Opioid therapy for chronic nonmalignant pain

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Long term administration of an opioid drug for chronic nonmalignant pain continues to be controversial, but is no longer uniformly rejected by pain specialists. This is true despite concerns that the regulatory agencies that oversee physician prescribing of opioid drugs continue to stigmatize the practice. The changing clinical perspective has been driven, in part, by widespread acknowledgement of the remarkably favourable outcomes achieved during opioid treatment of cancer pain. These outcomes contrast starkly with popular teaching about chronic opioid therapy and affirm the potential for prolonged efficacy, tolerable side effects, enhanced function associated with improved comfort and minimal risk of aberrant drug-related behaviours consistent with addiction. A large anecdotal experience in populations with nonmalignant pain suggests that these patients are more heterogeneous and that opioid therapy will greatly benefit some and will contribute to negative outcomes for others. The few controlled clinical trials that have been performed support the safety and efficacy of opioid therapy, but have been too limited to ensure generalization to the clinical setting. A critical review of the medical literature pertaining to chronic pain, opioid pharmacology and addiction medicine can clarify misconceptions about opioid therapy and provide a foundation for patient selection and drug administration. The available data support the view that opioids are no panacea for chronic pain, but should be considered in carefully selected patients using clinically derived guidelines that stress a structured approach and ongoing monitoring of efficacy, adverse effects, functional outcomes and the occurrence of aberrant drug-related behaviours.

Key Words: *Addiction, Drug dependence, Nonmaligant pain, Opioids, Pain therapy*

Thérapie opioïde pour la douleur chronique non cancéreuse

RÉSUMÉ : L'administration à long terme d'un médicament opioïde pour traiter la douleur chronique non cancéreuse reste sujet à controverse mais n'est plus rejetée de façon uniforme par les spécialistes de la douleur. Ceci est vrai même si l'on s'inquiète de ce que les organismes régulateurs qui supervisent la prescription médicale d'agents opioïdes persistent à stigmatiser cette pratique. Le changement de perspective clinique a été motivé en partie par une reconnaissance généralisée des résultats remarquablement favorables obtenus lors du traitement opioïde de la douleur cancéreuse. Ces résultats contrastent carrément avec ce qui est généralement enseigné sur l'administration à long terme d'un médicament opioïde et, confirment un potentiel d'efficacité durable, des effets secondaires supportables, une augmentation de la capacité fonctionnelle associée à une amélioration du bien-être et, un risque minimal de comportements aberrants liés au médicament compatibles avec une toxicomanie. Une vaste expérience anecdotique chez des populations souffrant d'une douleur non cancéreuse fait croire que ces patients sont plus hétérogènes et qu'une thérapie opioïde sera grandement bénéfique pour certains d'entre eux tandis que pour d'autres elle sera défavorable. Les quelques essais cliniques contrôlés qui ont été menés confirment l'efficacité et l'innocuité de la thérapie opioïde mais restent trop limités pour garantir la généralisation de ces résultats au contexte clinique. Une revue critique de la littérature médicale portant sur la douleur chronique, la pharmacologie opioïde et les médicaments qui entraînent une accoutumance peut clarifier les idées faussement reçues sur la thérapie opioïde et fournir une base pour la sélection des patients et pour le traitement médicamenteux. Les données dont on dispose actuellement soutiennent que les agents opioïdes ne sont pas une panacée pour la douleur chronique mais qu'ils devraient être envisagés chez des patients soigneusement sélectionnés en utilisant des lignes directrices dérivées de la pratique clinique qui insistent sur une approche structurée et un monitorage constant de l'efficacité, des effets indésirables, des résultats sur la capacité fonctionnelle et, du développement potentiel de comportements aberrants liés aux agents opioïdes.

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The traditional rejection of opioid therapy for chronic nonmalignant pain is based on the perceptions of transitory benefit and substantial cumulative risk. It is often taken as axiomatic that opioid efficacy inevitably wanes due to tolerance and that long term opioid administration yields persistent side effects, compromise of physical and psychosocial functioning, and addiction. If accurate, these perceptions justify the withholding of opioid therapy for all but the most extreme cases of chronic nonmalignant pain.

Recently, there has been a burgeoning effort to examine critically the empirical observations and analyses that have been adduced as supporting evidence for this view (1-18). This effort has been particularly encouraged by two sets of observations. First, experience gained during the management of cancer pain has demonstrated the potential for highly favourable outcomes from 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 clinical experience in the cancer population

Experience in the cancer population contrasts starkly with the pervasively negative view of opioid drugs. Numerous studies have confirmed that opioid treatment provides adequate relief to 70 to 90% of patients with cancer pain (19-32). Rather than augmenting patient distress, opioid therapy is widely perceived to be an effective means to temper it and offers the opportunity for better function and quality of life (33,34). On this basis, long term treatment with opioid drugs has been strongly advocated by pain specialists and both national and international medical organizations (31,32,35-44).

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 are significant clinical problems. 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

Physician prescribing of opioids is scrutinized by regulatory and law enforcement agencies, who have the difficult task of identifying and eliminating drug diversion and practices that threaten the public health (45,46). Physicians accept the necessity of such regulation (47), but need to be reassured that prescribing behaviour that is within the bounds of accepted medical practice will not lead to investigation or sanction. Those in law enforcement and the regulatory community have attempted to offer this reassurance (48).

Unfortunately, there is evidence that regulatory policies can contribute to the undertreatment of pain by either impeding access to controlled prescription drugs or negatively influencing prescribing behaviour (40,41,44,46,49-51). Impediments to access are exemplified by the existence of regulations in some American states that limit the number of tablets that may be prescribed per prescription. 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. This may be exhausting to both the patient and prescriber.

Regulatory policies can also negatively influence physician prescribing. 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 (52). Not surprisingly, the degree of concern about regulatory oversight was greatest with the drugs most often used in the management of severe pain, including morphine, hydromorphone and oxycodone.

Analysis of multiple copy prescription programs offers additional evidence of the influence of regulatory policies on physician prescribing. These programs monitor physician behaviour through the use of a special prescription form for controlled drugs. They offer unique 'point-of-sale' data and are strongly favoured by those in the regulatory and law enforcement communities (53).

Every state that has initiated a multiple copy prescription program has recorded a greater than 50% reduction in the prescribing of the regulated drugs (54). Although proponents have stated that this change reflects a lower rate of abuse, these claims have been disputed by pain specialists and others (49,55-57). Data from the federal Drug Abuse Warning Network have not confirmed that multiple copy prescription programs curtail prescription drug abuse (58), and surveys in Texas (59) and New York (60) suggest that the increased awareness of regulatory oversight induced by 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.

These observations indicate that physicians may react to the knowledge of regulatory scrutiny by limiting the use of controlled prescription drugs. Thus, clinicians may perceive some degree of personal risk in prescribing opioids, even if medical judgement supports this use. The reality of this perception has been buttressed by a recent nationwide survey of members of boards of medical examiners, which revealed that a substantial proportion of these regulators would 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 (61).

The possibility that medical decision-making is unduly influenced by regulatory policies should be viewed as a problem in need of redress. A critical reevaluation of the role of opioid therapy in the management of chronic nonmalignant pain is a useful element in this process.

OPIOID THERAPY FOR CHRONIC NONMALIGNANT PAIN: PUBLISHED EXPERIENCE

During the past decade, numerous surveys have detailed the favourable experience of clinicians who have administered opioid drugs to selected patients with nonmalignant pain (Table 1) (10,17,62-70). The most recent survey, for example, described

TABLE 1
Representative published surveys of opioid therapy for the treatment of chronic nonmalignant pain

Author	Patient #	Diagnosis	Opioids	Equivalent daily dose	Duration	Analgesic efficacy	Adverse effects	Comments
Taub (17)	313	Mixed	Mixed	Mean 10-20 mg (maximum 40 mg) oral methadone	Up to 6 years	Few details; all said to benefit	No toxicity; abuse in 13	8 of 13 problem cases had prior drug abuse
Tennant and Uelman (67)	22	Not stated	Not stated	Not stated	Not stated	Not stated	No abuse	All had failed pain clinics; 15 returned to work
France et al (62)	16	Mostly back pain	Mixed	Mean 8 mg (range 3-20) oral methadone	Mean 13 months (range 6-22)	Pain relief >50% in all, >75% in 13; sustained in 12	No toxicity; no abuse	12 of 16 improved function; higher doses needed in 5 over time
Portenoy and Foley (66)	38	Mixed; some neuropathic	Mixed	Median 10-20 mg (range <10-60) parenteral morphine	Median 3-4 years; range 6 months to 10 years	Adequate 11; partial 13; inadequate 14	No toxicity; abuse in 2	Both problem cases had prior drug abuse; marked gains in function uncommon but few details
Urban et al (69)	5	Phantom pain	Methadone	10-20	Mean 22 months (range 12-26)	At follow-up, all >50% relief	No toxicity; no abuse	Over time, relief waned in 1
Portenoy (12)	20	Mixed; some neuropathic	Mixed	Median 10-20 mg (range <10-50) parenteral morphine	Median <2 years; range 6 months to 10 years	Adequate 9; partial 10; inadequate 14	Personality change in 1; myoclonus in 1; abuse in 2	Marked gains in function uncommon but few details; with warning, both problem cases stopped abuse
Tennant et al (68)	52	Mixed	Mixed	Very variable; range 10-240 mg oral methadone	Duration of program not noted; opioid use averaged >12 years	Adequate 88%; partial 12%	Constipation in 20; edema in 12; adrenal insufficiency in 1; abuse in 9	Many medically ill, accounting for side effects; no dose increases needed
Zenz et al (70)	100	Mixed	Morphine; buprenorphine; dihydrocodeine	Variable; morphine range 20-2000 mg	Mean 224 days, range 14-1472 days	Good 51%; partial 28%	Constipation most common; no abuse	Overall improvement in performance status, with significant relationship between analgesia and improvement

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100 patients with diverse pain syndromes who received dihydrocodeine, buprenorphine or morphine for prolonged periods (70). More than half attained greater than 50% analgesia and performance status increased overall, with the largest improvement observed among those with the greatest relief of pain. There were no reported incidents of serious toxicity or drug-related behaviours suggestive of addiction or abuse.

In another recent survey, patients treated for sickle cell disease at a single university-based clinic were offered liberalized prescribing of opioids modelled on the treatment of cancer pain (71). During a two year follow-up period, emergency room visits declined by 67% and hospital admissions decreased by 44%. There was no increase in opioid abuse.

These surveys contrast with other published reports, which originate from multidisciplinary pain management programs and demonstrate an association between opioid use and heightened pain and functional impairment, neuropsychological toxicity, prevarication about drug use and poor treatment response (72-80). The patients described in these reports were said to improve when opioids were tapered and discontinued.

The conflicting results of these surveys suggest that there is a spectrum of patient response to long term opioid administration. At 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 behaviours. At the other end is a subpopulation that deteriorates during opioid therapy.

The disparities in this literature emphasize the inability to

glean definitive conclusions about opioid therapy from survey data. All surveys are subject to referral bias (clinicians tend to receive referrals that 'fit' their avowed interest) and observer bias. The outcomes described reflect the experience of a selected group of patients and may not be generalizable to other groups. Nonetheless, the existence of such diversity contradicts the traditional view that opioid therapy always leads to a poor outcome.

Opioid therapy has also been evaluated in a small number of controlled clinical trials that assessed a brief period of dosing in a specific population with nonmalignant pain. These studies, which have usually assayed codeine or a similar drug in arthritic patients, yielded mixed results and have questionable relevance to long term treatment (81-83). None has identified a problem with aberrant drug-related behaviours during this brief period of treatment.

OPIOID THERAPY FOR NONMALIGNANT PAIN: CRITICAL ISSUES

Like any other potential medical therapy, long term opioid administration for chronic nonmalignant pain must be evaluated in terms of safety and efficacy. The potential for addiction is a singular aspect of the safety considerations inherent in this approach.

Therapeutic efficacy

The efficacy of opioid therapy can be evaluated 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' (84). Most cancer patients with severe chronic pain undergo gradual escalation of the opioid dose until a favourable balance between analgesia and side effects is reached, or dose-limiting toxicity precludes further dose titration. 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 (85). Opioid responsiveness refers to the probability that 'adequate' analgesia (ie, satisfactory relief without intolerable and unmanageable side effects) can be attained during dose titration. Alternatively, the term can denote the degree of analgesia achieved at a dose associated with intolerable side effects.

The large interindividual variability in the responsiveness to opioid drugs can be ascribed to a variety of patient-related and pain-related factors (84). Studies in the cancer population, for example, have demonstrated that responsiveness is relatively reduced in the presence of an inferred neuropathic pathophysiology for the pain, incident pain (pain induced by specific manoeuvres), impaired cognitive function, a high level of psychological distress, ongoing use of relatively high opioid doses and a need for a rapid increase in the opioid dose (86,87). Genetic factors may also be involved, at least in the responsiveness to some drugs (88).

If nonmalignant pain generally, or any patient subgroup with nonmalignant pain (such as those with neuropathic pain, low back pain, headache or idiopathic pain), were known to be unresponsive to opioid drugs, the issue of long term therapy need not be addressed. Unfortunately, simple conclusions of this type are not tenable. Although factors associated with a greater or lesser degree of opioid responsiveness have been identified, none has sufficient predictive validity to determine clinical practice.

The influence of pain pathophysiology is illustrative (84,89). A neuropathic mechanism may reduce the overall responsiveness to opioid drugs (21,86,90,91), but does not exclude a favourable response in any individual case (66,69,70,84,85,87,92-95). Thus, the existence of findings consistent with a neuropathic mechanism cannot, by itself, justify a decision to withhold opioids on the basis of inefficacy. There is no clinically evaluative predictor of uniform opioid resistance, and consequently, the presumption of inefficacy can never be used as the primary justification for the decision to forego a trial of opioid therapy.

Durability of response: If tolerance to the analgesic effects of opioid drugs in humans occurred as rapidly and uniformly as tolerance to antinociceptive effects in experimental animal models (96,97), long term opioid therapy would have little clinical utility. Examination of this issue requires an understanding of the mechanisms believed to be involved in the development of tolerance and the fundamental differences between the experimental and clinical settings (98-100).

Studies of animal models have demonstrated that tolerance is receptor-selective and pharmacodynamic (that is, not attributable to pharmacokinetic processes). Although 'down-regulation' of receptors following opioid exposure has been postulated to be an important mechanism, it is probably not necessary for the development of tolerance (101). Rather, loss of efficacy over time probably relates to functional decoupling of opioid receptors from second messengers (101,102) and activity in various parallel systems that may involve cholecystokinin (103), excitatory amino acids (104) or other compounds. Thus, tolerance is a descriptive label that denotes a change over time in the relationship between drug concentration and effects, but does not specify the mechanism or mechanisms responsible for this change.

Although it is often assumed that tolerance develops in patients as it does in animal models, the response of humans who receive opioids for pain is far more complex. In the clinical setting, the need to escalate the dose due to increasing pain may relate to increased nociception or varying psychological or cognitive factors, none of which can be directly measured. That is, the 'driving force' for dose escalation may not be mere exposure to the opioid, which would be the case if true analgesic tolerance occurred, but rather may be any of numerous other processes related to worsening pain. Pharmacodynamic tolerance to opioid analgesia that is fundamentally similar to the phenomenon in animal models can be inferred only if an alternative cause for increasing pain cannot be found.

Despite evidence that tolerance to analgesic or nonanalgesic opioid effects does occur in humans following acute (105) or more prolonged (106-108) opioid administration, most clinical data indicate that analgesic tolerance is seldom the 'driving force' for dose escalation. Specifically, many surveys have demonstrated that opioid doses typically stabilize during long term administration (17,24,62,64-66,69,99,109-113). When the need for dose escalation occurs, it is usually readily explained by a worsening physical lesion (24,114) or a changing psychological state

(115). Analgesic tolerance, therefore, seldom compromises the efficacy of therapy, and concern about 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 (1-4,15,62,69,70,72-78,80). Some patients with nonmalignant pain who receive opioids apparently capitalize on improved comfort by increasing function, whereas others who receive the same drugs 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 (116-121). The appropriateness of opioid therapy for all patients with chronic nonmalignant pain cannot be generalized from this selected population.

Furthermore, opioid therapy has never been advocated as a substitute for a comprehensive pain management approach that incorporates psychological and rehabilitative treatments. For patients who are candidates for multidisciplinary pain management programs, opioid therapy could potentially become a complementary treatment for a small, selected population (62). 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 (122-125).

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. The latter issue will be discussed below.

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 (126), 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 (127,128) demonstrated that the occurrence of liver disease relates to concurrent alcohol use or other medical disorders, rather than ingestion of the opioid.

Recent studies in animal models revealed the existence of opioid-related dysimmune effects (129,130), which may involve functions that are antigen-nonspecific (such as natural killer cell activity and the production of cytokines) or antigen-mediated (131-135). Human data relevant to immune alteration are very limited, and there have been no worrisome clinical observations in the cancer population or the methadone-maintenance population. Although the potential for adverse immune effects is a serious concern that awaits evaluation in clinical studies, it is not appropriate to consider any practical changes in the therapeutic use of opioid drugs in the absence of additional data.

Persistent side effects: Many of the diverse clinical effects produced by opioids (136) 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 occurs commonly in the cancer population, but occasional patients experience other long-lasting adverse effects. In the methadone-maintenance population, approximately 10 to 20% of patients complain of persistent constipation, insomnia and decreased sexual function; a somewhat higher percentage report persistent sweating (127,128).

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

Cognitive impairment has been observed in surveys of patients referred to multidisciplinary pain management programs (75,78), opioid addicts and methadone-maintenance populations (137-139). Subtle changes in reaction time have also been demonstrated in cancer patients receiving long term systemic or spinal opioid therapy (140,141).

Although these data raise concerns, none of the studies controlled for concurrent use of centrally acting drugs, other medical disorders or history of head trauma, and, consequently, their extrapolation to the larger population with chronic pain may not be valid. Furthermore, some studies of methadone-maintained patients have not observed cognitive impairment (142,143), and a small study that compared a group of chronic pain patients treated with opioids alone with a group treated with benzodiazepine drugs noted significant cognitive effects only in the latter group (144). Another study in cancer patients suggested that cognitive impairment occurs immediately after dose escalation, but wanes over a period of weeks (145).

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 similar activities unless overt impairment is observed. Clinical experience in the methadone-maintenance population has been similar (146), and studies of driving records have not demonstrated any differences in the rates of infractions or accidents between methadone-maintained addicts and other drivers (147,148). In the absence of definitive studies, clinicians who administer opioids to patients with non-

TABLE 2
Representative aberrant drug-related behaviours

Probably more predictive of addiction
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 of the drug
Probably less predictive of addiction
Aggressive complaining about the need for more 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

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malignant pain must carefully assess the potential for subtle cognitive impairment over time; occasionally, this may require formal neuropsychological testing.

Risk of opioid 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.

Physical dependence: Physical dependence is a physiological phenomenon solely defined by the development of an abstinence syndrome following abrupt discontinuation of therapy, substantial dose reduction or administration of an antagonist drug (136,149-151). Patients are presumed to be physically dependent after repeated doses of an opioid have been administered for more than a few days. Although some definitions of addiction refer to physical dependence (152), the potential for abstinence is neither necessary nor sufficient for the diagnosis of addiction.

In routine medical settings, clinicians often label patients who are presumed to be at risk of abstinence (ie, physically dependent) using the general term 'dependent' or, far worse, the inaccurate descriptor 'addicted'. Given the stigma that may accompany the use of an incorrect label, clinicians should use the term 'physically dependent' when this fits the intended meaning.

Physical dependence does not preclude the rapid and uncomplicated tapering of opioid therapy (72,111,153) and is often perceived to be clinically unimportant as long as abstinence is avoided. Notwithstanding, it must be acknowledged that the possibility of other adverse effects, such as psychological and physical morbidity related to the syndrome of protracted abstinence (149,150,154) 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 phenomena might contribute to a 'downhill spiral', in which pain is sustained or maladaptive behaviours are perpetuated as a result of opioid use (15,155). Some type of similar process also has been suggested to explain 'rebound' headache, a syndrome of refractory pain ascribed to frequent use of short acting analgesics (156,157). Although there has been no systematic study of this putative phenomenon, the problematic nature of opioid therapy in some patients is unquestionable; 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, to allow monitoring of patient responses independent of the drug.

Addiction: Standard definitions of addiction have been developed from experience with substance abusers and are difficult to apply to patients who are receiving a prescribed therapy for an appropriate medical indication. The definition in a major pharmacology text (158) incorporates "relapse after withdrawal" and the definition promulgated by the World Health Organization (152) includes a reference to physical dependence. Similarly, the definition for psychoactive substance dependence in the *Diagnostic and Statistical Manual-III-R* (159) includes criteria based on both physical dependence and tolerance, and, therefore, may apply to most patients (160). The definition developed by a task force of the American Medical Association (151) 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.

All these definitions emphasize three types of aberrant phenomena: loss of control over drug use; compulsive drug use; and continued use despite harm. These phenomena must be operationalized for patients with chronic pain by reference to specific aberrant drug-related behaviours that may be encountered in clinical practice (Table 2). A priori, these behaviours 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) (161).

Although the diagnosis of an addiction disorder may be relatively straightforward in the patient who engages in highly aber-

rant behaviours, the more common situation, in which the patient occasionally demonstrates a less egregious behaviour, is far more challenging to assess. The complexity of this assessment is reflected in the terms 'therapeutic dependence' and 'pseudoaddiction', which have been developed to refer to phenomena observed during the management of cancer pain. Therapeutic dependence refers generally to the responses that may evolve in a patient who is administered a drug that provides a needed therapeutic outcome (162). The diabetic without access to insulin or the patient with angina who lacks a nitrate may express intense anxiety and manifest drug-seeking behaviour, both of which are considered appropriate within ill-defined limits. The term 'pseudoaddiction' refers more specifically to the drug-seeking behaviours that may be observed in the setting of uncontrolled pain (163).

Given this complexity, the diagnosis of addiction can only be entertained following an astute assessment of specific drug-related behaviours. This assessment must first ascertain if the observed behaviours cross a threshold and can be fairly labelled as aberrant; in some cases (eg, the patient who consumes less drug when pain spontaneously remits and consumes more than prescribed when pain flares) this may involve consideration of the prior instructions given to the patient.

If aberrant drug-related behaviour has occurred, the clinician must then explore its nature and implications. A recent lapse 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 an addiction disorder, whereas behaviours that have occurred repeatedly and suggest a more profound loss of control over drug use should be appropriately labelled as such. If the meaning of the behaviour is not clear, some time may be required to assess the patient correctly and to observe the reaction to additional requirements, such as frequent visits or periodic drug screens.

Risk of addiction: If a true addiction syndrome were a common occurrence among patients who are administered opioid drugs 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 can be classified as 'pseudoaddiction'. Unfortunately, published surveys have failed to report the prevalence of the various aberrant drug-related behaviours, 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 behaviours is needed.

Early surveys of addicts 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 (164). Combined with reports of high recidivism rates among detoxified addicts (165,166) and theoretical writings that linked addiction to the pharmacological properties of tolerance and physical dependence (167), these data supported the view that mere exposure to an opioid drug could induce and sustain addiction in previously normal patients.

Surveys of addicts, however, do not provide data that illuminate the prevalence of drug-related behaviours in the larger nonaddict population. Although surveys of pain patients are more relevant, the potential for selection bias discussed previously must again be addressed. The relatively high rate of aberrant drug use observed among patients referred to multidisciplinary pain management programs (72,73,77,79,80,168), for example, is difficult to interpret due to variability in the definitions applied to drug-related outcomes in these settings (169) and the highly selected nature of the populations.

In the absence of well-conducted longitudinal surveys of otherwise unselected populations with nonmalignant pain treated with opioid drugs, other data may be useful to clarify addiction liability. 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 (170). A nationwide survey of burn units found no cases of addiction in the information obtained about 10,000 patients treated for burn pain (171), and a survey of patients treated at a large headache centre could identify only three problem cases among 2369 patients who had access to opioid analgesics (172). Recent studies of patients who were allowed to self-administer an opioid for a period of weeks to treat mucositis pain following bone marrow transplant observed patterns of drug-taking behaviour that were inconsistent with the diagnosis of addiction (173).

These data, combined with the extensive and highly favourable experience garnered in the cancer population, are reassuring, particularly when compared with United States population prevalence rates for alcoholism (3% to 16%) and other forms of substance abuse (5% to 6%) (174). Although the studies are limited, they suggest that the considerable risk of iatrogenic addiction noted in surveys of addicts or patients referred to multidisciplinary pain programs overstate the likelihood of this complication among the larger population with chronic pain.

Other observations provide further supporting evidence of the latter conclusion. For example, the ease with which opioids can be discontinued during pain therapy (72) suggests that the mere exposure to an opioid does not inevitably induce severe drug craving, even among those with problematic drug-taking behaviour. Similarly, the existence of 'chippers', drug abusers who self-administer opioids on an intermittent basis (175), indicates that drug exposure alone does not lead inevitably to spiralling use.

Additional evidence may be gleaned from the many studies that suggest the existence of fundamental differences between addicts and patients. Although causality cannot be imputed from these studies, they support the conclusion that individuals who become addicts do so as a consequence of factors that extend beyond mere exposure to the drug. For example, the importance of situational factors in the genesis of addiction has been suggested by the observation that Vietnam war veterans who became addicted while serving overseas had far lower recidivism following detoxification and return to the United States than other addict populations (176). Similarly, the potential importance of personality variables is suggested by the high prevalence of psychopathy among addict populations (177,178).

Perhaps the most striking difference between addicts and patients is the variability in affective responses to an opioid. The

TABLE 3
Proposed guidelines for the management of opioid therapy for nonmalignant pain

1. Should be considered only after all other reasonable attempts at analgesia have failed
2. A history of substance abuse, severe character pathology and chaotic home environment should be viewed as relative contraindications
3. A single practitioner should take primary responsibility for treatment
4. Patients should give informed consent before the start of 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 possible with acute discontinuation) and understanding by female patients that children born when the mother is on opioid maintenance therapy will likely be physically dependent at birth
5. After drug selection, doses should be given on an around-the-clock basis; several weeks should be agreed upon 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 should raise questions about the potential treatability of the pain syndrome with opioids
7. Emphasis should be given to attempts to capitalize 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: prescription of an additional four to six 'rescue doses' to be taken as needed during the month; 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 behaviours 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)
    d) existence of aberrant drug-related behaviours
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 behaviours repeatedly during the course of therapy

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opioid-induced euphoria experienced by addicts occurs rarely among patients who receive an opioid for pain (179-181). Indeed, the usual experience of patients is dysphoria. This observation may suggest the existence of basic physiological differences in the response to opioids. In support of this conclusion is evidence from a recent twin study, which indicates that opioid addiction may have a genetic predisposition (182), a finding already confirmed for at least a subtype of alcoholism (183).

Together, these data suggest that the development of addiction cannot be ascribed solely to reinforcing properties inherent in the drug. Rather, addiction requires predisposing psychological, social and physiological factors that are presumably very uncommon in the large and heterogeneous population of patients with chronic pain. Consequently, the risk of addiction during opioid administration for chronic nonmalignant pain is probably very low.

Although credible, this conclusion is clearly based on limited data. To be prudent, the clinician must act on the assumption that addiction could be a possible outcome during the treatment of any patient. Clinical experience suggests that treatment should be undertaken very cautiously, and perhaps not at all in patients with a prior history of drug abuse, severe character pathology and chaotic family relationships, all of which are possible risk factors for problematic drug-taking. The experience of multidisciplinary pain management programs further encourages caution in the treatment of patients with idiopathic pain, high levels of psychological distress and disability, previous overuse of medical resources, or overuse of prescription or nonprescription drugs. Older patients may be at relatively less risk.

CONCLUSIONS

Although controlled trials are lacking, there is now substantial empirical evidence that a subpopulation of patients with chronic nonmalignant pain can attain a favourable outcome for prolonged periods using opioid drugs. On the basis of clinical experience and the foregoing analysis, guidelines for the use of opioid therapy in nonmalignant pain may be posited (Table 3). These guidelines, which attempt to balance the potential for salutary effects with 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 guidelines can be initiated in the form of a therapeutic clinical trial. During such a trial, close monitoring of the relevant end-points (specifically pain relief, side effects, physical and psychosocial functioning, and the development of aberrant drug-related behaviours) can determine whether therapy should be continued. To implement a trial, the patient must be fully informed and consent to the therapy.

Opioid therapy requires a working knowledge of the pharmacological techniques described in cancer pain literature (13, 32,35). Although some clinicians support specific approaches for nonmalignant pain, such as the use of long-acting drugs and no access to supplemental doses, it should be recognized that all such recommendations are based solely on anecdote.

Escalation of the opioid dose until either 'adequate' analgesia occurs or intolerable and unmanageable side effects supervene is the standard for cancer pain management (84), and presumably optimizes analgesic outcomes during the treatment of patients with nonmalignant pain as well. Dose escalation according to this principle may pose a problem, however, by fostering an intense focus on the therapy rather than rehabilitation, or by increasing 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 escalation is uncommon among patients with nonmalignant pain who have a favourable 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 from specialists in pain management at such times.

Long term opioid therapy must be accompanied by ongoing assessment of aberrant drug-related behaviours. This assessment must determine the impact of pain and psychological factors on drug-related behaviours 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 is not appropriate and the decision is made to continue therapy, a highly structured response to the aberrant behaviours is 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 similar interventions. Consultation with a specialist in addiction medicine may again be helpful.

At the present time, the available data do not permit doctrinaire pronouncements about the role of opioid therapy for nonmalignant pain. It is the responsibility of both clinicians and those in the regulatory community to eliminate misconceptions about tolerance, physical dependence, side effects and addiction, and thereby judge the appropriateness of the approach based on the medical exigencies of the individual case. Controlled clinical trials of long term opioid therapy are needed, but the lack of these trials should not exclude the empirical use of this approach when medical judgement supports it and treatment is undertaken with appropriate monitoring. Given the complexities of this therapy, documentation in the medical record of pain, side effects, functional status and drug-related behaviours must be ongoing and explicit.

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