Original Article

Evidence-Based Guidelines on the Use of Opioids in Chronic Non-Cancer Pain—A Consensus Statement by the Pain Association of Singapore Task Force

Kok Yuen Ho, [1]*MBBS, MMed (Anaes), FIPP*, Nicholas HL Chua, [2]*MBBS, MMed (Anaes), FIPP*, Jane M George, [3]*MBBS, MMed (Anaes), FAMS*, Sow Nam Yeo, [4]*MBBS, FANZCA, FFPMANZCA*, Norhisham Bin Main, [5]*MBBS, MRCP, FAMS*, Chee Yong Choo, [6]*MBBS, FANZCA, FFPMANZCA*, James WT Tan, [7]*MBBS, MMed (Anaes), FANZCA*, Kian Hian Tan, [3]*MBBS, FANZCA, FFPMANZCA*, Beng Yeong Ng, [8]*MBBS, MMed (Psychiatry), FAMS*

Abstract

Introduction: While opioids are effective in carefully selected patients with chronic non-cancer pain (CNCP), they are associated with potential risks. Therefore, treatment recommendations for the safe and effective use of opioids in this patient population are needed. Materials and Methods: A multidisciplinary expert panel was convened by the Pain Association of Singapore to develop practical evidence-based recommendations on the use of opioids in the management of CNCP in the local population. This article discusses specific recommendations for various common CNCP conditions. Results: Available data demonstrate weak evidence for the long-term use of opioids. There is moderate evidence for the short-term benefit of opioids in certain CNCP conditions. Patients should be carefully screened and assessed prior to starting opioids. An opioid treatment agreement must be established, and urine drug testing may form part of this agreement. A trial duration of up to 2 months is necessary to determine efficacy, not only in terms of pain relief, but also to document improvement in function and quality of life. Regular reviews are essential with appropriate dose adjustments, if necessary, and routine assessment of analgesic efficacy, aberrant behaviour and adverse effects. The reasons for discontinuation of opioid therapy include side effects, lack of efficacy and aberrant drug behaviour. Conclusion: Due to insufficient evidence, the task force does not recommend the use of opioids as first-line treatment for various CNCP. They can be used as second- or third-line treatment, preferably as part of a multimodal approach. Additional studies conducted over extended periods are required.

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Introduction

Studies show that the incidence of chronic pain is approximately 18% in Australia and developed countries in Europe.[1-3] In Asia, data from Hong Kong and Singapore indicate that chronic pain is experienced by about 10% of adults, with chronic pain being more common in women and older adults.[4,5] In Singapore, the prevalence of chronic pain (pain for ≥3 out of the past 6 months) doubled to 19.7% in those above 65 years old.[5]

With increasing life expectancy and low fertility rates in Singapore, the proportion of residents aged 65 and above will continue to rise. It has been projected that those above 65 years old will increase from 9.3% in 2011 to 21.5% by 2025.[6,7] This would naturally result in a marked increase in the number of patients with chronic pain which will lead to a negative impact on society and place a substantial burden on the healthcare system.[8] Therefore, the primary goal of reducing pain symptoms, improving function and quality of life[9] in chronic non-cancer pain (CNCP) patients becomes even more important.

[1]Raffles Pain Management Centre, Raffles Hospital
[2]Department of Anaesthesiology, Intensive Care and Pain Medicine, Tan Tock Seng Hospital
[3]Pain Management Centre, Singapore General Hospital
[4]The Pain Specialist, Mount Elizabeth Medical Centre
[5]Department of Geriatric Medicine, Khoo Teck Puat Hospital
[6]Department of Anaesthesia & Surgical Intensive Care, Changi General Hospital
[7]Department of Anaesthesia, National University Hospital
[8]Department of Psychiatry, Singapore General Hospital
Address for Correspondence: Dr Kok Yuen Ho, Raffles Pain Management Centre, Raffles Hospital, 585 North Bridge Road, #13-00, Singapore 188770.
Email: ho_kokyuen@rafflesmedical.com

Definition of Chronic Non-Cancer Pain

The International Association for the Study of Pain (IASP) defines chronic pain as: "pain that persists beyond normal tissue healing time, which is assumed to be 3 months".[10] It can be nociceptive (e.g. inflammatory, traumatic or degenerative in nature) or neuropathic (e.g. a lesion or disease affecting the somatosensory system) in nature. Chronic non-malignant pain, chronic pain of a non-malignant origin and chronic benign pain are other terms used to describe the same condition. Common CNCP conditions include musculoskeletal pain, neck and low back pain, fibromyalgia, headache, post-herpetic neuralgia, diabetic peripheral neuropathic pain, pelvic pain and ischaemic pain.

Rationale for Pain Association of Singapore Consensus Guidelines

Opioids are increasingly prescribed for the management of CNCP. The benefits of opioids in acute pain and cancer pain are well established but the long-term use in CNCP remains controversial.[11] While opioids are effective in carefully selected patients with non-cancer pain, they are associated with potential risks.[10] Therefore, treatment recommendations for the safe and effective use of opioids in chronic non-cancer pain are needed.

The Pain Association of Singapore convened a multidisciplinary expert panel in September 2011 to develop practical evidence-based recommendations on the use of opioids in the management of CNCP in Singapore. These guidelines are necessary for a number of reasons: (i) the gradual increase in the use of opioids in Singapore; (ii) greater awareness of chronic pain management; (iii) higher incidence of chronic pain with an ageing population; and (iv) lack of a structured education programme on pain medicine among doctors, especially on the appropriate use of opioids. The objective of the consensus guidelines is to provide recommendations on the use of opioids in CNCP.

Materials and Methods

A literature search for abstracts, clinical trials and meta-analyses evaluating weak and strong opioids in CNCP was performed using PubMed, Scopus and Cochrane Database of Systematic Reviews. Reference lists of relevant articles were also reviewed for appropriate publications. Search parameters were limited to combinations of terms related to CNCP and opioid treatment. Only published English language articles were included. The last search was performed in March 2012.

For the purpose of this topical review, evidence for the use of opioids in the more common CNCP conditions was evaluated in a systematic fashion and recommendations were made. The conditions included in this review are: neck pain, low back pain, musculoskeletal pain, chronic pelvic pain, headache, orofacial pain, persistent postsurgical pain, post-herpetic neuralgia, diabetic peripheral neuropathic pain, fibromyalgia, and ischaemic pain. The opioids (both parenteral and non-parenteral) included in this review were: morphine, pethidine, oxycodone, fentanyl, hydromorphone, buprenorphine, methadone, tapentadol and tramadol. The task force included tramadol in this review as it is a weak opioid mu-receptor agonist, even though its main mode of action is via serotonin and noradrenaline reuptake inhibition.[12]

Low Back Pain

Low back pain is usually defined as pain or discomfort localised below the costal margin and above the inferior gluteal folds, and may be accompanied by radicular pain. Point prevalence ranges from 12% to 33%.[13] Studies have shown that in up to 90% of patients, low back pain may not have a specific cause.[14]

There is evidence supporting short-term use of opioid analgesics for chronic low back pain in terms of pain relief and functional improvement.[15-17] A 2007 Cochrane review on the efficacy of opioids in adults with chronic low back pain concluded, on the basis of 3 studies, that tramadol was more effective than placebo for pain relief.[18] A comparative trial of tramadol and naproxen, determined that tramadol aided in pain relief but not functional improvement. Overall results were not statistically significant for either pain relief or functional improvement.[18]

Recent literature demonstrates that there are several long-acting opioid analgesics available for use in chronic low back pain, including extended-release oxycodone,[19] hydromorphone,[20] and morphine sulphate.[21,22] In an open-label study which included 392 patients with chronic moderate-to-severe low back pain, once-a-day extended-release morphine sulphate afforded better pain relief (P = 0.0125), improved sleep (P = 0.0026), physical functioning and ability to work than twice daily controlled-release oxycodone for 8 weeks.[21,22] Over the longer term, open-label extended-release hydromorphone for 6 months improved pain relief (P = 0.0002), sleep and quality of life in 113 patients with low back pain.[20]

A large 12-month study (n = 823), which included patients with low back pain, reported a significant decrease in mean pain intensity scores following treatment with extended-release oxycodone up to 80 mg twice daily (P <0.001). However, 21% of patients discontinued treatment due to adverse events.[19]

A recent Cochrane review, which included 15 studies (≥6 months' duration) in patients with musculoskeletal pain—

namely back pain—suggests that in well selected patients with no history of substance addiction or abuse, appropriate management of opioids can provide long-term pain relief.[23] However, studies are necessary to identify which patients are most likely to benefit from opioid therapy.

A recent study reported that in patients with low back pain, tapentadol, a μ-receptor agonist with noradrenergic reuptake inhibition, might have better tolerability compared to other opioids. However, it is not available locally at the time of publication of this guideline.[24] Transdermal buprenorphine[25] and fentanyl[26,27] have also been used for the treatment of chronic low back pain. However, transdermal buprenorphine is not available for prescription in Singapore. In a 13-month open, randomised multicentre study, Allan et al[27] demonstrated that transdermal fentanyl could be safely used in opioid-naïve patients with chronic low back pain, with a lower incidence of constipation.

Opioid treatment may have some utility when combined with physical rehabilitation and behavioral therapy.[28] Data from a recent review suggested that the opioids were associated with a high dropout rate due to insufficient pain relief and adverse effects and suggested that there was more high-quality evidence supporting spinal steroid injections rather than opioids in terms of analgesia and functional improvement in patients with low back pain.[29]

Recommendations

- Available evidence is lacking and only supports the use of opioids for up to 12 months for chronic non-specific low back pain. The task force recommends that opioids, including tramadol, be used as part of a multimodal treatment regime (Table 1).

Neck Pain

Neck pain is common. In the UK, the cumulative 1-year incidence of episodic neck pain is 18%.[30] A lifetime prevalence of neck pain of 65% and a 12-month prevalence of 54% was reported in Hong Kong.[31,32] Of individuals, 15% were considered to have moderate-to-severe pain.[32] There are various underlying causes for neck pain; the most common of which are biomechanical, axial neck pain, whiplash-associated disorder and cervical radiculopathy.[33]

Only 2 trials were identified that evaluated the use of opioids in chronic neck pain. Randomised controlled data in 116 Chinese patients with chronic neck pain demonstrated the efficacy of controlled-release oxycodone (5 to 10 mg twice daily for 28 days) in the management of acute pain episodes.[34] In patients with chronic neck pain, the frequency of acute pain episodes were significantly reduced from day 3 of treatment (P <0.05) and improvements were noted for both quality of life and quality of sleep (P <0.05). A small randomised, double-blind crossover study in adults

Table 1. Summary of Treatment Recommendations

Low back pain	• Evidence is lacking to support the use of opioids beyond 12 months. Opioids, including tramadol, should be used as part of a multimodal treatment regime.
Neck pain	• Evidence is lacking to support the long-term use of opioids. There are some benefits for the short-term use of oxycodone. • Opioids can be used as alternative therapy if other analgesic agents are ineffective.
Musculoskeletal pain	• Opioids are recommended as alternative therapy if other analgesic agents are ineffective.
Head/Orofacial pain	• For episodic headaches, opioids are recommended as rescue therapy only if first-line therapies are ineffective or contraindicated. • Daily opioids may help a minority of patients with chronic headache and frequent and disabling symptoms that fail to respond to other therapies. • Opioids are not recommended for trigeminal neuralgia, glossopharyngeal neuralgia and persistent idiopathic facial pain.
Chronic pelvic pain	• Evidence is lacking on the use of opioids. • Opioid therapy can be considered as part of multidisciplinary care and rehabilitation.
Persistent post-surgical pain	• There is some evidence to support the short-term efficacy of tramadol and strong opioids in the treatment of phantom limb pain (PLP). Tramadol may be better tolerated than strong opioids. • Opioids can be considered for treating PLP when non-opioid analgesics fail. • Evidence is lacking on the use of opioids for other forms of chronic post-surgical pain.
Fibromyalgia	• Evidence is lacking to support the use of opioids. The only exception is tramadol, which can be part of a multimodal approach to treatment.
Post-herpetic neuralgia	• Opioids can be considered in patients who fail therapy or develop intolerable side effects with TCAs, anti-convulsants or lignocaine patch. • Opioids can be used as an add-on therapy to further improve symptoms.
Diabetic peripheral neuropathic pain	• Current evidence suggests that opioids are as efficacious as monotherapy or as an add-on therapy in combination with TCA or anti-convulsants in the treatment of DPNP. • Opioids can be considered in patients who fail therapy or develop intolerable side effects with TCAs or anti-convulsants.
Peripheral vasculopathy	• Current evidence suggests that monotherapy with oral opioids may be used as an alternative to epidural infusions.

DPNP: diabetic peripheral neuropathic pain; PHN: post-herpetic neuralgia; PLP: phantom limb pain; PPSP: persistent post-surgical pain; TCA: tricyclic antidepressants

with whiplash-associated disorder grade II in the chronic stage (n = 30) reported a response to intravenous morphine (0.3 mg/kg) in 15 patients.[35] Response was defined as a minimum 50% reduction in pain intensity based on visual analogue scale ratings.

Recommendations

- There is limited evidence on the use of opioids in treating chronic neck pain. Whilst there are some benefits for the use of short-term oxycodone, there are no long-term data to support prolonged use.
- The task force recommends that opioids be used as alternative therapy if other analgesic agents are ineffective (Table 1).

Musculoskeletal pain

Musculoskeletal pain commonly occurs in the Asian population. In this section, it refers mainly to hip and knee joint pain. It was the most common pain diagnosis (46%) in a prospective cross-sectional survey of an outpatient pain management clinic in Hong Kong.[36]

Currently, available treatments for chronic musculoskeletal pain are associated with modest therapeutic benefits.[37] However, there are few randomised controlled trials substantiating the efficacy of opioids in the treatment of musculoskeletal pain.

The European League Against Rheumatism (EULAR) recommendations for the management of hip osteoarthritis state that opioid analgesics, with or without paracetamol, are useful alternatives in patients in whom nonsteroidal anti-inflammatory drugs, including cyclo-oxygenase type-2 selective inhibitors, are contraindicated, ineffective, and/or poorly tolerated.[38] Similarly, the Osteoarthritis Research Society International recommends opioids as second-line therapy when other pharmacological agents are ineffective.[39]

In 2009, a systematic Cochrane review of 10 trials with 2268 participants demonstrated small to moderate beneficial effects of opioids other than tramadol in the short-term therapy of patients with osteoarthritis of the hip and knee.[40] Although opioids provided greater pain relief and improved function over and above that observed with control therapies, these benefits were moderated by notable increases in the incidence of adverse effects leading to high rates of treatment discontinuation. Consequently, in osteoarthritic pain, non-tramadol opioids should not be routinely used.

Tramadol has been shown to reduce pain intensity, produce symptomatic relief and improve function[41,42] However, its use may be limited by adverse events which can lead to treatment discontinuation.[41,42] A systematic review of 11 randomised controlled trials (n = 1019) in patients receiving tramadol reported a 37% increase in the likelihood of experiencing a moderate improvement. However, tramadol was associated with a 2.6-fold increase in the risk of a major adverse event, resulting in participants suspending treatment, although there were no reports of any life-threatening event. Of every 8 patients on tramadol, 1 patient will discontinue treatment due to adverse events; the number needed-to-harm (NNH) was 8.[41,42]

Recommendations

- Opioids can provide mild-to-moderate pain relief and improved function but are limited by adverse effects. They are not recommended as a first-line treatment for chronic musculoskeletal pain.
- The task force recommends that opioids be used as alternative therapy if other analgesic agents are ineffective (Table 1).

Headache/Orofacial Pain

Headache Pain

The headache conditions referred to in this section include, but are not limited to, primary headache conditions such as migraine, tension-type headache (TTH) and cluster headaches as defined by the International Classification of Headache Disorders-II (ICHD).[43]

The role of opioids in the management of chronic headache remains controversial. For patients with headache, the role of opioids is complicated due to the closely related conditions of medication-overuse headache[44,45] and transformed migraine.[46] Bigal et al[47] stated that patients who consumed opioids for more than 8 days in a month were at greater risk for headache chronification. In fact, it was suggested that the frequent use of opioids, barbiturate-containing analgesics and triptans as abortive medications may be the primary risk factor leading to chronic daily headaches.[48] This is even the case when opioids are not used primarily for headaches but for other indications.[49]

According to the European Federation of Neurological Societies (EFNS) guideline on the treatment of TTH, opioids are not recommended for the treatment of TTH.[50]

The largest longitudinal headache study to date, phase 2 of the American Migraine Prevalence and Prevention (AMPP) study, showed that triptans were used by 18.3% of patients, opioids by 11.7%, and barbiturate medications by 6.1%.[51] Similarly, in a sample of 5796 individuals with migraine, 4076 (70.3%) were opioid non-users, 798 (13.8%) were previous users, and 922 (15.9%) were current opioid users. The data suggested that opioid use might be fraught with problems for some patients, with 16.6% of respondents who were currently using opioids, potentially meeting DSM-IV (Diagnostic and Statistical Manual of Mental Disorders–4th edition) criteria for dependence.[51]

Saper et al[52] assessed outcomes of 160 consecutively enrolled patients with chronic daily headache. The

authors found that 74% of patients either failed to benefit from opioids or discontinued therapy for intolerable and unmanageable adverse effects, clinical deterioration or worsening headache. Although a substantial percentage of patients reported at least 50% improvement on opioids, a significant number continued to report functional impairment in areas such as self-care, social activity, occupation, recreational activities and sexual behaviour. Problem drug behaviour (usually dose violations) was also reported in 50% of the 70 patients who remained on continual opioid therapy for at least 3 years.

In summary, opioid use in chronic headaches is associated with more severe headache-related disability, degree of symptom severity, comorbidities (such as depression and anxiety), and problematic drug behaviour.

Facial Pain

The type of facial pain referred to in this section includes, but is not limited to, trigeminal neuralgia, glossopharyngeal neuralgia and persistent idiopathic facial pain as defined by the ICHD-II.[43] There is a lack of substantial evidence regarding the systematic use of opioids in facial pain conditions specifically. Although patients with head, facial and neck pain were included in one study, no data were reported specifically for patients with orofacial pain or temporomandibular joint disorders.[53]

The 2010 revision of the EFNS guidelines for treatment of neuropathic pain does not recommend the use of opioids in the management of trigeminal neuralgia.[54,55]

Recommendations

- For the patient with episodic headaches, the task force recommends that opioids be used as rescue therapy only if first-line therapies are ineffective or contraindicated (Table 1).
- For the patient with chronic headache and frequent and disabling symptoms that fail to respond to other therapies, daily opioids may help a minority of patients but also have the propensity to cause harm.
- It is imperative for clinicians who recommend daily opioids for patients with intractable headaches to carefully balance the risks and benefits prior to initiating opioid therapy.
- Evidence regarding the use of opioids in facial pain is lacking. The task force does not recommend the use of opioids for facial pain conditions such as trigeminal neuralgia, glossopharyngeal neuralgia and persistent idiopathic facial pain (Table 1).

Chronic Pelvic Pain Syndrome

Chronic pelvic pain (CPP) is defined as non-malignant pain perceived in structures related to the pelvis of both males and females. It can be nociceptive or neuropathic in origin. There are often associated negative cognitive, behavioural, sexual, and emotional consequences.[56]

Multiple reviews on CPP have concluded that the current available treatment options are inadequate in controlling pain and suffering.[56,57] As the pathophysiology of CPP is not well understood, its treatment is often limited to symptom relief. A multidisciplinary approach is advocated in numerous reviews and guidelines.[56-59]

There is a lack of well-designed controlled clinical trials regarding the efficacy of opioids in the management of CPP. Recommendations are based on studies and reviews on opioids for chronic non-malignant pain in general. Guidelines developed by various expert groups acknowledge the use of opioids for severe pain under adequate supervision but recognise that opioids do not necessarily improve functional or psychological status.[56,57,60]

CPP is increasingly viewed as a condition that involves variable degrees of neuropathic pain and central sensitisation.[56,61,62] Hence, the effect of anti-neuropathic pain medications should be assessed at appropriate doses and combinations before the consideration of opioids. They may also be used in combination with opioids.[61] Despite the general notion that opioids are not the best agents for neuropathic pain, evidence suggests they are effective against certain symptoms, such as spontaneous pain, and several subtypes of evoked pain.[63,64]

Recommendations

- As there are no controlled trials evaluating opioids for the treatment of CPP, the task force recommends that opioids should be used with caution and under adequate supervision.
- Before considering opioids for CPP, known treatable causes for CPP should be excluded or all acceptable treatment modalities should be found to be ineffective. The algorithm for the diagnosis and treatment of CPP from the European guidelines on Chronic Pelvic Pain,[56] is a useful reference to ascertain this.
- The task force recommends multidisciplinary care and rehabilitation, in addition to opioid therapy, for the treatment of CPP (Table 1).

Persistent Postsurgical Pain

Persistent postsurgical or postoperative pain (PPSP) is defined as pain that has developed after a surgical procedure, persists 2 months after surgery and cannot be explained by other causes.[65,66] PPSP has been reported after a wide range of surgical procedures of which the most common are limb amputation, hernia repair, thoracic, breast and cardiac surgery.[65-67] The mechanisms of PPSP

are complex and poorly understood but it is clear that there is a component of neuropathic pain in this heterogeneous group of conditions. Most of the research has been directed at identifying the causes and risk factors for, and preventing the development of PPSP. There are few published good quality studies regarding the use of opioids for the treatment of PPSP. The majority of studies have focused on phantom limb pain (PLP).

Tramadol provided effective pain relief and was well tolerated in 94 treatment-naïve post-traumatic limb amputees with PLP. After one month of therapy, 51% (48/94) of patients responded to tramadol, 43% (40/94) of patients responded to amitriptyline, and 2% (2/94) responded to placebo.[68] No major adverse effects were noted and consistent and large antinociceptive effects on both the stump and the intact limbs were demonstrated with both tramadol and amitriptyline.[68] A double-blind, crossover trial in 12 patients with PLP, showed that up to 300 mg/day of oral morphine was superior to placebo, with 42% of patients obtaining more than 50% pain relief after one month.[69] Another double-blind, crossover trial in 60 amputees reported a 53% mean reduction in the intensity of post-amputation pain with morphine (up to 180 mg/day) compared with placebo and mexilitine (up to 1200 mg/day).[70] The numbers needed to treat (NNT) to obtain 50% and 33% decreases in pain intensity with morphine were 5.6 and 4.5, respectively. However, pharmacotherapy with morphine was associated with a higher rate of side effects and there was no improvement in self-reported levels of overall functional activity and pain-related interference in daily activities.[70]

A Cochrane review on the use of opioids in PLP noted that morphine was effective in decreasing pain intensity in the short-term with moderate adverse effects. The authors concluded that the short- and long-term effectiveness of opioids in terms of pain reduction, function, mood, sleep, quality of life, satisfaction and adverse effects remained unclear.[71] In spite of this, a UK-based primary care epidemiological survey reported that opioid analgesics were the most common initial treatment prescribed for PLP.[72]

Recommendations

- There is some evidence to support the short-term efficacy of tramadol and strong opioids in the treatment of phantom limb pain (PLP). Tramadol may be better tolerated than strong opioids.
- Evidence is lacking on the long-term efficacy and adverse effects of tramadol and strong opioids in PLP.
- The task force recommends opioids for the treatment of PLP when conventional pharmacotherapy with non-opioid analgesics fails (Table 1).

Fibromyalgia

Fibromyalgia is characterised by chronic widespread pain (hyperalgesia, allodynia) and is associated with symptoms such as fatigue, sleep abnormalities and psychological distress.[73] The prevalence of this disease was found to be 2% in a US population survey.[74] There is much debate about both the usefulness and safety of opioids as a medication for patients with fibromyalgia. Emerging evidence indicates that therapies that target central pain mechanisms may provide the greatest benefit.[75-77]

The short- or long-term use of opioids in patients with fibromyalgia syndrome is prevalent.[78] Approximately 14% to 37% of patients diagnosed with fibromyalgia are being treated with opioids.[79-81]

While patients with fibromyalgia find that opioids are highly effective analgesics,[82] many healthcare professionals and researchers feel that there is little evidence that opioids provide significant pain relief in fibromyalgia. Furthermore, there are concerns regarding the potential for tolerance and addiction associated with long-term opioid use.

To date, there are no randomised controlled trials addressing the use of opioids in the management of fibromyalgia. A 4-year non-randomised trial of 38 patients with fibromyalgia receiving opioid therapy found no significant improvement in pain levels.[83]

Tramadol is recommended for the treatment of fibromyalgia in the EULAR guidelines.[83] While data on the benefits of opioids are lacking, tramadol-based combination therapy appears to be effective in the management of fibromyalgia pain. A double-blind, randomised controlled trial of 315 patients showed that tramadol/acetaminophen was effective in reducing pain levels (P <0.001) and improving Fibromyalgia Impact Questionnaire scores (P = 0.008), and was also well tolerated.[82] This combination also significantly improves Health-Related Quality of Life (HRQoL), specifically physical functioning, and physical and bodily pain (P <0.01).[84]

Recommendations

- There is a lack of evidence to support the use of opioids in the treatment of fibromyalgia. The only exception is the use of tramadol. However, the efficacy of tramadol may be related to its unique serotonin and noradrenaline reuptake inhibition activity and not its opioid receptor activity.
- The task force does not recommend opioids in the treatment of fibromyalgia. Tramadol can be considered as part of a multimodal approach to treatment (Table 1).

Post-herpetic Neuralgia

Post-herpetic neuralgia (PHN) is a chronic neuropathic pain condition that develops in some patients after a herpes zoster (shingles) infection. The incidence increases with age and affects 7.8% of adults above the age of 60 years.[85] Guidelines issued by the NeuPSIG (2007) and EFNS54 have recommended strong opioids and tramadol as second-line therapy for the treatment of PHN.

Morphine has demonstrated efficacy in a randomised, placebo-controlled, crossover study comparing opioids, tricyclic antidepressants (TCAs) and placebo.[86] The NNT for a 50% reduction in pain was 2.7 (range, 1.9 to 4.2). Similar efficacy was also demonstrated with methadone (average daily dose of 15 mg/day). Morphine, but not methadone, provided significantly greater pain relief compared with TCAs. Overall, opioids were preferred by subjects who completed all treatment arms and were well tolerated.[86]

Extended-release formulations of oxycodone, at doses of 20 to 60 mg/day, were effective in a placebo-controlled crossover trial involving 38 patients with PHN.[87] The NNT for a 50% reduction in pain was 2.5 (range, 1.7 to 5.1). This was comparable with a meta-analysis of 2 trials evaluating oxycodone, morphine and methadone that calculated an NNT of 2.67 for opioids.[88]

A randomised, double-blind, active- and placebo-controlled, 4-period crossover trial in 57 patients (including 22 with PHN) compared 4 treatments: morphine (target dose 120 mg/day), gabapentin (3200 mg/day), morphine (60 mg/day) plus gabapentin (2400 mg/day), and active placebo (lorazepam, 1.6 mg/day). Morphine but not gabapentin significantly improved mean pain intensity. While morphine–gabapentin combination therapy was significantly superior to either monotherapy alone, the clinical significance may be limited with only a 20% lower mean pain intensity compared to placebo.[89]

A recent randomised controlled trial did not show greater efficacy when oxycodone was used in combination with pregabalin in PHN. However, in this study, a low dose of 10 mg/day of oxycodone was used.[90]

Recommendations

- The task force does not recommend opioids as first-line treatment for PHN (Table 1). It can be considered in patients who fail therapy or develop intolerable side effects with TCAs, anti-convulsants or lignocaine patch.
- For patients who are partial responders to conventional medications, opioids can be an add-on therapy to further improve symptoms. However, higher doses of opioids (e.g. >10 mg oxycodone per day) may be needed.

Diabetic Peripheral Neuropathic Pain

Painful neuropathy is a common, often progressive complication of diabetes. Symptoms can include tingling, burning, lancinating pain, hyperaesthesia and allodynia in a glove and stocking distribution affecting the limbs.[91]

There are a number of agents available for the treatment of diabetic peripheral neuropathic pain (DPNP), and several recent guidelines have published recommendations on the treatment for DPNP.[92,93] The Toronto Expert Panel on Diabetic Neuropathy recommends opioids, such as tramadol, morphine and controlled-release oyxcodone as second-line therapy for DPNP.[92] Evidence-based guidelines have also been developed by various national working groups.[93] According to these guidelines there is evidence to support the efficacy of opioids (morphine, tramadol, controlled-release oxycodone) in DPNP and these agents should be considered as a treatment option.[93]

In a randomised open study, tramadol 37.5 mg plus acetaminophen 325 mg was similarly effective to gabapentin 300 mg in 163 patients with DPNP with similar mean reductions in pain intensity observed in both groups.[94]

In a 4-week randomised crossover study involving 36 patients, controlled-release oxycodone, 10 to 40 mg every 12 hours, significantly reduced mean daily pain ($P = 0.0001$), total pain and disability ($P = 0.004$). The NNT was 2.6.[95] In diabetics with moderate-to-severe neuropathic pain (n = 159), controlled-release oxycodone, 10 to 60 mg every 12 hours, reduced the average daily pain intensity compared with placebo in a multicentre randomised 6-week trial.[96] The majority of patients receiving oxycodone experienced opioid-related adverse events including constipation (42%), somnolence (40%), nausea (36%), and dizziness (32%).

Data are limited with regard to the benefits of combination therapy.[92] However, a well-designed, 4-period crossover trial in 57 patients (including 35 with DPNP) confirmed the superior efficacy of the combination of gabapentin and morphine compared with either monotherapy alone as indicated by the patient's mean pain intensity. Beneficial effects were achieved at lower doses than with either agent administered as monotherapy. However, there was only a 20% lower mean pain intensity when combination therapy was compared with placebo.[89]

In a randomised controlled trial, prolonged-release oxycodone was administered as adjunct therapy in 338 patients with moderate-to-severe DPNP despite existing gabapentin treatment.[97] Oxycodone for 12 weeks enhanced the effects of gabapentin therapy and was well tolerated: notable improvements were reported for pain relief ($P = 0.003$), reduced need for rescue medication ($P = 0.03$) and improved sleep ($P < 0.05$). In contrast, a recent randomised controlled trial did not show greater efficacy

when oxycodone was used in combination with pregabalin in DPNP. However, in this study, a low dose of 10 mg/day of oxycodone was used.[90]

Recommendations

- Current evidence suggests that opioids are as efficacious as monotherapy or as an add-on therapy in combination with TCA or anti-convulsants in the treatment of DPNP.
- The task force does not recommend opioids as first-line therapy for DPNP (Table 1). Opioids can be considered in patients who fail therapy or develop intolerable side effects with TCAs or anti-convulsants.

Peripheral Vascular Disease

Peripheral vascular disease (PVD) refers to a disorder of the circulatory system that excludes the involvement of the heart and brain. The term is more synonymous with peripheral arterial obstructive disease of the lower limbs which is multifactorial in origin. Impaired arterial circulation to the affected limb causes pain manifesting as intermittent claudication, night pains, rest pain or continuous ischaemic pain.

There is a paucity of well-designed studies on the use of opioids for pain in PVD. An initial study by Aurilio et al[98] showed that the addition of transdermal buprenorphine to a peridural combination of morphine and ropivacaine (Transtec transdermal device plus ropivacaine and morphine, TTDS) was safer and more effective when compared with peridural combination alone for patients with Fontaine grade 3 to 4 vasculopathy. In a follow-up open-label, prospective, randomised trial, the TTDS group had better pain control, improved sleep and fewer side effects.[98] However, transdermal buprenorphine is not available for use locally.

Samolsky Dekel et al[99] conducted an observational, retrospective study of patients with Fontaine stage 3 to 4 vasculopathy who presented with moderate-to-severe pain. They compared the use of epidural bupivacaine with slow-release oxycodone for those who had a contraindication to epidural infusion of local anaesthetics. Pain control with oxycodone was similar at rest but less effective during dynamic activity when compared with epidural bupivacaine. Treatment side effects were rare in both groups.[99]

Recommendations

- Current evidence suggests that monotherapy with oral opioids may be used as an alternative to epidural infusions. A trial of opioid therapy should be instituted with other treatment modalities like rehabilitation, risk factor management and lifestyle modification to improve function and exercise performance.

Stepwise Approach to Prescribing Opioids for Chronic Non-Cancer Pain

A stepwise approach is important in selecting the appropriate patient for opioid therapy (Table 2). There must be a plan for discontinuing opioids when treatment fails to meet predetermined goals for significant pain relief and enhanced quality of life. The aim should be improved function without the expectation of complete alleviation of pain.

Initial Evaluation and Referral

Opioids are a valuable alternative when patients do not respond to other analgesics and treatment regimes. One of the primary issues when prescribing opioids is how to balance the benefit of pain relief and the risk of opioid abuse. Risk stratification is a key step in deciding if a patient is suitable for opioid therapy. Clinicians must be cognisant of potential risk factors when assessing whether a patient with CNCP is an appropriate candidate for opioid therapy.[100] A complete history and physical examination, including assessment of psychosocial factors and family history is part of the initial assessment for patient risk stratification.[9,101]

An ongoing, past and family history of addiction must be evaluated.[102] This is because a personal or family history of alcohol or drug abuse is highly predictive of opioid abuse, misuse or other aberrant drug-related behaviours.[103] Younger age and the presence of psychiatric comorbidites may also be predictive of opioid abuse. At-risk patients should therefore be referred to a specialist trained in addiction medicine or pain medicine for further evaluation.

Validated screening tools are useful adjuncts used in major pain centres around the world for risk stratification. The Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R),[104] the Opioid Risk Tool (ORT)[105] and the Diagnosis, Intractability, Risk, Efficacy (DIRE) Instrument[106] may be useful in some patients but are not commonly employed. However, detailed individualised assessment remains key in selecting patients for opioid therapy.

Informed Consent

If the patient is deemed suitable for a trial of opioid therapy, informed consent should be obtained prior to initiation of therapy, preferably in the form of an opioid treatment agreement with the patient (Appendix 1).[107] Goals of therapy, expectations, risks and benefits as well discontinuation of opioid therapy if there are no improvements in pain or function should be discussed.

Table 2. Stepwise Approach for Prescribing Opioid Therapy in Non-Cancer Pain[9,108]

Initial Evaluation	• Detailed medical history and physical examination to include: nature and intensity of pain, current and previous pain treatment, effect of pain on physical and psychosocial function, history of substance abuse. • Assess risk of substance abuse, misuse and addiction with appropriate screening tools e.g. SOAPP-R, ORT, DIRE.
Referral	• Patients with a personal or family history of alcohol or drug abuse are at risk of aberrant drug-related behaviour and should be referred to a specialist with expertise in addiction medicine or pain management for assessment.
Informed Consent	• Obtain informed consent before starting opioid therapy. • Establish an opioid agreement with the patient. • Discuss goals, expectations, risks, benefits and alternatives to chronic opioid therapy.
Initiation	• Choice of opioid, initial dose, and titration should be individualised and based on patient's medical condition. • A short-term trial of opioid lasting from 4 to 8 weeks is recommended. • Decision to proceed with long-term therapy should be based on the outcome of the trial e.g. efficacy, side effects, meeting goals, etc
Monitoring	• Regular monitoring is recommended for all patients on chronic opioid therapy. • In patients at low risk for adverse outcomes and on stable doses of opioids, monitoring at least once every 3 to 6 months may be sufficient. • More frequent monitoring is suggested after initiation of therapy or changes in opioid doses and in patients at higher risk for aberrant drug related behaviours, those in an occupation demanding mental acuity, and in older adults or patients with comorbid medical conditions. • For patients at high risk for adverse outcomes, monitoring on a weekly (or more frequent) basis may be required. • Monitoring of the following is recommended: pain severity, functional ability, progress towards achieving therapeutic goals, presence of adverse effects and presence of aberrant drug related behaviours. • Pill counts, family member or caregiver interviews, and use of prescription monitoring programme data can be useful supplements. • Periodic urine drug screening is recommended in all high-risk patients.
Discontinuation	• Patients should be tapered or weaned off chronic opioid therapy when they engage in serious or repeated aberrant drug related behaviours or diversion, experience intolerable adverse effects, or make no progress towards meeting therapeutic goals. • When a patient is taking more than 200 mg morphine or its equivalent per day without any significant pain relief, discontinuation of opioid therapy should be considered. • Tapering can often be achieved in the outpatient setting in patients without severe medical or psychiatric comorbidities • Weekly reduction in dose by 10% is generally well tolerated without symptoms of opioid withdrawal. • In more complex cases, detoxification in a rehabilitation setting can be helpful, especially for patients unable to reduce their opioid dose in a less structured setting. • If the aberrant behaviours are related to addiction, addiction treatment resources should be made available.

Initiation of Opioid Therapy

Initial opioid therapy must be based on identifying the minimal effective dose at which pain is controlled balanced with minimal adverse effects, in an individually-tailored pharmacological programme. While opioids are associated with a variety of adverse effects these can often be minimised with careful drug titration and maintenance.[109] Commonly encountered side effects include constipation, sedation, nausea and vomiting.

Oral opioids are preferred over injectable opioids because of ease of administration. Sustained-release formulations are also preferred over immediate-release formulations as steady plasma drug concentrations can be achieved. Pethidine is available for intravenous or intramuscular administration. However, it has no unique clinical advantages over other opioids such as morphine. Accumulation of its active metabolite, norpethidine, can in fact potentially cause neurotoxicity. Pethidine also possesses higher potential for abuse compared to other opioids, as it produces more intense euphoria after drug injection.[110] The general consensus from various working groups is that pethidine has no role in the management of CNCP.[111]

A short-term trial of opioid therapy over 4 to 8 weeks is generally recommended. During the trial, the physician should see the patient more frequently to make dose adjustments based on pain intensity, side effects, and functional improvements. The task force recommends a trial duration of 8 weeks and upper titration dose limit of 200 mg of oral morphine or its equivalent dose per day,[112] beyond which the harm may outweigh the benefits of opioid therapy in non-cancer pain.[113] The decision to proceed with long-term opioid therapy should be based on the trial outcomes. These outcomes may also be discussed with patients at the initiation of the trial to foster a better understanding of trial and treatment objectives. Opioids can be continued if there is a satisfactory response to the initial therapeutic trial with acceptable side effects.

Dose Titration and Monitoring

Dose titration is necessary to establish the optimal and

minimal effective dose while minimising the likelihood of adverse effects. In most controlled studies, the opioid dose was ≤180 mg of morphine or equivalent per day.[114] A recent cohort study reported an 8.9-fold increase in overdose risk for patients receiving ≥100 mg/day for CNCP, indicating that there is a direct link between dosage and the risk of overdose.[115]

Regular monitoring is therefore recommended for all patients on chronic opioid therapy. The risk of polypharmacy and the risk of drug interactions must always be taken into consideration.[109] The patient's medication history, including additions or replacements with new medications for other medical conditions, should be reviewed at every visit.

In the first 5 years after the onset of a chronic pain problem, patients are at increased risk for developing problems and disorders associated with new drug use. The risk appears to be highest among those with a history of drug use disorder or psychiatric comorbidity.[116] Not infrequently, a history of substance abuse emerges only after the current misuse of medications has been identified, thus requiring physicians to monitor treatment closely.

It is estimated that the incidence of aberrant medication-taking behaviour ranges from 5% to 24%, and the prevalence of current substance use disorders may be as high as 50%.[117,118] Even higher rates are reported in patients with a history of substance abuse.[117] The prescribing physician must be vigilant in detecting signs of opioid abuse or diversion.

Patients at low risk for drug abuse or on stable doses of opioids can be reviewed once every 2 to 3 months. More frequent monitoring is recommended for patients at high risk for aberrant drug-related behaviours, or when there are changes in opioid doses. Assessment and documentation of four domains (4 As), namely, analgesia, activities of daily living, adverse effects and aberrant drug-taking behaviour, should be included in every visit.[119]

Adherence monitoring is crucial in order to ensure appropriate opioid use and avoid abuse. Risk reduction measures may include urine drug screening, pill counts, and regular office visits.[107,120]

Discontinuation of Opioid Therapy

Controversy surrounds the long-term use of opioid for chronic nonmalignant pain.[121] Studies generally last less than 18 months and are complicated by high rates of discontinuation because of adverse events or insufficient pain relief. Opioids should be slowly tapered to avoid withdrawal and completely discontinued if the risks (side effects, toxicities, aberrant drug-related behaviour) outweigh the objective benefits (analgesia, functional improvements).

Opioid therapy should be tapered off when a patient is found to exhibit aberrant drug-related behaviour or diversion, or experiences intolerable adverse effects (Table 3). When pre-determined therapeutic goals, namely pain reduction and functional improvement, are not achieved,[111] despite escalating the opioid dose to more than 200 mg morphine or its equivalent per day, discontinuation of therapy should be considered. A gradual reduction in dose which is well tolerated will prevent symptoms of opioid withdrawal.[9]

Patients should be referred to an appropriate specialist for further evaluation where other forms of therapy, including surgery, interventional procedures or psychological therapy, are available.

Table 3. Types of Aberrant Drug Behaviour

• Doctor shopping
• Forging prescriptions
• Stealing or borrowing drugs
• Multiple episodes of loss or theft of prescription drugs
• Not following prescribed dose and schedule
• Multiple unauthorised dose increases
• Pushing for higher dose of opioids
• Repeatedly seeking drugs from other providers or emergency departments
• Noncompliance with non-pharmacological components of pain treatment (e.g. physiotherapy, psychological therapy)
• Showing up only for medication appointments (e.g. misses, cancels, or no-shows at other appointments)
• Concurrent use of illicit drugs (e.g. heroin, cocaine, methamphetamine, marijuana, others)
• Concurrent use of alcohol
• Tobacco use
• Past history of abuse of prescription medications or illicit drugs
• Requests for specific drugs, especially a preference for immediate-release over sustained-release preparations
• Positive urine drug test for illicit drugs or unauthorized drugs
• Appearing intoxicated
• Deterioration of function at work, in the family or socially

Conclusion

In spite of the widespread use of opioids in the management of CNCP conditions, there is a paucity of well-designed studies to make strong evidence-based recommendations. The specific recommendations made by the task force for various CNCP conditions are based on the best available evidence, the majority of which are not observed beyond 3 months' duration. Additional studies conducted over extended periods are therefore required.

Proper patient assessment is necessary before initiating a trial of opioid therapy. An opioid treatment agreement must be established and urine testing is recommended when aberrant drug behaviour is suspected. Regular follow-up with routine assessment of analgesia, activities of daily

living, aberrant behaviour and adverse effects will assist the physician in dose titration. Discontinuation of opioid therapy should be considered whenever therapeutic goals are not achieved.

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Appendix 1

Opioid Therapy Agreement for Chronic Pain Management

Dr. _____ is prescribing an opioid called _____ for you for a diagnosis of _____.

This decision was made because your condition is serious and/or other treatments have not helped your pain.

The purpose of this agreement is to protect your access to controlled substances and to protect our ability to prescribe for you.

The long-term use of opioids is controversial because of uncertainty regarding their long-term benefit and the risk of addiction.

(Males only) Chronic opioid use has been associated with low testosterone levels in male. This may affect your mood, stamina, physical performance and libido.

(Females only) If you plan to become pregnant or believe that you have become pregnant while taking opioids, you should inform your obstetrician and your pain physician. If you should carry a baby to delivery while taking opioids, the baby will be physically dependent on opioids.

Strict accountability is necessary for prescription of opioids and you agree to the following:

1. All opioids must come from your pain physician whose signature appears below or, during his or her absence, by the covering physician.
2. All opioids must be obtained from your hospital pharmacy, where possible.
3. You may not share, sell, or allow others to have access to your opioid medications.
4. You are expected to inform your pain physician of any new medications or medical conditions, and of any adverse effects you experience from any of the medications that you take. You should not change the dose of your opioid therapy without informing your doctor.
5. The prescribing physician has permission to discuss all diagnostic and treatment details with other healthcare professionals who look after you for purposes of maintaining accountability.
6. These medications should not be stopped abruptly, as withdrawal symptoms are likely to develop.
7. Random urine or blood toxicology screens may be requested.
8. Original containers or blister packs of medications should be brought in during every consultation or as requested by your prescribing doctor.
9. Opioids may be hazardous or lethal to a person who is not tolerant to their effects, especially a child. You must keep them out of reach of such people.
10. Medications may not be replaced if they are lost, misplaced or destroyed intentionally or inadvertently. If your medication has been stolen, you must complete a police report regarding the theft.
11. Early refills will generally not be given. You must keep your scheduled appointments to obtain a refill of your medication.
12. If legal authorities have questions concerning your treatment, all confidentiality is waived and these authorities may be given full access to our records of opioid administration.
13. Failure to adhere to these policies may result in cessation of therapy with opioids.
14. Treatment with opioids is initially a trial and continued prescription will depend on whether opioids are beneficial for your condition. Your physician has the right, based on his professional opinion, not to escalate or to withdraw opioid therapy if your functional status has not improved with maintenance opioid therapy.

15. The risks of opioid therapy include constipation, nausea, vomiting, drowsiness, respiratory depression etc. The potential benefits of opioid therapy include better pain relief, improved sleep and function. You acknowledge that you have received such advice.
16. You affirm that you have full right and power to sign and be bound by this agreement, and that you have read, understood, and accepted all of its terms.

Doctor's Signature and Date	Patient's Signature and Date
Doctor's Name and Stamp	Patient's Name