SPECIAL ARTICLE

Use of opioid analgesics for the treatment of chronic noncancer pain –
A consensus statement and guidelines from the Canadian Pain Society, 2002

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1. Pain of all types is undertreated in our society. The pediatric and geriatric populations are especially at risk for undertreatment. Health professionals’ fears regarding iatrogenic addiction, diversion of prescribed opioids to the illicit market and regulatory scrutiny create a significant barrier to the optimum prescribing of opioids for pain.

2. Chronic noncancer pain (CNCP) is generally defined as pain that has been present for at least six months; pain lasting longer than the expected time to tissue healing or resolution of the underlying disease process; or pain due to a condition where there is ongoing nociception or neuropathic pain. CNCP is different from acute pain in both its presentation and pathophysiology. Progress in basic science research is leading to the gradual discovery of the biochemical and structural mechanisms of peripheral and central sensitization that maintain chronic pain. It is therefore possible that treatments that are more specific will become available in the future.

3. Patients with CNCP require a thorough assessment before physicians can decide on treatment. A patient with chronic pain may have physical, psychological, social and/or behavioural contributors to suffering that may require specific attention in a comprehensive treatment plan.

4. Many treatment options exist for CNCP, including physical, psychological, pharmacological and surgical options. In the absence of good evidence for a specific, curative treatment for a given pain problem, a trial of long term opioid therapy is a legitimate medical practice when a reasonable trial of other treatment modalities fails to improve comfort or function for the patient. There are very few types of pain that would absolutely preclude a trial of opioid therapy.

5. Tolerance and/or physical dependence on regular opioid use in a patient in pain are not, by themselves, evidence of an addictive disorder. Addiction is a biopsychosocial disorder characterized by the compulsive use of a substance and a preoccupation with obtaining it, despite evidence that its continued use results in physical, emotional, social or economic harm. A patient with a past history of, or risk factors for, addiction should not necessarily be precluded from a careful trial of opioid therapy, although in such a case consultant advice might be sought.

6. Opioid analgesics are generally safe medications when prescribed with appropriate monitoring. The literature has not reported any evidence of organ damage from the long term therapeutic use of opioids. With appropriate titration and stable dosing, tolerance usually develops to most of the side effects of opioid therapy, including cognitive impairment. Nausea and constipation are the two most common early side effects and can be managed prophylactically.

7. A key principle in the treatment of all types of pain with opioids is dosing to effect or to the point of persistent and unacceptable side effects. In patients with round-the-clock pain, opioids should be dosed in a pharmacologically appropriate, time-contingent dosing regimen, rather than an as required (PRN) dosing regimen. The use of an opioid analgesic with a long duration of action can improve patient compliance, thus facilitating better tolerance to side effects such as cognitive impairment and may reduce the fluctuation in pain based on PRN dosing regimens. In the opioid-naive patient, failure to realize at least partial analgesia with incremental dose titration may indicate that the pain syndrome is unresponsive to opioid therapy; however, in
some patients with more severe pain problems, significant analgesia may only occur after a threshold dose of opioid has been reached.

8. The goal of long term opioid therapy is improved quality of life for the patient in pain. This improvement should include, as a minimum, a significant decrease in pain severity and/or a favourable change in the pain characteristics, and, ideally, an improvement in physical, psychological, social and occupational functioning. The patient on long term opioids needs to be reassessed periodically to ensure an ongoing benefit of treatment. Physicians should carefully reassess a patient who demonstrates repeated episodes of aberrant drug-related behaviour or whose function declines because of opioid therapy. In some cases, it may be appropriate to taper and discontinue opioid therapy to reassess the patient’s condition when not taking opioids.

9. The use of long term opioid therapy in CNCP does not preclude the concurrent use of other treatments such as nonopioid analgesics, or physical or psychobehavioural modalities. However, the use of any type of sedative medication that may also cause additive, long term cognitive impairment should be avoided, if possible.

10. Adequate documentation is essential to demonstrate the evaluation process, including consultations and relevant investigations, the rationale for long term opioid therapy in the context of the overall management plan and the periodic review of patient status. In addition, documentation is required to demonstrate compliance with federal controlled substance legislation.

DEFINITION OF CHRONIC NONCANCER PAIN
Chronic noncancer pain (CNCP) is defined as pain that has been present for at least six months or that has persisted longer than the expected time for tissue healing or resolution of the underlying disease process. CNCP can occur because of conditions involving ongoing nociception, such as the inflammation of various arthritic conditions, or due to damage or dysfunction of the pain pathways, such as in neuropathic pain. Other previously used terms for this type of pain include chronic nonmalignant pain, chronic pain of nonmalignant origin and chronic benign pain. Autonomic features suggestive of acute pain, such as anxiety, sweating, tachycardia and hypertension, often do not accompany chronic pain. CNCP is believed to serve no inherent biological function. Even with the clinical diagnostic ‘tools’ available today, we are still limited in our ability to localize precisely and define exactly the mechanism of many types of chronic pain. Pain research is discovering the neural mechanisms that both augment and maintain pain signal transmission in chronic pain syndromes. Thus, chronic pain is not simply a symptom of an underlying disease process that can be treated with the expectation that the pain will disappear.

THE NEED FOR A CANADIAN PAIN SOCIETY CONSENSUS STATEMENT
1. In the past several years, there has been growing recognition on the part of health care providers, government regulators and the public that the undertreatment of pain is a major societal problem (1). Despite numerous published guidelines, current literature continues to document the issue that acute pain, such as postoperative pain and pain in the emergency department, is often poorly managed (2). Although there has been significant progress, cancer pain continues to be undertreated (3). Patients with acquired immunodeficiency syndrome also suffer from poorly recognized and undertreated pain. One significant barrier to better pain management is the reluctance of physicians to utilize opioid therapy to its full potential.

2. A bioethicist writes, “To leave a person in avoidable pain and suffering should be regarded as a serious breach of fundamental human rights” (4).

3. In 1997, the Canadian Pain Society published a position statement on pain relief that included the following statements: Almost all acute and cancer pain can be relieved, and many patients with chronic nonmalignant pain can be helped. Patients have the right to the best pain relief possible.... [H]ealth professionals need to understand pain management strategies, including non-pharmacological techniques and the appropriate use of opioids (5).

4. Previously, opinion regarding the appropriate use of opioid analgesics in the management of CNCP was not as clear as in the case of acute pain and cancer pain. The College of Physicians and Surgeons of Alberta (6), Nova Scotia (7) and Quebec (8), and the Chronic Pain Section of the Ontario Medical Association (9) have each published guidelines supporting the appropriate use of opioids for the treatment of CNCP. The American Pain Society (APS) and the American Academy of Pain Medicine (AAPM) likewise published a joint national consensus statement in 1997 (10). The Federation of State Medical Boards of the United States also endorsed the use of opioids for chronic pain (11). A committee of the College of Physicians and Surgeons of Ontario (CPSO) reviewed the evidence up until November 1998 and published its evidence-based recommendations in December 2000 (12). Based on the evidence, this report also supports the use of opioid therapy for CNCP. There have been further randomized controlled trials published since the analysis of the CPSO recommendations (see “Evidence for Opioid Therapy” below). However, in spite of growing evidence and supportive guidelines, many physicians still remain reluctant to utilize opioids to their full potential. Concerns regarding iatrogenic addiction, diversion of prescribed opioids to the illicit market and the fear of regulatory sanctions remain significant barriers to optimum pain management. As a national organization of pain professionals, it is therefore appropriate that the Canadian Pain Society publish and periodically update this Canadian consensus statement on this evolving area of medicine.

5. The present document does not in any way sanction the inappropriate prescribing of opioid analgesics, nor does it endorse opioid therapy as the only treatment modality for chronic pain. It recognizes that the prescribing of long term opioid therapy may still be considered controversial by some pain treatment professionals. It is intended, however, as a means to raise awareness and to educate both Canadian physi-
TREATMENT OPTIONS FOR CNCP
1. Chronic pain can have multiple causes and a myriad of perpetuating factors. Therefore, the optimal management involves a comprehensive assessment leading to an individualized treatment approach that uses a combination of treatment options and takes into account the local availability of pain treatment resources.

2. Many strategies and options exist to treat CNCP. These include, but are not restricted to, active modalities such as stretching, therapeutic exercise, stress management skills, biofeedback and cognitive-behavioural approaches; passive modalities such as massage, manipulation, nerve and trigger point injections and transcutaneous electronic nerve stimulation; pharmacotherapy, including nonopioid analgesics as well as opioids; and palliative surgical procedures, such as implanted dorsal column stimulators, implantable drug delivery pumps and neurodestructive procedures.

3. When a specific, curative treatment exists for a given pain problem, with good evidence for its effectiveness and acceptable risks for the patient, it should always be offered first to the patient. In the absence of a specific curative therapy, it makes sense to try treatment options along an orderly continuum from least invasive, with the lowest risk of adverse effects and the best evidence for effectiveness, to treatments that are more invasive, carry a higher risk of serious adverse effects and have less evidence for effectiveness.

4. Using the above principle, opioid analgesics are usually not recommended as first-line therapy in the treatment of mild to moderate CNCP. However, they are a valid treatment option in patients with moderate to severe pain who have failed to respond to a reasonable trial of other standard treatment modalities. In the treatment continuum approach, a trial of titrated opioid therapy should be considered before a recommendation for destructive, palliative procedures.

5. Pediatric and geriatric patients also suffer from conditions causing chronic nociceptive and neuropathic pain. In both of these patient groups, pain is often under-recognized and undertreated. When dosed according to weight, children and adolescents respond to opioids very similarly to the way adults do. Geriatric patients are often more sensitive to opioid side effects and may have changes in renal function, which can affect opioid pharmacokinetics. With careful titration and monitoring, both the pediatric and geriatric populations can benefit from opioid therapy.

THE EVOLVING EVIDENCE FOR OPIOID THERAPY
1. Until the early 1980s, medical opinion held that opioid analgesics were not indicated for the treatment of CNCP. Surveys originating in multidisciplinary pain programs suggested that the regular use of opioid analgesics would lead to greater psychological stress, impaired cognition, and a high risk of addiction and poor outcomes (13). These studies reported on highly selected patients using short-acting opioids on an as required (PRN) basis and did not consider the cognitive impact of the frequent use of sedatives among their subjects.

2. Subsequent case series and the results of randomized controlled trials have challenged these opinions with evidence that opioids can provide significant relief in noncancer pain with improved function and a low risk of addiction or other serious adverse effects (11). Furthermore, these studies suggest that there are very few types of chronic pain for which a trial of long term opioid therapy would be contraindicated.

3. In 1996, a multispecialty committee of the CPSO performed a systematic review of the literature up until November 1998 on the treatment of chronic nonmalignant pain. Before the publication of their final report in December 2000, the committee received extensive feedback from treatment professionals across Ontario as well as from other jurisdictions. The report’s conclusions regarding the evidence for opioid therapy included the following statements:

These controlled trials from our systematic literature search support the conclusion that sustained-release opioid therapy benefits selected patients with chronic musculoskeletal and neuropathic pain... Significant pain relief can be achieved with a low risk of psychological dependence or addiction in the absence of a history of substance abuse. Cognitive impairment can be minimized or eliminated with an individualized dose titration program (12).

Since the end of 1998, an additional six placebo controlled trials have been published, providing further evidence for the effectiveness of opioid therapy in improving the quality of life of patients with musculoskeletal arthritic and neuropathic pain (14-19). None of these trials has studied large numbers of patients, nor have the patients been studied for longer than six months, but this is no different from the existing situation with studies of opioid use in cancer pain. A reasonable summation of these results would suggest that, on average, the number of patients needed to treat (NNT) to find one that responds to opioid therapy with at least a 50% reduction in pain is approximately three. This is comparable to the NNT for tricyclics and antiepileptic drugs. The range of pain reduction across studies, relative to placebo, varied from 20% to 50%.

4. In 1993, the College of Physicians and Surgeons of Alberta became the first professional licensing body in North America to publish guidelines for opioid use in chronic nonmalignant pain (6). These guidelines were the first in North America to endorse the use of long term opioid analgesics as an acceptable option for treating CNCP. Since that time, the College of Physicians and Surgeons of a number of other Canadian provinces have adopted variations of the ‘Alberta Guidelines’.

5. In the United States, an increasing number of medical jurisdictions have published opioid therapy guidelines of their own. In March 1997, the AAPM and the APS published a joint consensus statement entitled, “The use of opioids for the treatment of chronic pain” (10). This statement accepted the use of opioids for chronic pain as “legitimate medical therapy”, Finally, the Federation of State Medical Boards of the United
and acknowledges their contribution.

6. In a 1997 public policy statement on the rights and responsibilities of physicians prescribing opioid analgesics for the treatment of pain, the American Society of Addiction Medicine (ASAM) made a series of recommendations supporting the use of opioids for chronic pain, providing there is appropriate assessment and monitoring (20). In 2000, the Canadian Society of Addiction Medicine published its own “Policy Statement on the Use of Opioids for the Treatment of Chronic Pain” (21). Both of these statements offer guidance and support for the physician who chooses to prescribe long term opioid therapy.

7. A joint consensus committee of the AAPM, the APS and the ASAM published a consensus statement in 2001, clarifying the definitions of addiction in patients who take opioids for the treatment of CNCP (22).

8. This updated consensus statement from the Canadian Pain Society includes elements from all of the above sources and acknowledges their contribution.

MANY COMMONLY HELD ASSUMPTIONS STILL CREATE BARRIERS TO THE OPTIMUM USE OF OPIOIDS IN CNCP

Addiction
Misinterpreting and labelling the efforts of patients to get relief from their pain as addiction or drug-seeking behaviour can result in stigmatization and unnecessary withholding of opioid analgesics. Clinicians as well as regulators can confuse the desperate search for pain relief with abuse or addiction. Addiction is a biopsychosocial disorder characterized by the compulsive use of a substance and the preoccupation with obtaining it, despite evidence that its continued use results in physical, emotional, social or economic harm. The joint AAPM / APS / ASAM consensus statement (2001) defines addiction in the context of pain treatment with opioids as “a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following ‘4Cs’: impaired Control over drug use, Compulsive use, Consequences or continued use despite harm, and Craving” (22). Previous studies suggested that the development of true iatrogenic addiction is rare when opioids are carefully prescribed for the relief of acute or cancer pain. Older literature from chronic pain clinics reported rates of opioid abuse and addiction as high as 18%, but these studies lacked control groups and used nonstandardized diagnostic criteria (23,24). Careful screening of patients for risk factors may further reduce the possibility of unrecognized iatrogenic opioid addiction (25,26). In addition, some evidence is emerging regarding patients with concurrent addictive disorders and CNCP who might benefit from the judicious use of opioid analgesics when prescribed with appropriate caution and monitoring (27,28).

Tolerance
Tolerance to the adverse effects of opioid analgesics, such as euphoria, somnolence and nausea, appears to develop readily and is a welcome clinical phenomenon. Analgesic tolerance occurs when progressively higher doses of opioids are required to maintain pain control. This was previously thought to be a universal occurrence and therefore limited the efficacy of opioids on a long term basis. Experience with cancer patients has shown that analgesic tolerance is rarely the driving force for dose escalation when opioids are dosed to effect. An increase in the analgesic requirements of cancer pain patients is usually due to the progression of the patient’s disease. Recent anecdotal clinical experience suggests that the development of progressive analgesic tolerance in chronic pain occurs in a small percentage of patients. When true tolerance does occur, it does not necessarily preclude further achievement of adequate analgesia. Clinicians can manage this physiological phenomenon by titrating the dose of opioid, switching to an alternate opioid, or adding adjuvant medications. Tolerance is one of the criteria for addiction that is listed in the “Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition” (DSM-IV) (29). However, according to the joint consensus statement (2001), “tolerance to prescribed drugs does not constitute sufficient evidence of psychoactive substance use disorder or addiction” (22). It should not, therefore, be used to diagnose addiction in the absence of other criteria listed above.

Physical dependence
Physical dependence to opioid analgesics is a common physiological phenomenon characterized by the appearance of a constellation of signs and symptoms associated with a sudden decrease in opioid dose, abrupt termination of regular opioid use, or when an opioid antagonist is administered. Common symptoms include coriza, tremors, sweats, chills, lacrimation, abdominal cramps, arthralgias and myalgias, vomiting and diarrhea. Physical dependence, in the absence of other indicators, is neither predictive nor diagnostic of addiction. Most cancer patients on scheduled opioid therapy become physically dependent. Although abrupt withdrawal of opioid therapy is not life threatening, it is rarely necessary in the skilled and sensitive treatment of patients. If the need to discontinue long term opioid therapy arises, withdrawal symptoms can be minimized by the gradual tapering of opioid therapy and the use of adjunctive medication to decrease the abstinence syndrome.

Opioid dosage
Patients exhibit tremendous interindividual variability with respect to the pharmacokinetics, pharmacodynamics and side effect profile of a given opioid. This variability may involve genetic heterogeneity in opioid receptors, metabolic pathways or other as yet unknown genetic factors. Two clinical generalizations that can be made are that elderly patients usually tolerate lower doses than do younger patients and that neuropathic pain usually requires higher opioid doses than nociceptive pain. The key principle used in all types of pain management with opioids is known as ‘dosing to effect’. Opioid analgesics should be started at a low dose and carefully titrated at a pharmacologically appropriate interval until an adequate level of analgesia is obtained, or until persistent and unmanageable side effects warrant a re-evaluation of therapy. In the opioid-naïve patient, failure to realize at least partial analgesia with incremental dose titration may indicate that the pain syndrome is unresponsive to opioid therapy; however, in
some patients with more severe pain problems, significant analgesia may occur only after a threshold dose of opioid has been reached. The use of long term parenteral opioid therapy for CNCP increases the risks of treatment and should only be considered in exceptional circumstances.

Two examples where parenteral opioids may be useful are: the patient with well-documented trials of several oral opioids, including methadone, who has clearly demonstrated analgesic efficacy but has persistent intolerable and unmanageable side effects; and the patient whose oral route of administration is no longer feasible (eg, esophageal stricture, bowel obstruction, etc).

Support from an experienced pain consultant is strongly recommended before initiating long term parenteral opioids. The higher risks of this type of treatment obligate the prescriber to monitor the patient very carefully.

Side effects
There is no recorded risk in the medical literature of direct permanent organ damage due to the appropriate therapeutic use of opioid therapy. This is in contrast to most other classes of analgesics in use today. Respiratory depression caused by opioid analgesics tends to occur largely in opioid naive patients. It is a short-lived phenomenon that tends to be antagonized by the ongoing presence of some pain. In CNCP, the risk of respiratory depression with oral dosing is extremely low and can be further minimized with careful titration. Because of its long and variable half-life, oral methadone does carry an increased risk for respiratory depression and requires special precautions. Constipation is a common initial side effect of opioid therapy and is usually more difficult to treat than to prevent. It is, therefore, important to manage this side effect prophylactically using a stepped approach involving adequate dietary fibre, stool softeners, osmotic agents and, if necessary, intermittent stimulant laxative use. The daily, long term use of stimulant laxatives should be avoided, if possible. A small number of patients are extremely sensitive to the constipating effects of opioids and require more vigorous measures to maintain bowel function. In severe cases, discontinuation of opioid therapy may be required. In the near future, nonabsorbable, mu opioid antagonists may offer a solution to this problem. Nausea is also a common early side effect of regular opioid therapy, and usually resolves with continued use within days. Antinauseants may be recommended during the initial titration phase. Sedation and cognitive deficits are also early side effects for which tolerance with continued use frequently develops once stable dosing has been achieved. There is little current evidence that the long term use of scheduled, stable dose opioid therapy leads to clinically significant cognitive or psychomotor deficits in patients with CNCP. Recent evidence suggests that pain itself can have an adverse effect on cognitive performance, which is improved with opioid analgesia (30,31). The longest clinical experience with patients taking opioids is over 35 years of continuous use in the methadone-maintained population of opioid addicts. Studies of this population have shown no related organ toxicity and no increase in markers of cognitive dysfunction such as motor vehicle accidents or infractions of driving codes. A study of cancer patients taking stable, long term opioid therapy compared with a group taking no opioids demonstrated no significant difference in functions related to driving ability (32). This observation has been duplicated in subsequent studies (33-38). Cognitive deficits in opioid-treated patients are more often due to the concurrent use of sedative medications such as benzodiazepines. Therefore, the use of sedatives in patients taking long term opioid therapy should be avoided where possible.

Opioid responsiveness
Pain specialists previously believed that certain types of pain, such as neuropathic pain, were ‘resistant’ to opioid analgesics. This opinion was challenged by subsequent research and recent randomized controlled trials that demonstrated that neuropathic pain can respond to opioids but often requires higher doses and/or combination with adjuvant analgesics.

The opioid responsiveness of a given pain syndrome in a particular patient refers to the balance of analgesia versus adverse effects. It is a dynamic process over time, which can be affected by factors such as the type of pain, the physiology and sex of the particular patient and the characteristics of the particular opioid. For some types of pain in certain patients, a given opioid can provide very effective analgesia at low doses, with minimal adverse effects. For other pain syndromes, higher doses of opioids may be required which, in a particular patient, may result in unacceptable persistent side effects, even with careful titration. Early understanding of opioid pharmacology assumed that all opioid analgesics shared the same mechanism of action and were thus completely interchangeable. Clinical and experimental evidence is now evolving for interindividual variability in responsiveness to the different opioids – due to genetic heterogeneity of opioid receptors or other as yet unknown factors. For example, morphine, the prototype mu receptor agonist, may cause more side effects than analgesia in a given patient than hydromorphone, another mu agonist; or oxycodone, which appears to have both mu and kappa agonist activity; or methadone, a mu agonist with N-methyl-D-aspartate receptor blocking properties. Recent research on the genetic polymorphism of opioid receptors supports the concept that blending opioids in some patients may improve efficacy. Therefore, before labelling a patient in pain as ‘unresponsive to opioids’, clinicians should consider the following actions: provide an adequate therapeutic trial by dosing to effect; allow adequate time during titration for tolerance to adverse effects to develop; demonstrate a consistently unfavourable balance of intolerable adverse effects to analgesia; duplicate this in a sequential trial of different opioid analgesics; and add a second opioid, at low dose, to one which is providing inadequate relief.

Patients whose pain is found to be unresponsive to an adequate trial of opioid therapy should not be assumed to have psychogenic pain or to be malingering.

Diversion
Preventing the diversion of opioid analgesics for illicit use is the concern of every conscientious prescriber, but strategies to discourage diversion should not take precedence over effective pain management. The risk of diversion can be reduced when prescribers practise with an awareness of the characteristic patterns of drug diversion and drug-seeking patients. According to
the Canadian Society of Addiction Medicine, public policy statement, "physicians who are practising medicine in good faith and who use reasonable medical judgment regarding the prescription of opioids for the treatment of pain should not be held responsible for the wilful and deceptive behaviour of patients who successfully obtain opioids for nonmedical purposes" (21).

KNOWLEDGE IS EVOLVING
1. Ongoing research is slowly unravelling the mysteries of chronic pain. As new information becomes available, it is expected that consensus statements such as the present one will continue to be revised. Physicians who prescribe long term opioid therapy to patients with CNCP are encouraged to stay abreast of these developments by reading relevant peer reviewed literature and by attending continuing medical education courses.

2. As clinical knowledge advances, it is hoped that treatments will become increasingly available that specifically remove or correct the underlying cause of many pain syndromes. However, until this is possible, the treatment of the pain itself, with whatever modality is most effective, is a necessary part of medical practice, subject to the need to take toxicity, side effects, patient preference and availability (including cost) into account.

PRINCIPLES OF PRACTICE FOR THE USE OF OPIOID ANALGESICS
1. It is clear that physicians, other health care providers, government regulators and law enforcement agencies seek guidance from each other or seek consensus through discussion regarding the appropriate use of opioid analgesics in the treatment of CNCP. Regulators and law enforcement authorities are charged with the dual responsibilities of preventing drug diversion without interfering with the appropriate medical use of opioid analgesics. As such, they require guidelines that establish the use of opioids to treat chronic pain as a legitimate medical practice. At the same time, prescribers have been shown to be reluctant to prescribe opioid analgesics because of fear of regulatory scrutiny. Guidelines may help to alleviate the regulatory concerns of prescribers, thus increasing the probability of optimum prescribing of opioids.

2. The Canadian Pain Society believes that guidelines for prescribing long term opioid therapy should be an extension of the basic principles of good medical practice. It is hoped that those organizations developing clinical practice guidelines will make use of the following principles.

GENERAL PRINCIPLES OF APPROPRIATE PAIN MANAGEMENT WITH OPIOIDS
Evaluation of the patient
Each patient with CNCP should be thoroughly evaluated before the institution of long term opioid therapy. If possible, the specific cause of the pain should be determined and specific therapy, if available, should be offered. Evaluation of the patient should include at least the following information:

- detailed pain history and the results of previous treatments;
- assessment of the impact of pain on the patient's family or significant others;
- directed physical examination, including musculoskeletal examination, to look for clues to specific pain syndromes;
- review of previous diagnostic studies and assessments. Additional investigation or consultation, if required, to fill in gaps in the previous diagnostic workup;
- assessment of coexisting illnesses and treatments and their effect on the patient and on the pain;
- assessment of significant psychological, social or behavioural factors that may affect the current pain problem or future treatment plans. This includes an assessment of risk factors for addiction (Appendix 1).

Complete assessment of the pain
A complete assessment of the pain problem should precede the initiation of a trial of opioid therapy, but this does not require the duplication of previous investigations or consultations. In cases of severe pain, it may be acceptable to treat the patient's pain while investigations are proceeding.

Types of pain
When a specific curable pain syndrome cannot be diagnosed, it may be useful to classify the type of pain into the following two main categories based on the inferred pathophysiology.

Nociceptive pain is usually due to continuous stimulation of specialized pain receptors in such tissues as the skin, bones, joints and viscera. It is often indicative of ongoing tissue damage. Typical examples include osteoarthritis and chronic pancreatitis.

Neuropathic pain is due to nerve damage or abnormal processing of signals along the pain systems of the peripheral and central nervous system. Examples include postherpetic neuralgia, phantom limb pain, pain resulting from spinal cord injuries and sympathetically mediated pain. Most chronic pain syndromes involve one or both of the above mechanisms.

‘Idiopathic’ pain was a term used previously to describe pain that did not precisely fit into either of the above categories. As knowledge evolves regarding central and peripheral sensitization of the central nervous system, many types of 'idiopathic' pain have turned out to have a nociceptive or neuropathic origin or a mixture of the two.

Assess psychological contributors
All types of pain can have a psychosocial component. Depressive symptoms frequently accompany CNCP and contribute to patient suffering. It is generally accepted by pain specialists that depression is more likely to be a secondary effect of the pain itself, rather than the reverse. Some patients with chronic pain and symptoms of major depression may demonstrate decreased suffering when depression is treated. For others, depressive symptoms diminish when pain is adequately treated. The term 'psychogenic pain' has been used in the past to define pain that was believed to be caused by or primarily influenced by a psychopathological process. The use of this term is now discouraged because it lacks precision and has the potential to stigmatize patients when applied inappropriately. True primary psychological pain disorders are very rare and should be classified using the criteria of the International Classification of Disease.
Association for the Study of Pain (39) or the DSM-IV (29). Care should be taken when assigning the diagnosis of 'Pain Disorder' from DSM-IV. This diagnosis has exclusion criteria, which are frequently ignored. If a physical condition, mood disorder or an anxiety disorder is a better explanation for the pain, then Pain Disorder per DSM-IV should not be diagnosed.

Assess for risk of addiction
An important component of the psychosocial evaluation for opioid therapy is the assessment of the risk of addiction. Because an unrecognized addictive disorder can complicate the treatment of chronic pain, it is worthwhile to screen patients to identify those who may need an assessment that is more detailed. A basic, suggested set of screening questions is included in Appendix 1. Patients with a past history of addiction should not necessarily be denied a trial of opioid therapy, but will require more careful prescribing and closer follow-up.

Who should be considered for a trial of opioid therapy?
Nociceptive and neuropathic pain syndromes can both be considered for a trial of opioid therapy. Patients with neuropathic pain may require higher doses of opioid therapy to achieve significant analgesia and may benefit from the concurrent use of adjuvant analgesics from the tricyclic antidepressant, anticonvulsant or antiarrhythmic classes. Other types of pain, without a definitive diagnosis, may also be treated with opioid therapy, but previous guidelines have suggested that a trial of opioids be prescribed cautiously with specific goals and careful monitoring to document an ongoing benefit.

When would a trial of opioid therapy be indicated?
In patients with mild to moderate pain, a trial of long term opioid therapy may be indicated for patients who have failed to respond to a reasonable documented trial of nonpharmacological and nonopioid pharmacological modalities. In patients with moderate to severe pain, it is more likely that opioids will be initiated much earlier and are more likely to be combined with adjuvant pain medications and other nonpharmacological treatments.

Treatment plan
The treatment plan should be individualized to the patient and to the pain problem. The physician should consider the gamut of appropriate treatment approaches, including physical methods, multidisciplinary pain management programs, cognitive and behavioural strategies, pharmacotherapy and various other invasive and noninvasive techniques. The choice may depend on many factors such as cost, availability of timely services, comorbidity, patient preferences, and physical and psychosocial impairments related to the pain. For some patients, simply decreasing the severity of their pain is all that is required to improve their quality of life. For others, a more intensive comprehensive treatment plan that addresses the psychological, social and behavioural contributors to their suffering is required.

Goals of treatment
The primary purpose of long term opioid therapy should be improved quality of life for the patient. Therefore, improved pain control is a reasonable and appropriate goal of treatment.

In CNCP, it is usually not realistic to set a goal of total elimination of the pain. Instead, the patient and physician need to negotiate a treatment plan to find the optimum balance of pain relief, functional improvement and medication side effects. To help patients improve their level of physical and psychological function, it is often useful to develop with the patient a list of functional goals. These might include specific targets for physical activity, performance of activities of daily living, hobbies or return to work. The attainment of these goals can be used as evidence of the efficacy of long term opioid therapy. However, failure to achieve fully all functional goals should not necessarily be construed as a therapeutic failure. On the other hand, a persistent decline in physical or psychological function in association with the institution of opioid therapy should cause the physician to reassess carefully the benefits of ongoing treatment with opioids. In some cases, a gradual dose reduction, possibly leading to the discontinuation of opioid therapy, may be required.

Obtain informed consent
If a trial of opioid analgesics is selected, the physician should obtain informed consent from the patient or the patient's guardian. Informed consent should include a discussion of the risks and benefits of opioid therapy, as well as the conditions under which opioids will be prescribed. A suggested list of discussion points is included in Appendix 2. In most practice settings in Canada, a documented verbal consent will usually suffice. For patients assessed to be at higher risk of noncompliance with the agreed upon treatment plan, physicians may find it helpful to use a written therapeutic agreement, setting out the terms and conditions for prescribing opioid therapy. A sample blank agreement has been included in Appendix 3.

Time-contingent dosing
When prescribing an opioid analgesic for around-the-clock pain, it should also be dosed around-the-clock in a pharmacologically appropriate, time-contingent, dosing schedule. There is no pharmacological rationale for a dose ceiling for opioids. Long term opioid therapy should be started at a low dose and carefully titrated until an adequate level of analgesia is obtained, or until unmanageable and persistent side effects warrant a decreased dose or a change in therapy. In the opioid-naive patient, failure to realize at least partial analgesia with incremental dose titration may indicate that the pain syndrome is unresponsive to opioid therapy; however, in some patients with more severe pain problems, significant analgesia may only occur after a threshold dose of opioid has been reached. Use of an opioid with a long duration of action has many advantages for treating chronic pain. It can facilitate patient compliance with round-the-clock dosing and provide a more consistent blood level of the opioid, thereby allowing better tolerance to side effects such as cognitive impairment. It may reduce the risk of addiction as well as the reinforcement of pain behaviour based on PRN opioid dosing regimens. During the titration phase, reasonable doses of breakthrough opioid may be provided and can be used to assess the adequacy of the overall opioid dose. A goal of optimal opioid titration for a stable chronic pain condition is to decrease the frequency of breakthrough doses to a minimum.
Consultation as needed
Consultation with a specialist in pain medicine, or with a pain psychiatrist or psychologist may be warranted, depending on the expertise of the practitioner and the complexity of the presenting problem. Consultants in pain medicine are not always available on a timely basis to primary care physicians. Therefore, a consultation with a specialist in pain management should not be a prerequisite to the use of opioid therapy. The presence of addiction or a comorbid psychiatric disorder may require comanagement with a specialist in addiction medicine or a psychiatrist, respectively.

Periodic review of the patient
Periodic review of the patient is an essential part of ongoing management with opioid therapy. As with the initial evaluation of the patient, reassessment of the patient’s pain is based mainly on the patient’s self-report. In assessing the efficacy of opioid therapy, it may be helpful to utilize collateral sources of information, such as family members, employers, etc. Periodic re-examination is warranted to assess the nature and evolution of the pain complaint and to ensure the ongoing benefit of opioid therapy. It is recommended that the following “5 A’s” be specifically documented at follow up visits:

- **Analgesia**: record the patient’s self-reported level of pain using some type of quantitative scale such as a Visual Analogue Scale or a verbal rating scale from 0 to 5 or from 0 to 10.

- **Activities**: record the level of physical and psychological function, listing specific activities where appropriate.

- **Adverse effects**: record any side effects of opioid therapy (such as drowsiness, nausea and vomiting, constipation and sweating) and their management.

- **Abuse behaviours**: record any suspicious drug-seeking or other aberrant drug-related behaviours observed by the physician or reported by others, along with the action taken by the physician.

- **Adequate documentation**: when writing a prescription for opioid therapy, be certain to record the name of the drug, the strength, the number of dosage units and how the drug is to be taken. Record any changes to opioid therapy and the reasons for them.

Managing the adverse effects of opioids
The adverse effects of opioid therapy may sometimes contribute to a persistent decrease in function. In some cases, a gradual reduction in the dosage of opioid therapy – possibly leading to the discontinuation of opioid therapy – may be the appropriate course of action.

Documentation
Documentation is essential to demonstrate the evaluation process, including consultations and relevant investigations, the rationale for long term opioid therapy in the context of the overall management plan, and the periodic review of patient status. In addition, documentation is required to demonstrate compliance with federal controlled substance legislation.

APPENDIX 1
Suggested addiction screening questions
In screening patients with chronic noncancer pain for addiction risk, the clinician is primarily interested in assessing for patients with a history of alcohol abuse or dependence, or with a history of polydrug abuse. A patient who has a past history of abusing one substance is at higher risk for abusing other psychoactive substances. The purpose of screening is not to deny patients opioids for pain, but to identify the small subgroup at higher risk who require more detailed assessment and more careful monitoring.

As part of the lifestyle history, patients can be asked directly, in a routine, nonjudgmental manner regarding current habits, including smoking, drinking and drug use. Try to quantify any positive responses by asking how often, how much and whether the current use is related to any consequences. Ask about a past history of alcohol and/or drug use and related consequences, including any experimental use as a teen or young adult. Ask about any family history of alcohol, drug or psychiatric problems.

The Screening Instrument For Substance Abuse Potential (SISAP) is a five-item screening tool created by Coombs et al (1) in 1996 that helps the clinician to categorize patients into lower or higher risk of abusing prescribed opioids. It requires that the physician already know the patient or have collateral information to confirm the accuracy of the answers. It has a high false positive rate but a low false negative rate when tested against the database of a large (n=11,634) Canadian epidemiological survey of alcohol and drug use. It has not yet been prospectively tested in a formal clinical trial.

The five SISAP questions are:
1. If you drink alcohol, how many drinks do you have on a typical day?
2. How many drinks do you have in a typical week?
3. Have you used marijuana or hashish in the past year?
4. Have you ever smoked cigarettes?
5. What is your age?

Use caution when prescribing opioids for the following patients:
1. Men who exceed four drinks per day or 16 drinks per week
2. Women who exceed three drinks per day or 12 drinks per week
Use caution when prescribing opioids for the following patients (continued):

3. A patient who admits to marijuana or hashish use in the past year. (It is recreational use of cannabis for euphoric effect that is of concern. The use of tetrahydrocannabinol derivatives to treat pain is still very controversial. Clinicians should exercise caution in prescribing opioid therapy to a patient who is using smoked cannabis regularly. This would not preclude a trial of an approved pharmaceutical cannabinoid as an adjuvant in complex pain problems.)

4. A patient under 40 years of age who smokes.

The majority of patients will pass the screen and are probably at low risk of abusing opioids, but clinical judgment is still required. The SISAP questions ask about recent drug or alcohol use and may therefore miss a patient who is at risk because of a previous history of chemical abuse or dependency. A simple but effective question to ask is:

“Has your use of alcohol or other drugs ever caused a problem for you or those close to you?”

A positive answer to the above or to any of the SISAP questions suggests further assessment.

The CAGE-AID questions comprise a quick screening tool to assess for the risk of serious alcohol or drug problems:

“In the past have you ever:

- a) felt that you wanted or needed to Cut down on your drinking or drug use?
- b) been Annoyed by others’ complaining about your drinking or drug use?
- c) felt Guilty about the consequences of your drinking or drug use?
- d) had a drink or a drug in the morning (Eye-opener) to decrease hangover or withdrawal symptoms?”

One positive response to any one of the CAGE-AID questions would suggest caution. Two or more positive responses may have a sensitivity varying from 60% to 95% and specificity from 40% to 95% in diagnosing serious alcohol or drug problems. The predictive value is highly dependent on the population screened (2-4). The CAGE screen used by itself seems to have less predictive value in the elderly, college students, women and certain ethnic groups. Two or more positive responses on the CAGE should strongly suggest a formal assessment by an addiction professional before prescribing long term opioid therapy.

The Two-Item Conjoint Screening Test (TICS) screens for current substance use disorders covering both alcohol and drugs:

1. “In the last year have you ever drunk or used drugs more than you meant to?”
2. “Have you felt you wanted or needed to cut down on your drinking or drug use in the last year?”

A positive response to either of the above questions has demonstrated a sensitivity of 80% in a random sample of adult primary care patients when compared with the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM), a reliable and validated diagnostic instrument based on the Diagnostic and Statistical Manual of Mental Disorder criteria (5). The negative predictive value of 93% means that this screen will miss only 7% of patients with substance use disorders. The following characteristics may further identify a patient at higher risk for abusing opioids:

- A previous history of chemical abuse or dependency
- A family history of alcohol, drug abuse or significant psychiatric illness
- A personal history of previous physical, sexual or emotional abuse
- Patients with borderline, antisocial or psychopathic personality disorders
- A patient living in a high-risk environment (others involved in drug misuse)
- A previous diagnosis of social phobia, bipolar affective disorder, psychotic disorder, attention deficit hyperactivity disorder

The presence of any of the above problems does not preclude the use of opioids for pain but does obligate the clinician to assess, prescribe and monitor much more carefully.

REFERENCES:


Further Reading

APPENDIX 2

Informed consent – suggested discussion points

1. Describe and explain the purpose of opioid therapy (less pain rather than no pain) with the patient and/or guardian, along with an explanation of the common side effects and their management. Preventive management of constipation should be specifically discussed. The small risk of addiction in low risk patients should be addressed and differentiated from tolerance and physical dependence. Warn the patient regarding withdrawal symptoms due to the abrupt discontinuation of opioids. Discuss the concept of dose titration and the importance of time-contingent dosing versus as required dosing for around-the-clock pain. Discuss the appropriate use of breakthrough medication.

2. Advise the patient and/or guardian that drowsiness is a common side effect during titration of opioid therapy. The patient should not drive a car or operate dangerous machinery until this phase of drowsiness has passed. Failure to comply with this advice may result in a duty to report to the provincial Ministry of Transportation.

3. The patient and/or guardian should be warned not to change the dosage of opioid analgesic nor the dosing interval without specific instructions from the doctor. The patient should be made aware that repeated unsanctioned dosage changes may compromise the physician-patient relationship.

4. Inform the patient and/or guardian that regular follow-up appointments are required to monitor the effectiveness of opioid treatment and to manage side effects. The frequency of follow-up appointments will vary depending on the phase of treatment – titration versus stable dosing.

5. Inform the patient and/or guardian that prescriptions for opioid analgesics should be obtained only from one physician or, in the absence of that physician, his or her designate. The patient should have all prescriptions for psychoactive medication dispensed at one pharmacy, except in emergencies. Inform the patient and/or guardian that seeking opioid treatment from other physicians and pharmacies without informing the prescribing physician undermines the trust essential to prescribing long term opioid therapy.

6. Advise the patient and/or guardian to keep the opioid analgesics in a safe and secure place out of the reach of children; and to not give, lend or sell the medication to anyone else.

7. Warn the patient and/or guardian that there is a potential for significant cognitive dysfunction if opioids are combined with sedatives such as benzodiazepines, barbiturates or muscle relaxants. The patient and/or guardian should be warned not to consume any of the above substances without first discussing this with the physician.

8. Although the potential for abuse or addiction to prescribed opioid analgesics is small in low risk patients, the concurrent abuse of illicit substances such as marijuana, cocaine, stimulants, hallucinogens, heroin or the consumption of alcohol in a high risk pattern identifies an individual at increased risk for also abusing opioids. The use of these substances may also interfere with the therapeutic effect of opioids or cause increased side effects such as cognitive dysfunction. It is therefore advisable that the patient abstain from taking any psychoactive substances without first discussing this with the physician. Advise the patient and/or guardian that the physician may, from time to time, take specific actions to monitor for this possibility such as periodic blood and/or urine drug screening or hair analysis. This may also include an assessment with a specialist in addiction medicine.

9. Inform the patient and/or guardian that, as part of ongoing treatment, the physician may request additional consultations and assessments, or recommend other concurrent treatment modalities. The clinician should carefully reevaluate a patient who consistently refuses to cooperate with recommendations for treatments other than opioid therapy.

10. Inform the patient and/or guardian that, aside from better pain control, a key measure of the efficacy of long term opioid therapy is improved physical and psychological function at home and/or work. The patient and the physician may therefore discuss a set of reasonable specific functional goals. The physician will assess progress toward these goals at each visit, and will utilize this information in evaluating the overall success of long term opioid therapy. Persistent functional decline on opioids may result in the re-evaluation of the patient and a reassessment of the treatment plan.
APPENDIX 3

Sample basic therapeutic agreement (for patients at higher risk of noncompliance with opioid therapy)

1. I, ____________________________ agree that Dr ___________________________ will be the only physician prescribing OPIOID (also known as NARCOTIC) pain medication and that I will obtain all of my prescriptions for opioids at one pharmacy. The exception would be in an emergency situation or in the unlikely event that I run out of medication due to a prescribing or dispensing error. In such cases, I will inform my physician as soon as possible.

2. I will take the medication at the dose and frequency prescribed by my physician. I agree not to increase the dose of opioid medication without first obtaining permission from my physician.

3. I will attend all reasonable appointments, treatments and consultations as requested by my physician.

4. I understand that the common side effects of opioid therapy include nausea, constipation, sweating and itchiness of the skin. Drowsiness may occur when starting opioid therapy or when increasing the dosage. I agree to refrain from driving a motor vehicle or operating dangerous machinery until such drowsiness disappears and my doctor agrees that I am fit to drive again.

5. I understand that using long-term opioids to treat chronic pain may result in the development of a physical dependence on this medication, and that sudden decreases or discontinuation of the medication may lead to the symptoms of opioid withdrawal. I understand that opioid withdrawal is uncomfortable but not life threatening.

6. I understand that there is a small risk that I may become addicted to the opioids I am being prescribed. As such, my physician may require that I have additional blood, urine or hair testing and/or see an addiction specialist should a concern about addiction arise during my treatment.

7. I understand that the use of any mood-modifying substance, such as tranquilizers, sleeping pills, alcohol or illicit drugs (such as cannabis, cocaine, heroin or hallucinogens) can cause adverse effects or interfere with opioid therapy. Therefore I agree to refrain from the use of all of these substances without prior agreement from my physician.

8. I agree to be responsible for the secure storage of my medication at all times. I agree not to give or sell my prescribed pain medication to any other person. I understand that the physician may choose not to replace lost medication until the next regular renewal date.

9. By signing this agreement I waive my right of medical confidentiality and give my physician consent to contact any other health care provider, pharmacy, legal authority, or regulatory agency to obtain or provide information related to any potential misuse of my medications.

10. I understand that if I break this agreement, my physician reserves the right to stop prescribing opioid medications for me.

Signed in _____________________ on _____________,

(city) (date)

_________________________ _________________________
(patient) (witness)
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