Regional Anesthesia and Pain

Trends in opioid use for chronic neuropathic pain: a survey of patients pursuing enrollment in clinical trials

[Évolution de l'usage des opioïdes contre la douleur neuropathique chronique : une enquête auprès de patients voulant participer à des essais cliniques]

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Purpose: Clinical trials suggest that opioids relieve neuropathic pain and decrease pain-related disability. We conducted a pilot study of current prescribing trends and patients' attitudes towards opioids for neuropathic pain.

Methods: A patient questionnaire was completed by individuals pursuing enrollment in neuropathic pain clinical trials at our facility.

Results: Of 154 patients with diabetic neuropathy (55.2%), postherpetic neuralgia (29.9%), idiopathic peripheral neuropathy (9.7%) and other neuropathies (5.2%), 73.4% complained of inadequate pain control, the mean pain duration was 4.7 (SD = 4.4) yr and the mean pain intensity (0–10) was 7.7 (SD = 2.3). In this group, 40.9% had never tried opioids and 24.7% had never tried any opioids, tricyclic antidepressants or anticonvulsants. Only 9.7% were receiving long-acting opioids or "around the clock" dosing whereas 25.3% were receiving opioids on an "as needed" basis. Opioids combined with tricyclic antidepressants and/or anticonvulsants were used in 11.0%. Fear of addiction and adverse effects were expressed by 31.8% and 46.8% respectively.

Conclusion: These data suggest that barriers to opioid therapy for neuropathic pain include patients', and possibly physicians', fears of addiction and adverse effects, which are exaggerated in light of current evidence. The merits of continuous treatment with sustained-release opioids, "as needed" dosing with short-acting preparations, or combining opioids with other agents are discussed. Continued research and communication between health professionals, law enforcement officials and legislators is vital in order to facilitate appropriate opioid use which has a minimal negative impact on the public yet optimally benefits individuals who suffer from disabling neuropathic pain.

Objectif : *Les essais cliniques montrent que les opioïdes soulagent les douleurs neuropathiques et diminuent l'incapacité reliée à la douleur. Notre étude pilote porte sur les modes courants de prescriptions et les attitudes des patients face aux opioïdes contre la douleur neuropathique.*

Méthode *Un questionnaire adressé aux patients a été rempli par des malades intéressés à participer à des essais cliniques sur la douleur neuropathique à notre établissement.*

Résultats : *Des 154 patients présentant une neuropathie diabétique (55,2 %), une névralgie postherpétique (29,9 %), une neuropathie périphérique idiopathique (9,7 %) ou d'autres neuropathies (5,2 %), 73,4 % se plaignaient d'un soulagement incomplet de la douleur. La durée moyenne des douleurs chroniques était 4,7 ans (écart type = 4,4) et l'intensité moyenne, de 7,7 (écart type = 2,3) sur une échelle de 0–10. Parmi eux, 40,9 % n'avaient jamais pris d'opioïdes et 24,7 % n'avaient jamais pris aucune forme d'opioïdes, d'antidépresseurs ou d'anticonvulsivants tricycliques. Seulement 9,7 % avaient des opioïdes à action prolongée ou des dosages continus et 25,3 % prenaient des opioïdes au besoin. Une combinaison d'opioïdes et d'antidépresseurs ou d'anticonvulsivants tricycliques était utilisée par 11,0 % des malades. La crainte d'une accoutumance et des effets indésirables a été exprimée par 31,8 % et 46,8 % respectivement.*

Conclusion : *Les obstacles au traitement de la douleur neuropathique par des opioïdes comprennent des craintes des patients, et probablement des médecins, d'une accoutumance ou des effets indésirables, ce qui semble exagéré à la lumière des données actuelles. Les mérites du traitement continu avec des opioïdes à libération lente, des dosages "au besoin" avec des préparations à action brève ou des combinaisons d'opioïdes et d'autres médicaments*

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This work was supported by CIHR Grant #MCT-38149 and Queen's University Grant #383-861.

Accepted for publication May 27, 2002.

Revision accepted August 29, 2002.

sont discutés. La recherche et les échanges continus entre les professionnels de la santé, les responsables de l'application de la loi et les législateurs sont d'une importance vitale pour faciliter l'usage approprié des opioïdes avec le minimum d'impact négatif sur le public, mais des avantages optimaux pour les malades qui souffrent de douleurs neuropathiques invalidantes.

CHRONIC pain exerts a profound negative impact on quality of life and healthcare expenditures and has been estimated to cost North American society in excess of $79 billion/year.[1] Recent epidemiological studies suggest that 25 to 40% of the population in industrialized countries suffer from chronic pain and that up to two-thirds of these people are either partially or totally disabled for periods of weeks to months.[2] Analgesic drug treatment remains a major component of multidisciplinary and multimodal chronic pain management regimens and contributes to pain reduction as well as functional improvement.[3]

Opioid narcotics such as morphine are currently the mainstay of treatment for moderate to severe postsurgical and cancer-related pain.[4] More recently, evidence has been mounting to suggest that therapeutic benefits of opioids outweigh their risks in a subgroup of patients with chronic non-malignant pain.[5,6] In the primary care setting, effective management of pain due to nerve injury or disease (i.e., neuropathic pain) is a continuing challenge given the side effect profiles and limited efficacy of available treatments such as tricyclic antidepressants and anticonvulsants.[7–9] Mu-receptor opioid agonists have been shown to reduce pain in a number of preclinical neuropathic pain models.[10–12] In humans, several randomized controlled trials have demonstrated that opioids reduce pain intensity,[13–15] and furthermore, decrease neuropathic pain-related disability.[16] Despite evidence of safety and efficacy in acute and cancer pain, studies have shown that physician and patient concerns about addiction and other adverse effects continue to be, often unwarranted, barriers to pain management in these settings.[17–19] Such studies identify and challenge these barriers and have resulted in important measures aimed at promoting the appropriate and beneficial use of opioids.[20] Preliminary data suggest similar barriers to opioid use for chronic non- malignant pain.[21] However, neuropathic pain, in particular, is associated with unique pathophysiological and demographic features that distinguish it from chronic pain in general and data regarding barriers to opioid therapy for neuropathic pain are lacking. Therefore, we have initiated a research endeavour aimed at identifying barriers to appropriate opioid use in neuropathic pain. Using a patient questionnaire, this pilot study examines patient attitudes and opioid prescribing trends in neuropathic pain patients pursuing enrollment in analgesic clinical trials.

Methods

Ethics approval was obtained from the Queen's University Research Ethics Board. Individual questionnaires were completed by neuropathic pain patients either referred by physicians from Queen's University's Southeastern Ontario Health Sciences Centre (SEOHC) catchment area or self-referred in response to neuropathic pain clinical trial advertisements from our facility. The study period extended from March 1, 2001 to November 30, 2001. All questionnaires were completed over the telephone by our research coordinator (J.B.) who transcribed verbal responses onto individual forms. Patients were asked: 1) demographic information (name, gender and age); 2) pain related information (diagnosis, duration, worst pain intensity [0–10 scale] in the past month and whether referred to a neurologist or pain specialist); 3) current and previously tried treatments (including drug names, doses and dosing schedules); and 4) patient attitudes regarding pain treatments (fear of addiction, fear of adverse effects and whether current analgesic regimen is controlling pain). Individual questionnaires were excluded from the results if the patient was suffering from a non-neuropathic pain syndrome or if the clinical diagnosis was uncertain or unknown. In cases where the patient was unsure of the answer to a particular question (e.g., diagnosis, previous drug dosage etc.), consent was obtained from that individual to consult with their primary physician and/or pain specialist and review available medical records. Descriptive statistics were used to represent these data.

Results

Demographics and pain features

In total, 154 patients (85 F:69 M, mean age 64.6 [SD = 12.1]) completed the questionnaire. Of these, 123 were self-referred, and 31 were physician referred. Diagnoses included diabetic neuropathy (55.2%), postherpetic neuralgia (29.9%), idiopathic peripheral neuropathy (9.7%), and other neuropathic pain (5.2%; lumbar radiculopathy [3], trigeminal neuropathy [2], post-chemotherapy neuropathy [1], neuropathic cancer pain [1], and occipital neuralgia [1]). Overall mean pain duration was 4.7 [SD = 4.4] yr and overall mean pain intensity (0–10 scale) was 7.7 [SD = 2.3].

TABLE I Demographics and pain features of studied patients

Gender distribution (total n = 154)	85 (55.2%) female	69 (44.8%) male
Referral for clinical trial enrollment	123 (79.9%) self-referred	31 (20.1%) physician referred
Diagnostic categories	Painful diabetic neuropathy	85 (55.2%)
	Postherpetic neuralgia	46 (29.9%)
	Idiopathic peripheral neuropathy	15 (9.7%)
	Other	8 (5.2%)
Mean age	64.6 (SD = 12.1) yr	
Mean pain duration	4.7 (SD = 4.4) yr	
Mean pain intensity (0–10 scale)	7.7 (SD = 2.3)	

Presented patient numbers and percentages are tabulated from the entire study population of 154 patients. SD = standard deviation.

TABLE II Opioid treatment features and patient attitudes

Patients in whom drugs were never tried	63 (40.9%) never tried opioids	38 (24.7%) never tried any opioid, TCA or AC
Strength of currently used opioid	31 (20.1%) weak opioid (e.g., codeine)	23 (14.9%) strong opioid (e.g., morphine)
Concomitant analgesics with current opioid	37 (24.1%) receiving opioid as single agent	17 (11.0%) receiving opioid combined with TCA and/or AC
Dosing schedule of current opioid	39 (25.3%) receiving opioid on "as needed" basis	15 (9.7%) receiving long-acting or "around the clock" opioids
Patient concerns regarding analgesics	72 (46.8%) fear side effects	49 (31.8%) fear drug addition

Presented patient numbers and percentages are tabulated from the entire study population of 154 patients. TCA = tricyclic antidepressant; AC = anticonvulsant.

Pain treatment features and patient attitudes

Of all patients, 71.4% had never seen a pain specialist, 40.9% had never tried (either in the past or at the time of questioning) any opioid, and 24.7% had never tried any antineuropathic analgesics (e.g., opioids, tricyclic antidepressants, or anticonvulsants). At the time of questioning, 35.1% were taking opioids (codeine, with or without acetaminophen - 20.1%, stronger opioids including morphine, oxycodone, hydromorphone and transdermal fentanyl - 14.9%). Regarding other treatments at the time of questioning, 19.5% were taking anticonvulsants, 17.5% were taking tricyclic antidepressants, and 9.1% were using topical, or non-pharmacological therapies (including capsaicin and other topical creams/ointments, acupuncture, reflexology, and magnet therapy). Of all patients, 11.0% were receiving opioids in combination with a tricyclic antidepressant and/or anticonvulsant and 24.1% were receiving opioids as single agent therapy (not considering the acetaminophen contained in several preparations). Only 9.7% were receiving long-acting opioid preparations or "around the clock" dosing whereas 25.3% were receiving opioids (17.5% with low-dose codeine) on an "as needed" basis. At the time of questioning, 73.4% complained of inadequate pain control. Fear of addiction and adverse effects were expressed by 31.8% and 46.8% respectively.

Discussion

The use of opioids for chronic non-malignant pain is associated with several complex issues for both physicians and patients only some of which include: 1) the occurrence of common yet reversible side effects such as sedation and constipation; 2) the social, ethical and legal implications of prescribing and using a regulated narcotic; 3) the potential for illicit drug diversion; and 4) the risk of rare but potentially longstanding psychological opioid addiction.[5] For these reasons, prescribing long-term opioids must be done in a careful and controlled manner. While the management of chronic pain might seem less problematic without opioids, the therapeutic potential of this class of drugs is too great to pass up. Furthermore, it has been suggested that patients with pain due to a discrete nerve injury or clear-cut neuropathy are more likely to benefit from opioids than patients in whom pain and disability far exceed the presumed etiology or pathophysiology of their condition.[22] Therefore, iden-

tifying barriers to appropriate opioid use for neuropathic pain in particular is critical for the benefits of these drugs to be realized.

This pilot study indicates that, in patients with poorly controlled neuropathic pain who pursue enrollment in analgesic clinical trials, 35.1% are receiving opioids. However, a more detailed examination of these treatment patterns shows that 25.3% are receiving opioids only on an "as needed" basis, 24.1% are receiving opioids as single agent therapy and 20.1% are receiving low-dose weak opioids (e.g., codeine). Furthermore, 40.9% had never tried any opioids and 24.7% had never tried any antineuropathic analgesics (e.g., tricyclic antidepressants, opioids or anticonvulsants). Non-pharmacological and alternative therapies are not widely used in this group.

The observations that 24.7% had never tried any antineuropathic analgesics and 71.4% had never seen a pain specialist suggest some treatment barriers which are not directly related to the issue of opioid therapy but warrant discussion nonetheless. In particular, patients' and physicians' denial of pain have been previously identified as possible causes for pain to go untreated.[18,23] With the example of diabetic neuropathic pain, symptoms tend to develop more slowly than peripheral nerve deterioration[24] and this insidious progression may make patients more likely to accept pain as part of their chronic illness. Also, this study group represents older patients (especially those with postherpetic neuralgia) who have been observed to complain less about existing pain.[18] Primary physicians who first encounter a patient's chronic pain syndrome are often preoccupied with the management of other more threatening medical problems, especially in diabetics or elderly patients with multisystem disease. Furthermore, access for referral to subspecialty pain clinics may, in some settings, be limited.[25] Nevertheless, widespread education of both physicians and patients is vital in order to reinforce the validity of chronic non-malignant pain and emphasize the potential for pain management to improve quality of life.

More specific to the issue of opioid use, these data indicate that 46.8% of patients expressed fears of adverse drug effects and 31.8% were afraid of drug addiction. Opioids do indeed cause adverse effects that commonly include sedation, cognitive dysfunction, nausea/vomiting and constipation.[4] However, patient concerns about adverse effects are sometimes exaggerated[26] and uninformed thus causing unnecessary avoidance of useful treatments. Therefore, it must be emphasized to patients that there is a great deal of individual variation in the occurrence of such side effects and gradual dose titration may allow for the determination of an optimal opioid dose. For example, a recent study of the opioid analgesic, tramadol, showed that slowing the rate of dose titration reduced the rate of adverse effect-related study withdrawal.[27] Regarding fear of addiction, the historical association of opioids with centuries of illicit misuse[28] may cause patients, in the most extreme sense, to relate long-term opioid therapy with the stigma of becoming a heroin addict. However, it is critical to note that opioid treatment of pain rarely results in addiction. In particular, one article reported only four documented cases of addiction following treatment of 11,882 patients with opioids[29] while another observed no addiction in over 10,000 opioid-treated patients.[30] It should be noted though that these low rates might reflect the risk of opioid addiction in patients with no previous history of addiction or substance abuse. Given data to suggest that 3–16% of North Americans have an addictive disorder, it is equally important to point out that such individuals may be at higher risk of cross-addiction thus possibly precluding opioid therapy in this group.[31] Once again, physicians must engage in evidence-based patient education and screening in order to put concerns about opioid addiction into a realistic context.

Results of this study reveal three patterns of opioid treatment: i) "as needed" or "prn" treatment; ii) continuous treatment with long-acting or "around the clock" opioids; and iii) combining opioids with other antineuropathic analgesics such as tricyclic antidepressants and/or anticonvulsants. Although prospective longitudinal studies are lacking in this area, speculation on the effect of each of these approaches on the possible consequences of long-term opioid therapy may suggest the merits and shortcomings of each. Some consequences of long-term opioid therapy to consider include: a) physical dependence (i.e. withdrawal syndrome/symptoms upon discontinuation); b) intermittent "on-off" withdrawal phenomena; c) opioid tolerance (i.e., diminishing analgesia for a given opioid dose, or increasing opioid requirement); d) pain disinhibition or facilitation (e.g., reduction in pain threshold); e) drug reinforcement/addiction; and f) opioid diversion (i.e., illicit selling of prescription drugs for street use).[31] These consequences all appear to be possible with "as needed" opioid use and it has been further hypothesized that intermittent administration of short-acting opioids maximizes the risk of drug reinforcement/addiction given the more rapid onset/offset of euphoria which may lead to drug craving. For this reason, it has been suggested that continuous treatment with long-acting opioids is likely to minimize the risk of intermittent "on-off" withdrawal phenomena as well as

reinforcement/addiction. However, opioid tolerance and pain disinhibition/facilitation remain possible and physical dependence is quite likely.[31] Opioid diversion has been previously thought to be less likely with long-acting opioids due to reduced street value compared to short-acting opioids. However, recent reports suggest that abuse and diversion of long-acting drugs such as controlled-release oxycodone (Oxycontin®) is an important problem.[32] Finally, combining opioids with other antineuropathic analgesics that act through different mechanisms may result in a synergistic interaction that enhances pain relief at lower doses thus resulting in fewer side effects. For example, if the analgesic effects of opioids and tricyclic antidepressants are more additive than their sedative effects when co-administered, then therapy with this combination is superior to single agent therapy. On the other hand, if the sedative effects of opioids and tricyclic antidepressants add up to greater degree than do the analgesic effects, then this would not be a useful combination. Thus, future research is needed to determine whether a given combination is superior to single agent therapy with either of its components.[33] Previously proposed algorithmic approaches to drug therapy of neuropathic pain have included initial trials of tricyclic antidepressants, followed, as necessary, by anticonvulsant and/or antiarrhythmic (e.g., mexiletine) drugs and only after failing these treatments, trial of a long-acting opioid.[34] However, as more is learned about the safety and tolerability of long-term opioid therapy for chronic neuropathic pain, the place of opioids in such algorithms may change.

In summary, these data suggest that barriers to long-term opioid therapy for chronic neuropathic pain include patients', and possibly physicians', fears of opioid addiction and adverse effects, which are exaggerated in light of current evidence. Accumulating data from clinical trials support both safety and efficacy of opioids in neuropathic pain. It is therefore critical to implement clinical strategies for the optimal use of opioids in this setting. This requires future research into the long-term consequences of different models of opioid administration such as continuous treatment with long-acting opioids, "as needed" dosing, or combining opioids with other agents. Finally, continued multidisciplinary research and communication between health professionals, law enforcement officials and legislators is vital in order to facilitate appropriate opioid use which has a minimal negative impact on the public yet optimally benefits individual patients who suffer from disabling neuropathic pain.

Acknowledgements

The authors wish to thank Mr. Allan Bell for his valuable assistance with data management and Dr. Dwight Moulin for thoughtful comments made on previous versions of this manuscript.

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