. Other patients may appropriately continue therapy within rigid guidelines. Consideration should be given to consultation with an addiction medicine specialist.
- (12) At each visit, assessment should specifically address:
 - (a) comfort (degree of analgesia);
 - (b) opioid-related side-effects;
 - (c) functional status (physical and psychosocial); and
 - (d) existence of aberrant drug-related behaviors.
- (13) Use of self-report instruments may be helpful but should not be required.
- (14) Documentation is essential and the medical record should specifically address comfort, function, side-effects, and the occurrence of aberrant behaviors repeatedly during the course of therapy.

Table 2: Proposed Guidelines for the Management of Opioid Therapy for Nonmalignant Pain.

Reprinted with permission from R.K. Portenoy, "Opioid Therapy for Chronic Nonmalignant Pain: Current Status," in H.L. Fields and J.C. Liebeskind, eds., *Progress in Pain Research and Management* (Seattle: IASP Press, Vol. 1, 1994): at 274.

escalations is uncommon among patients with nonmalignant pain who have a favorable response to opioid treatment. Thus, the need for a higher dose should engender a careful evaluation of the medical and psychosocial status of the patient. The clinician may find it useful to seek additional consultations with specialists in pain management at such times.

Long-term opioid therapy must be accompanied by ongoing assessment of aberrant drug-related behaviors. This assessment should determine the impact of pain and psy-

chological factors on drug-related behaviors and distinguish the development of an addiction disorder from a less serious problem. If the diagnosis of addiction is supported, a targeted therapeutic approach is needed and consultation with a specialist in addiction medicine is recommended. If the diagnosis of addiction would not be appropriate and the decision is made to continue therapy, a highly structured response to the aberrant behaviors is still required. These may incorporate new explicit instructions for dosing (perhaps with a written contract), more frequent visits,

smaller prescriptions, periodic urine screens, ongoing psychotherapy, or other interventions. Consultation with a specialist in addiction medicine may again be helpful. Patients who are perceived to have a relatively high risk of aberrant behaviors (such as those with a previous history of substance abuse) should have these controls incorporated into the treatment from the start. These patients are also candidates for a conservative approach to therapy, which might apply some of the anecdotal recommendations noted previously (for example, use of long-acting drugs, no supplemental "as needed" doses, and avoidance of parenteral doses).

The available data do not permit doctrinaire pronouncements about the role of opioid therapy for nonmalignant pain. Rather, the assessment of this therapy is slowly evolving as experienced is gained. Although additional controlled clinical trials of long-term opioid therapy are needed, the lack of these trials should not exclude the empirical use of this approach when medical judgment supports it and treatment is undertaken with appropriate monitoring. This monitoring should repeatedly evaluate analgesia, incidence and severity of opioid side-effects, current physical and psychosocial functioning, and the occurrence of any aberrant drug-related behaviors. Given the complexities of this therapy, documentation of these endpoints in the medical record is essential.

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References

1. A consensus statement that acknowledges the acceptance of opioid therapy in selected patients has been endorsed by the boards of directors of both the American Pain Society and the American Academy of Pain Specialists. To evaluate the preceding debate in the pain literature, see S.F. Brena and S.H. Sanders, "Opioids in Nonmalignant Pain: Questions in Search of Answers," *Clinical Journal of Pain*, 7 (1991): 342-45; C. Chabal et al., "Narcotics for Chronic Pain: Yes or No? A Useless Dichotomy," *American Pain Society Journal*, 1 (1991): 276-81; C. Chabal et al., "The Psychosocial Impact of Opioid Treatment," *American Pain Society Journal*, 1 (1992): 289-91; W.E. Fordyce, "Opioids, Pain and Behavioral Outcomes," *American Pain Society Journal*, 1 (1992): 282-84; C.J. Glynn et al., "Opioids in Nonmalignant Pain: Questions in Search of Answers," *Clinical Journal of Pain*, 7 (1991): 346; G.K. Gourlay and D.A. Cherry, "Can Opioids Be Successfully Used to Treat Severe Pain in Nonmalignant Conditions?," *Clinical Journal of Pain*, 7 (1991): 347-49; A.F. Merry et al., "Opioids in Chronic Pain of Nonmalig-

nant Origin: State of the Debate in New Zealand," *European Journal of Pain*, 13 (1992): 39-43; R.G. Newman, "The Need to Redefine Addiction," *N. Engl. J. Med.*, 18 (1983): 1096-98; R.K. Portenoy, "Opioid Therapy in the Management of Chronic Back Pain," in C.D. Tollison, ed., *Interdisciplinary Rehabilitation of Low Back Pain* (Baltimore: Williams & Wilkins, 1989): 137-58; R.K. Portenoy, "Opioid Therapy in Nonmalignant Pain," *Journal of Pain and Symptom Management*, 5 (1990): S46-S62; R.K. Portenoy, "Chronic Opioid Therapy for Persistent Noncancer Pain: Can We Get Past the Bias?," *American Pain Society Bulletin*, 1 (1991): 1-5; R.K. Portenoy, "Inadequate Outcome of Cancer Pain Treatment: Influences on Patient and Clinician Behavior," in R.B. Patt, ed., *Problems in Cancer Pain Management: A Comprehensive Approach* (Philadelphia: J.B. Lippincott, 1992): 119-28; R.K. Portenoy, "Opioid Therapy for Chronic Nonmalignant Pain: Current Status," in H.L. Fields and J.C. Liebeskind, eds., *Progress in Pain Research and Management* (Seattle: IASP Press, Vol. 1, 1994): 247-87; R.K. Portenoy, "Opioid Therapy for Chronic Nonmalignant Pain: A Review of the Critical Issues," *Journal of Pain and Symptom Management*, 11 (1996): 203-17; R.K. Portenoy and R. Payne, "Acute and Chronic Pain," in J.H. Lowinson, P. Ruiz, and R.B. Millman, eds., *Substance Abuse: A Comprehensive Textbook* (Baltimore: Williams & Wilkins, 1992): 691-721; S.R. Savage, "Addiction in the Treatment of Pain: Significance, Recognition, and Management," *Journal of Pain and Symptom Management*, 8 (1993): 265-78; J. Schofferman, "Long-Term Use of Opioid Analgesics for the Treatment of Chronic Pain of Nonmalignant Origin," *Journal of Pain and Symptom Management*, 8 (1993): 279-88; S.A. Schug, A.F. Merry, and R.H. Acland, "Treatment Principles for the Use of Opioids in Pain of Nonmalignant Origin," *Drugs*, 42 (1991): 228-39; A. Taub, "Opioid Analgesics in the Treatment of Chronic Intractable Pain of Non-Neoplastic Origin," in L.M. Kitahata and D. Collins, eds., *Narcotic Analgesics in Anesthesiology* (Baltimore: Williams & Wilkins, 1982): 199-208; M. Zenz, "Morphine Myths: Sedation, Tolerance, Addiction," *Postgraduate Medical Journal*, 67 (1991): S100-S102; and N. Hagen et al., "Guidelines for Managing Chronic Non-Malignant Pain," *Canadian Family Physician Medicine*, 41 (1995): 49-53.

2. J.J. Bonica, "Treatment of Cancer Pain: Current Status and Future Needs," in H.L. Fields, R. Dubner, and R. Cervero, eds., *Advances in Pain Research and Therapy* (New York: Raven Press, Vol. 9, 1985): 589-616; L. Jorgensen et al., "Treatment of Cancer Pain Patients in a Multidisciplinary Pain Clinic," *Pain Clinic*, 3 (1990): 83-89; D.E. Moulin and K.M. Foley, "Review of a Hospital-Based Pain Service," in K.M. Foley, J.J. Bonica, and V. Ventafridda, eds., *Advances in Pain Research and Therapy, Second International Congress on Cancer Pain* (New York: Raven Press, Vol. 16, 1990): 413-27; R.K. Portenoy, "Cancer Pain: Epidemiology and Syndromes," *Cancer*, 63 (1989): 2298-307; S.A. Schug, D. Zech, and U. Dorr, "Cancer Pain Management According to WHO Analgesic Guidelines," *Journal of Pain and Symptom Management*, 5 (1990): 27-32; S.A. Schug et al., "A Long-Term Survey of Morphine in Cancer Pain Patients," *Journal of Pain and Symptom Management*, 7 (1992): 259-66; F. Takeda, "Results of Field Testing in Japan of the WHO Draft Interim Guidelines on Relief of Cancer Pain," *Pain Clinic*, 1 (1986): 83-89; F. Toscani and M. Carini, "The Implementation of WHO Guidelines for the Treatment of Advanced Cancer Pain at a District General Hospital in Italy," *Pain Clinic*, 3 (1989): 37-48; V. Ventafridda, M. Tamburini, and F. DeConno, "Comprehensive Treatment in Cancer Pain," in H.L. Fields, R. Dubner, and F. Cervero, eds., *Advances in Pain Research and Therapy* (New York: Raven Press, Vol. 9, 1985): 617-28; V. Ventafridda et al., "A Validation Study of the WHO Method for Cancer Pain

- Relief," *Cancer*, 59 (1987): 850-56; S. Vijayaram et al., "Experience with Oral Morphine for Cancer Pain Relief," *Journal of Pain and Symptom Management*, 4 (1989): 130-34; V.A. Walker et al., "Evaluation of WHO Analgesic Guidelines for Cancer Pain in a Hospital-Based Palliative Care Unit," *Journal of Pain and Symptom Management*, 3 (1988): 145-49; World Health Organization, *Cancer Pain Relief* (Geneva: World Health Organization, 1986); World Health Organization, *Cancer Pain Relief and Palliative Care* (Geneva: World Health Organization, 1990); and World Health Organization, *Cancer Pain Relief, With a Guide to Opioid Availability* (Geneva: World Health Organization, 2nd ed., 1996).
3. R.K. Portenoy, "Pain and Quality of Life: Theoretical Aspects," in D. Osoba, ed., *Quality of Life in Cancer Patients* (New York: CRC Publ., 1991): 279-92; and V. Ventafridda et al., "Pain and Quality of Life Assessment in Advanced Cancer Patients," in V. Ventafridda et al., eds., *Assessment of Quality of Life and Cancer Treatment* (Amsterdam: Excerpta Medica, 1986): 183-92.
 4. American Pain Society, *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain* (Skokie: American Pain Society, 3rd ed., 1992); M. Angell, "The Quality of Mercy," *N. Engl. J. Med.*, 306 (1982): 98-99; K.M. Foley, "The Relationship of Pain and Symptom Management to Patient Requests for Physician-Assisted Suicide," *Journal of Pain and Symptom Management*, 6 (1991): 289-97; Health and Public Policy Committee, American College of Physicians, "Drug Therapy for Severe Chronic Pain in Terminal Illness," *Annals of Internal Medicine*, 99 (1983): 870-73; W.T. McGivney and G.M. Crooks, "The Care of Patients with Severe Chronic Pain in Terminal Illness," *JAMA*, 251 (1984): 1182-88; J.P. Morgan, "American Opiophobia: Customary Underutilization of Opioid Analgesics," *Advances in Alcohol and Substance Abuse*, 5 (1985): 163-73; Portenoy (1992), *supra* note 1; J. Stjernsward, "Cancer Pain Relief: An Important Global Public Health Issue," in H.L. Fields, R. Dubner, and F. Cervero, eds., *Advances in Pain Research and Therapy* (New York: Raven Press, Vol. 9, 1985): 555-58; M. Swerdlow and J. Stjernsward, "Cancer Pain Relief—An Urgent Problem," *World Health Forum*, 3 (1982): 325-30; World Health Organization (1986), *supra* note 2; World Health Organization (1990), *supra* note 2; World Health Organization (1996), *supra* note 2; and M. Zenz and J. Sorge, "Is the Therapeutic Use of Opioids Adversely Affected by Prejudice and Law?," *Recent Results in Cancer Research*, 121 (1991): 43-50.
 5. H.W. Clark and K.L. Sees, "Opioids, Chronic Pain and the Law," *Journal of Pain and Symptom Management*, 8 (1993): 297-305; G.R. Haislip, "Impact of Drug Abuse on Legitimate Drug Use," in C.S. Hill and W.S. Fields, eds., *Advances in Pain Research and Therapy* (New York: Raven Press, Vol. 11, 1989): 205-11; and C.S. Hill, "Influence of Regulatory Agencies on the Treatment of Pain and Standards of Medical Practice for the Use of Narcotics," *Pain Digest*, 1 (1991): 7-12.
 6. R.T. Angarola and S.D. Wray, "Legal Impediments to Cancer Pain Treatment," in C.S. Hill and W.S. Fields, eds., *Advances in Pain Research and Therapy* (New York: Raven Press, Vol. 11, 1989): 213-31; W.T. Edwards, "Optimizing Opioid Treatment of Postoperative Pain," *Journal of Pain and Symptom Management*, 5 (1990): S24-S36; C.S. Hill, "Relationship Among Cultural, Educational and Regulatory Agency Influence on Optimum Cancer Pain Treatment," *Journal of Pain and Symptom Management*, 5 (1990): S37-S45; Hill, *supra* note 5; Morgan, *supra* note 4; Portenoy (1992), *supra* note 1; and Zenz and Sorge, *supra* note 4.
 7. D.E. Weissman, D.E. Joranson, and M.B. Hopwood, "Wisconsin Physicians' Knowledge and Attitudes About Opioid Analgesic Regulations," *Wisconsin Medical Journal*, 90 (1991): 671-75.
 8. G.T. Gitchel, "Existing Methods to Identify Retail Drug Diversion," in J.R. Cooper, D.J. Czechowicz, and S.P. Molinari, eds., *Impact of Prescription Drug Diversion Control Systems on Medical Practice and Patient Care* (Washington, D.C.: U.S. Government Printing Office, National Institute on Drug Abuse, Research Mono. 131, 1993): 132-40.
 9. United States Department of Justice, *Drug Enforcement Administration: Multiple Copy Prescription Program Resource Guide* (Washington, D.C.: U.S. Government Printing Office, 1987).
 10. Angarola and Wray, *supra* note 6; J.R. Cooper et al., "Prescription Drug Diversion Control and Medical Practice," *JAMA*, 268 (1992): 1306-10; R.K. Portenoy, "The Effect of Drug Regulation on the Management of Cancer Pain," *New York State Journal of Medicine*, 91 (1991): 13S-18S; and M.M. Reidenberg, "Effect of the Requirement for Triplicate Prescriptions for Benzodiazepines in New York State," *Clinical Pharmacology and Therapeutics*, 50 (1991): 129-31.
 11. T.R. Jacob, "Multiple Copy Prescription Regulation and Drug Abuse: Evidence from the DAWN Network," in B.B. Wilford, ed., *Balancing the Response to Prescription Drug Abuse* (Chicago: American Medical Association, 1990): 205-17.
 12. K.A. Sigler et al., "Effects of a Triplicate Prescription Law on Prescribing of Schedule II Drugs," *American Journal of Hospital Pharmacology*, 41 (1984): 108-11; and M. Weintraub et al., "Consequences of the 1989 New York State Triplicate Benzodiazepine Prescription Regulations," *JAMA*, 266 (1991): 2392-97.
 13. D.E. Joranson et al., "Opioids for Chronic Cancer and Non-Cancer Pain: A Survey of State Medical Board Members," *Federal Bulletin*, 4 (1992): 15-49.
 14. C. Thurel, T. Bardin, and E. Boccard, "Analgesic Efficacy of an Association of 500 mg Paracetamol Plus 30 mg Codeine Versus 400 mg Paracetamol Plus 30 mg Dextropropoxyphene in Repeated Doses for Chronic Lower Back Pain," *Current Therapy and Research*, 50 (1991) 463-73; G.J. Vlok and J.P. Van Vuren, "Comparison of a Standard Ibuprofen Treatment Regimen with a New Ibuprofen/Paracetamol/Codeine Combination in Chronic Osteoarthritis," *South Africa Medical Journal*, 1 Supp. (1987): 1-6; W. Arkininstall et al., "Efficacy of Controlled-Release Codeine in Chronic Non-Malignant Pain: A Randomized, Placebo-Controlled Clinical Trial," *Pain*, 62 (1995): 169-78; C. Boissier et al., "Acceptability and Efficacy of Two Associations of Paracetamol with a Central Analgesic (Dextropropoxyphene or Codeine): Comparison in Osteoarthritis," *Journal of Clinical Pharmacology*, 32 (1992): 990-95; and R.S. Lloyd et al., "The Efficacy and Tolerability of Controlled-Release Dihydrocodeine Tablets and Combination Dextro-propoxyphene Paracetamol Tablets in Patients with Severe Osteoarthritis of the Hips," *Current Medical Research Opinion*, 13 (1992): 37-48.
 15. D.E. Moulin et al., "Randomised Trial of Oral Morphine for Chronic Non-Cancer Pain," *Lancet*, 347 (1996): 143-47.
 16. D. Brookoff and R. Palomano, "Treating Sickle Cell Pain Like Cancer Pain," *Annals of Internal Medicine*, 116 (1992): 364-68. R.D. France, B.J. Urban, and F.J. Keefe, "Long-Term Use of Narcotic Analgesics in Chronic Pain," *Social Science and Medicine*, 19 (1984): 1379-82; J. Green and M. Coyle, "Methadone Use in the Control of Nonmalignant Chronic Pain," *Pain Management*, Sept./Oct. (1989): 241-46; E.S. Krames and R.M. Lanning, "Intrathecal Infusional Analgesia for Nonmalignant Pain: Analgesic Efficacy of Intrathecal Opioid With or Without Bupivacaine," *Journal of Pain and Symptom Management*, 8

- (1993): 539–48; J.L. Plummer et al., “Long-Term Spinal Administration of Morphine in Cancer and Non-Cancer Pain: A Retrospective Study,” *Pain*, 44 (1991): 215–20; Portenoy (1990), *supra* note 1; R.K. Portenoy and K.M. Foley, “Chronic Use of Opioid Analgesics in Non-Malignant Pain: Report of 38 Cases,” *Pain*, 25 (1986): 171–86; Taub, *supra* note 1; F.S. Tennant and G.F. Uelman, “Narcotic Maintenance for Chronic Pain: Medical and Legal Guidelines,” *Postgraduate Medicine*, 73 (1983): 81–94; F.S. Tennant et al., “Chronic Opioid Treatment of Intractable Non-Malignant Pain,” *Pain Management*, Jan./Feb. (1988): 18–36; B.J. Urban et al., “Long-Term Use of Narcotic-Antidepressant Medication in the Management of Phantom Limb Pain,” *Pain*, 24 (1986): 191–97; and M. Zenz, M. Strumpf, and M. Tryba, “Long-Term Opioid Therapy in Patients with Chronic Nonmalignant Pain,” *Journal of Pain and Symptom Management*, 7 (1992): 69–77.
17. See Zenz, Strumpf, and Tryba, *id.*
18. See Brookoff and Palomano, *supra* note 16.
19. F.P. Buckley, W.A. Sizemore, and J.E. Charlton, “Medication Management in Patients with Chronic Non-Malignant Pain. A Review of the Use of a Drug Withdrawal Protocol,” *Pain*, 26 (1986): 153–66; R. D. Finlayson, T. Maruta, and B.R. Morse, “Substance Dependence and Chronic Pain: Profile of 50 Patients Treated in an Alcohol and Drug Dependence Unit,” *Pain*, 26 (1986): 167–74; R.D. Finlayson et al., “Substance Dependence and Chronic Pain: Experience with Treatment and Follow-Up Results,” *Pain*, 26 (1986): 175–80; T. Maruta, “Prescription Drug-Induced Organic Brain Syndrome,” *American Journal of Psychiatry*, 135 (1978): 376–77; T. Maruta and D. W. Swanson, “Problems with the Use of Oxycodone Compound in Patients with Chronic Pain,” *Pain*, 11 (1981): 389–96; T. Maruta, D.W. Swanson, and R.E. Finlayson, “Drug Abuse and Dependency in Patients with Chronic Pain,” *Mayo Clinic Proceedings*, 54 (1979): 241–44; S.L. McNairy et al., “Prescription Medication Dependence and Neuropsychologic Function,” *Pain*, 18 (1984): 169–77; L.B. Ready, E. Sarkis, and J.A. Turner, “Self-Reported vs. Actual Use of Medications in Chronic Pain Patients,” *Pain*, 12 (1982): 285–94; and J.A. Turner et al., “Drug Utilization Pattern in Chronic Pain Patients,” *Pain*, 12 (1982): 357–63.
20. See Portenoy (1990), *supra* note 1.
21. B.S. Galer et al., “Individual Variability in the Response to Different Opioids: Report of Five Cases,” *Pain*, 49 (1992): 87–91.
22. E. Bruera et al., “The Edmonton Staging System for Cancer Pain: Preliminary Report,” *Pain*, 37 (1989): 203–10; and S. Mercadante et al., “Predictive Factors in Advanced Cancer Pain Treated Only by Analgesics,” *Pain*, 50 (1992): 151–55.
23. S. Arner and B.A. Meyerson, “Lack of Analgesic Effect of Opioids on Neuropathic and Idiopathic Forms of Pain,” *Pain*, 33 (1988): 11–23; Bruera et al., *id.*; R.C. Kupers et al., “Morphine Differentially Affects the Sensory and Affective Pain Ratings in Neurogenic and Idiopathic Forms of Pain,” *Pain*, 47 (1991): 5–12; and Moulin and Foley, *supra* note 2.
24. N.I. Cherny et al., “Opioid Responsiveness of Cancer Pain Syndromes Caused by Neuropathic or Nociceptive Mechanisms: A Combined Analysis of Controlled Single Dose Studies,” *Neurology*, 44 (1994): 857–61; Galer et al., *supra* note 21; A.R. Jadad et al., “Morphine Responsiveness of Chronic Pain: Double-Blind Randomised Crossover Study with Patient-Controlled Analgesia,” *Lancet*, 339 (1992): 1367–71; H.J. McQuay et al., “Opioid Sensitivity of Chronic Pain: A Patient-Controlled Analgesia Method,” *Anaesthesia*, 47 (1992): 757–67; Mercadante et al., *supra* note 22; Portenoy (1990), *supra* note 1; Portenoy and Foley, *supra* note 16; M.C. Rowbotham, L.A. Reisner-Keller, and H.L. Fields, “Both Intravenous Lidocaine and Morphine Reduce the Pain of Posttherapeutic Neuralgia,” *Neurology*, 41 (1991): 1024–28; Urban et al., *supra* note 16; and Zenz, Strumpf, and Tryba, *supra* note 16.
25. A.K. Louie and E.L. Way, “Overview of Opiate Tolerance and Physical Dependence,” in O.F. Almeida and T.S. Shippenberg, eds., *Neurobiology of Opioids* (New York: Springer-Verlag, 1991).
26. See Portenoy (1989), *supra* note 1.
27. F.J. Brescia et al., “Pain, Opioid Use and Survival in Hospitalized Patients with Advanced Cancer,” *Journal of Clinical Oncology*, 10 (1992): 149–55; K.M. Foley, “Changing Concepts of Tolerance to Opioids: What the Cancer Patient Has Taught Us,” in C.R. Chapman and K.M. Foley, eds., *Current and Emerging Issues in Cancer Pain: Research and Practice* (New York: Raven Press, 1993): 331–50; France, Urban, and Keefe, *supra* note 16; Hill, *supra* note 6; R.M. Kanner and K.M. Foley, “Patterns of Narcotic Drug Use in a Cancer Pain Clinic,” *Annals of the New York Academy of Science*, 362 (1981): 161–72; Krames and Lanning, *supra* note 16; B.M. Onofrio and T.L. Yaksh, “Long-Term Pain Relief Produced by Intrathecal Morphine Infusion in 53 Patients,” *Journal of Neurosurgery*, 72 (1990): 200–09; Plummer et al., *supra* note 16; Portenoy and Foley, *supra* note 16; Schug et al., *supra* note 1; Taub, *supra* note 1; R.G. Twycross, “Clinical Experience with Diamorphine in Advanced Malignant Disease,” *International Journal of Clinical Pharmacology, Therapy and Toxicology*, 9 (1974): 184–98; and Urban et al., *supra* note 16.
28. C.R. Chapman, A.E. Aola, and J.J. Bonica, “Illness Behavior and Depression in Pain Center and Private Practice Patients,” *Pain*, 6 (1979): 1–7; J. Crook and E. Tunks, “Defining the ‘Chronic Pain Syndrome’: An Epidemiological Method,” in H.L. Fields, R. Dubner, and R. Cervero, eds., *Advances in Pain Research and Therapy* (New York: Raven Press, Vol. 9, 1985): 871–78; J. Crook et al., “Epidemiologic Comparison of Persistent Pain Sufferers in a Specialty Pain Clinic and in the Community,” *Archives of Physics, Medicine and Rehabilitation*, 67 (1986): 451–55; J. Crook, R. Weir, and E. Tunks, “An Epidemiological Follow-Up Survey of Persistent Pain Sufferers in a Group Family Practice and Specialty Pain Clinic,” *Pain*, 36 (1989): 49–61; R.A. Deyo et al., “Prognostic Variability Among Chronic Pain Patients: Implications for Study Design, Interpretation, and Reporting,” *Archives of Physical Medicine and Rehabilitation*, 69 (1988): 174–78; and I. Pilowsky, C.R. Chapman, and J.J. Bonica, “Pain, Depression, and Illness Behavior in a Pain Clinic Population,” *Pain*, 4 (1977): 183–92.
29. D.C. Turk and T.E. Rudy, “Neglected Topics in the Treatment of Chronic Pain Patients—Relapse, Noncompliance and Adherence Enhancement,” *Pain*, 44 (1991): 5–28.
30. E. Bruera and M.J. Miller, “Non-Cardiogenic Pulmonary Edema After Narcotic Treatment for Cancer Pain,” *Pain*, 39 (1989): 297–300.
31. M.J. Kreek, “Medical Safety and Side-Effects of Methadone in Tolerant Individuals,” *JAMA*, 223 (1973): 665–68; and M.J. Kreek, “Medical Complications in Methadone Patients,” *Annals of the New York Academy of Science*, 311 (1978): 110–34.
32. P.K. Arora et al., “Morphine-Induced Immune Alterations In Vivo,” *Cell Immunology*, 126 (1990): 343–53; R.M. Donohoe et al., “Morphine Depression of T Cell E-Rosetting: Definition of the Process,” *Federal Procedures*, 44 (1985): 95–99; T.K. Einstein et al., “Immunosuppression to Tetanus Toxoid Induced by Implanted Morphine Pellets,” *Annals of the New York Academy of Science*, 594 (1990): 377–79; T.W. Molitor et al., “Chronic Morphine Administration Impairs Cell-Mediated Immune Re-

- sponses in Swine," *Journal of Pharmacology and Experimental Therapeutics*, 260 (1992): 581-86; P.K. Peterson et al., "Opioid-Mediated Suppression of Interferon-Production by Cultured Peripheral Blood Mononuclear Cells," *Journal of Clinical Investigations*, 80 (1987): 824-31; Y. Shavit et al., "Opioid Peptides Mediate the Suppressing Effect of Stress on Natural Killer Cell Cytotoxicity," *Science*, 223 (1984): 188-90; and R.J. Weber et al., "Opiate Receptor Mediated Regulation of the Immune Response In Vivo," *National Institute of Drug Abuse* (Washington, D.C.: U.S. Government Printing Office, National Institute on Drug Abuse, Research Mono. 76, 1987): 341-48.
33. See Kreek (1973), *supra* note 31; and Kreek (1978), *supra* note 31.
34. J.P. Zacny, "A Review of the Effects of Opioids on Psychomotor and Cognitive Functioning in Humans," *Experimental Clinical Psychopharmacology*, 3 (1995): 432-66.
35. P. Sjogren and A. Banning, "Pain, Sedation and Reaction Time During Long-Term Treatment of Cancer Patients with Oral and Epidural Opioids," *Pain*, 39 (1989): 5-12; and A. Banning and P. Sjogren, "Cerebral Effects of Long-Term Oral Opioids in Cancer Patients Measured by Continuous Reaction Time," *Clinical Journal of Pain*, 6 (1990): 91-95.
36. A. Vainio et al., "Driving Ability in Cancer Patients Receiving Long-Term Morphine Analgesia," *Lancet*, 346 (1995): 667-70.
37. See Bruera et al., *supra* note 22.
38. McNairy et al., *supra* note 19; Maruta, *supra* note 19; B.H. Rounsaville et al., "Neuropsychological Impairment in Opiate Addicts: Risk Factors," *Annals of the New York Academy of Science*, 362 (1981): 79-90; W.R. Martin et al., "Methadone—A Reevaluation," *Archives of General Psychiatry*, 28 (1973): 286-95; and C.A. Haertzen and N.T. Hooks, "Changes in Personality and Subjective Experience Associated with the Chronic Administration and Withdrawal of Opiates," *Journal of Nervous and Mental Disease*, 148 (1969): 606-14.
39. N. Hender et al., "A Comparison of Cognitive Impairment Due to Benzodiazepines and to Narcotics," *American Journal of Psychiatry*, 137 (1980): 828-30; P.W. Appel and N.B. Gordon, "Digit-Symbol Performance in Methadone-Treated Ex-Heroin Addicts," *American Journal of Psychiatry*, 133 (1976): 1337-40; and W.K. Lombardo, B. Lombardo, and A. Goldstein, "Cognitive Functioning Under Moderate and Low Dose Methadone Maintenance," *International Journal of Addiction*, 11 (1976): 389-401.
40. N.B. Gordon, "Influence of Narcotic Drugs on Highway Safety," *Accident Analysis Preview*, 8 (1976): 3-7; and D.V. Babst et al., *Driving Records of Methadone Maintained Patients in New York State* (Albany: New York State Narcotic Control Commission, 1973).
41. V.P. Dole, "Narcotic Addiction, Physical Dependence and Relapse," *N. Engl. J. Med.*, 286 (1972): 988-92; W.R. Martin and D.R. Jasinski, "Physiological Parameters of Morphine Dependence in Man-Tolerance, Early Abstinence, Protracted Abstinence," *Journal of Psychology Research*, 7 (1969): 9-17; and R.C. Rinaldi et al., "Clarification and Standardization of Substance Abuse Terminology," *JAMA*, 259 (1988): 555-57.
42. World Health Organization, *Technical Report No. 516, Youth and Drugs* (Geneva: World Health Organization, 1973); and American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders* (Washington, D.C.: American Psychiatric Association, 4th ed., 1994).
43. A. Wikler, *Opioid Dependence: Mechanisms and Treatment* (New York: Plenum Press, 1980).
44. Buckley, Sizemore, and Charlton, *supra* note 19; L.M. Halpern and J. Robinson, "Presenting Practices for Pain in Drug Dependence: A Lesson in Ignorance," *Advanced Alcohol Substance Abuse*, 5 (1985): 184-97; and Kanner and Foley, *supra* note 27.
45. S. Dai et al., "Heroin Self-Administration by Rats: Influence of Dose and Physical Dependence," *Pharmacology, Biochemistry, Behavior*, 32 (1989): 1009-15.
46. R.A. Brodner and A. Taub, "Chronic Pain Exacerbated by Long-Term Narcotic Use in Patients with Nonmalignant Disease: Clinical Syndrome and Treatment," *Mount Sinai Journal of Medicine*, 45 (1978): 233-37; and Schofferman, *supra* note 1.
47. N. Matthew, "Drug-Induced Headache," *Neurologic Clinics*, 8 (1990): 903-12; and J.R. Saper, "Daily Chronic Headache," *Neurologic Clinics*, 8 (1990): 891-902.
48. J.H. Jaffe, "Drug Addiction and Drug Abuse," in A.G. Gilman et al., eds., *The Pharmacological Basis of Therapeutics* (New York: Macmillan, 7th ed., 1985): 532-81.
49. World Health Organization, *supra* note 42.
50. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders* (Washington, D.C.: American Psychiatric Association, 3rd ed., rev., 1987); and American Psychiatric Association, *supra* note 42.
51. See Clark and Sees, *supra* note 5.
52. See Rinaldi et al., *supra* note 41.
53. See Portenoy (1992), *supra* note 1.
54. D.E. Weissman and J.D. Haddox, "Opioid Pseudoaddiction—An Iatrogenic Syndrome," *Pain*, 36 (1989): 363-66.
55. M. Rayport, "Experience in the Management of Patients Medically Addicted to Narcotics," *JAMA*, 156 (1954): 684-91.
56. D.D. Simpson, L.J. Savage, and M.R. Lloyd, "Follow-Up Evaluation of Treatment of Drug Abuse During 1969 to 1972," *Archives of General Psychiatry*, 36 (1979): 772-80; and G.E. Vallaint, "A 20-Year Follow-Up of New York Narcotic Addicts," *Archives of General Psychiatry*, 29 (1973): 237-41.
57. See Wikler, *supra* note 43.
58. R.G. Black, "The Clinical Syndrome of Chronic Pain," in L.K.Y. Ng and J.J. Bonica, eds., *Pain, Discomfort and Humanitarian Care* (New York: Elsevier, 1980): 207-09; Buckley, Sizemore, and Charlton, *supra* note 19; Finlayson, Maruta, and Morse, *supra* note 19; Maruta, Swanson, and Finlayson, *supra* note 19; and Ready, Sarkis, and Turner, *supra* note 19.
59. D.A. Fishbain, H.L. Rosomoff, and R.S. Rosomoff, "Drug Abuse, Dependence, and Addiction in Chronic Pain Patients," *Clinical Journal of Pain*, 8 (1992): 77-85.
60. R.F. Kaiko, K.M. Foley, and P.Y. Grabinski, "Central Nervous System Excitatory Effects of Meperidine in Cancer Patients," *Annals of Neurology*, 13 (1983): 180-85; and J.H. Jaffe, "Misinformation: Euphoria and Addiction," in C.S. Hill and W.S. Fields, eds., *Advances in Pain Research and Therapy* (New York: Raven Press, Vol. 11, 1989): 163-74.
61. J. Porter and H. Jick, "Addiction Rare in Patients Treated with Narcotics," *N. Engl. J. Med.*, 302 (1980): 123.
62. S. Perry and G. Heidrich, "Management of Pain During Debridement: A Survey of U.S. Burn Units," *Pain*, 13 (1982): 267-80.
63. J.L. Medina and S. Diamond, "Drug Dependency in Patients with Chronic Headache," *Headache*, 17 (1977): 12-14.
64. C.R. Chapman and H.F. Hill, "Prolonged Morphine Self-Administration and Addiction Liability: Evaluation of Two Theories in a Bone Marrow Transplant Unit," *Cancer*, 63 (1989): 1636-44.
65. D.A. Regier et al., "The NIMH Epidemiologic Catchment Area Program," *Archives of General Psychiatry*, 41 (1984): 934-58.
66. D.B. Graeven and W. Folmer, "Experimental Heroin

Users: An Epidemiologic and Psychosocial Approach," *American Journal of Drug and Alcohol Abuse*, 4 (1977): 365-75.

67. L.N. Robins, D.H. Davis, and D.N. Nurco, "How Permanent Was Vietnam Drug Addiction?," *American Journal of Public Health*, 64 (1974): 38-43.

68. W.M. Grove et al., "Heritability of Substance Abuse and Antisocial Behavior: A Study of Monozygotic Twins Reared Apart," *Biology and Psychiatry*, 27 (1990): 1293-304.

69. R.M. Anthenelli and M.A. Schuckit, "Genetics," in J.H. Lowinson, P. Ruiz, and R.B. Millman, eds., *Substance Abuse: A Comprehensive Textbook* (Baltimore: Williams & Wilkins, 1992):

39-50.

70. R.G. Newman, "The Need to Redefine Addiction," *N. Engl. J. Med.*, 18 (1983): 1096-98.

71. R.B. Coombs et al., "The SISAP: A New Screening Instrument for Identifying Potential Opioid Abusers in the Management of Chronic Nonmalignant Pain Within General Medical Practice," *Pain Research and Management*, 1 (1996): 155-62.

72. Acute Pain Management Guideline Panel, "Acute Pain Management," *Clinical AHCPR Practice Guideline* (Rockville: Agency for Health Care Policy and Research, Pub. No. 92-0032, Feb. 1992).