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Responsible Prescribing of Opioids for the Management of Chronic Pain

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Contents

Abstract

The management of patients with chronic pain is a common clinical challenge. Indeed, chronic pain is often inadequately controlled in patients with cancer and in those with non-cancer chronic pain. Because of the complex nature of chronic pain, successful long-term treatment is more difficult than for acute pain. Most often acute pain is nociceptive, whereas chronic pain can be nociceptive (i.e., in

response to noxious stimuli), neuropathic (i.e., initiated by a primary lesion or dysfunction in the nervous system) or mixed in origin.

Opioids are the current standard of care for the treatment of moderate or severe nociceptive pain. Opioids mediate their actions by binding and activating receptors both in the peripheral nervous system and those that are found in inhibitory pain circuits that descend from the midbrain to the spinal cord dorsal horn. Opioid agonists exert a number of physiological responses including analgesia, which increases with increasing doses.

The use of opioids to manage pain in patients with cancer is well accepted. The WHO step-wise algorithm for analgesic therapy based on pain severity reserves the use of opioid therapy for moderate and severe pain. The WHO algorithm has proven to be highly effective for the management of cancer pain. However, the use of opioids to treat patients with chronic non-cancer pain is controversial because of concerns about efficacy and safety, and the possibility of addiction or abuse. The results of clinical surveys and retrospective case series involving patients with non-cancer chronic pain have been inconsistent in regard to resolving these controversial issues.

The oral route of drug administration is most appropriate for patients receiving opioids; although rectal, transdermal and parenteral routes of administration are used in specific situations. For continuous chronic pain, opioids should be administered around-the-clock and several long-acting formulations are available that require administration only once or twice daily. Opioid doses should be titrated according to agent-specific schedules to maximise pain relief and maintain tolerability. Adverse effects include constipation, nausea and vomiting, sedation, cognitive impairment and respiratory depression. Tolerance to the analgesic and adverse effects as well as physical dependence, which causes withdrawal symptoms upon discontinuance, may occur with opioid use. Estimates of addiction rates among patients with chronic non-cancer pain range from 3.2 to 18.9%.

Successful pain treatment and symptom management is an attainable goal for the majority of patients with chronic pain. Further controlled clinical trials are needed to define the role of opioid therapy in chronic non-cancer pain, and to establish criteria for patient selection and specific treatment algorithms.

1. Chronic Pain and the Use of Opioids

Over the past 10–20 years, several studies were published documenting inadequate pain control in patients with postoperative, cancer and non-malignant chronic pain.[1-4] This information spurred professional societies and governmental and regulatory agencies to develop standards and guidelines for the management of acute and cancer pain.[5] These organisations, which included the WHO, the International Association for the Study of Pain (IASP), the US Agency for Health Care Policy and Research (AHCPR), and the Joint Commission for Accreditation of Healthcare Organisations (JCAHO), continue to work toward the humane goals of relieving unnecessary pain and improving patient quality of life. While successful in changing many of the perceptions and practices of healthcare professionals who treat pain, barriers, limitations and controversies remain, particularly in the treatment of chronic pain. This article reviews the role of commonly used opioids for the treatment of chronic pain, with a focus on selecting treatments based on the individual patient's need for pain control.

2. Pain Definitions

The IASP defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'.[6] Pain is generally categorised as acute or chronic. Acute pain serves the necessary function of alerting the body to harmful or potentially harmful stimuli. It occurs because of trauma, a medical or surgical procedure, or a disease flare concomitant to a chronic medical condition. Acute pain typically is of short duration and its treatment is relatively straightforward.[7] In contrast, chronic pain is far more complex and difficult to treat. It persists longer than 3–6 months – beyond the time that healing normally occurs. While it is frequently associated with disease processes such as cancer, AIDS, rheumatoid arthritis and osteoarthritis, it also occurs in disorders that do not have a specific diagnosis, such as low back pain and failed back surgery.[7] Chronic pain syndromes unfortunately are quite common. From estimates of the prevalence of individual conditions, Bonica concluded that one in three Americans experiences chronic pain.[8] Table I provides characteristics of chronic pain.

Chronic pain can be nociceptive, neuropathic or mixed in origin. Nociceptive pain initiates when primary afferent nociceptors in the peripheral nervous system – Aδ fibres and C fibres – are activated by noxious thermal, mechanical or chemical stimuli secondary to tissue injury. After peripheral stimulation, information is transmitted to second-order projection neurones in the dorsal horn of the spinal cord, where pain signals are interpreted and modulated. Second-order projection neurones then transmit pain signals through several ascending tracts that terminate throughout the brain stem, thalamus and cortex. The transmission of impulses in ascending pathways is modified by endogenous opiates, as well as non-opiate inhibitory influences from descending pathways that moderate pain.[9] Pain perception reflects a complex interplay between stimulation and inhibition.

Table I. Characteristics of chronic pain

Pain lasting beyond the time that normal healing occurs (>3–6 months)
Associated with specific and non-specific medical conditions:
cancer
AIDS
rheumatoid arthritis
osteoarthritis
low back pain
spinal stenosis
failed back surgery
Estimated to occur in one of every three Americans
May be nociceptive and/or neuropathic in origin

Neuropathic pain is caused or initiated when tissue injury leads to a primary lesion or dysfunction in the nervous system itself.[6] Accumulating evidence suggests that a key pathogenic event in neuropathic pain occurs in the central nervous system (CNS). A continuing barrage of spontaneous pain signals from damaged C fibre nociceptors causes spinal cord neurones in the dorsal horn to become hyperexcitable, a phenomenon known as central sensitisation. Central sensitisation manifests in symptoms such as hyperalgesia, a heightened response to pain, and secondary hyperalgesia, pain sensitivity beyond the primary site of tissue injury. Over time, allodynia, the sensation of pain from a normally non-painful stimulus, also can develop as a result of abnormal central processing of input from Aβ fibres.[10,11] While central sensitisation is recognised to be a critical element, the development of neuropathic pain is a complex process involving numerous putative mechanisms. Chronic pain is the end result of an interplay of pathogenic mechanisms that may be nociceptive, neuropathic or mixed in origin.

Studies in experimental animal models suggest that chronic exposure to opioids can have the paradoxical effect of inducing a state of hyperexcitability in the CNS. Rohde and colleagues have shown that the tolerance that occurs with long-term exposure to morphine has features in common with central sensitisation.[12] The clinical relevance of these findings remains to be fully explored. Some have suggested that this phenomenon in part explains the limited utility of opioids

in non-nociceptive pain that has been demonstrated in some, but not all, clinical studies.[13,14]

3. Opioid Actions

Opioids are the current standard of care for the treatment of moderate to severe pain. In fact, they have been the mainstay of pain treatment for thousands of years.[15] In ancient times, opium, which is derived from the juice of the opium poppy, *Papaver somniferum*, was used to fight cough and diarrhoea, and to relieve pain through its euphoria-inducing properties.[16] Opium contains more than 20 active alkaloid compounds, of which morphine is the most potent and was the first to be isolated, in 1806.[15] The purification of other compounds from opium soon followed and widespread use of purified agents began in the mid-nineteenth century. Currently available opioid drugs include products directly derived from opium, such as morphine, codeine and thebaine, and their many semi-synthetic derivatives.[15]

Opioids mediate their actions by binding and activating receptors that comprise part of an endogenous descending pathway that normally operates to modulate pain. Endogenous opioid peptides (met-enkephalin, leu-enkephalin, β-endorphin, dynorphin A, dynorphin B, α-neoendorphin) and opioid receptors are found throughout inhibitory pain circuits, which descend from the midbrain via the rostral ventromedial medulla to the spinal cord dorsal horn.[15] Opioid receptors and endogenous opioid peptides also have been identified in the peripheral nervous system. During inflammation, endogenous opioids secreted by immune and inflammatory cells have been shown to activate opioid receptors on sensory nerve terminals to inhibit nociception.[17]

Opioid receptors consist of three subtypes: μ (mu), δ (delta) and κ (kappa). Most of the clinically useful opioid drugs, for which morphine serves as the prototype, are relatively selective for μ receptors. These drugs are full agonists. Their interactions with opioid receptors stimulate physiological responses. In addition to analgesia, stimulation of μ receptors affects mood and rewarding behaviour, and alters respiratory, cardiovascular, gastrointestinal and neuroendocrine functions.[15] Full agonists have no ceiling to their analgesia. Analgesia increases as the dose is raised until adequate pain control is achieved or dose-limiting adverse effects occur.[18] In practice, this requires dose escalation to identify the balance between maximum analgesic efficacy and tolerability of adverse effects.[18]

4. Considerations in Chronic Pain Management

It is well recognised that patient responses to pain as well as to different opioid agents can be highly variable.[19] Dose escalation in one patient may result in successful pain relief, whereas the same agent in another patient may cause intolerable adverse effects without adequate pain control. While the mechanisms that underlie these differences are not well understood, it is obvious that clinicians must be knowledgeable in the use of commonly available agents in order to effectively individualise treatment.[15] In addition, they must know general principles of opioid treatment: whom to treat; how to match analgesic therapy to pain severity; available routes of administration; appropriate dose administration regimens; dosage levels for treatment initiation and titration; common adverse events; and effects of opioid therapy such as tolerance to most adverse effects and physical dependence. An overview of these issues and of commonly available agents is provided in the following subsections.

4.1 Patient Selection

Opioid therapy is the cornerstone of pain management in patients with cancer or those who are terminally ill. The role of opioids in relieving moderate to severe pain in these patient populations is universally accepted and supported. In contrast, the use of opioids to relieve pain in patients with chronic non-cancer pain remains quite controversial. This controversy is based on concerns that opioids may be ineffective, unsafe, and lead to addiction or abuse.[20] The substantial clinical experience in patients with cancer has been encouraging. Not

only have opioids proved to be effective and 'safe', but also problems stemming from addiction or abuse have been minimal.[20,21] However, there are further concerns that opioid therapy in patients with chronic non-cancer pain would shift the patient's sense of control toward an external agent for relief of pain, engendering a sense of dependency on the medical system, and neglecting other treatment goals such as increased function and return to normal activities.[22]

There are few good data on the efficacy of opioids in patients with chronic non-cancer pain. Clinical surveys and case series have provided much of the published information. Overall, large clinical surveys generally reported favourable outcomes in selected patients.[20,21] On the other hand, retrospective case series, most of which originated from pain management programmes, reported few treatment benefits.[20,21] Several randomised clinical trials have sought to determine whether opioids are effective in patients with neuropathic pain (extensively reviewed by Dellemijn[23]). Results were variable: some studies found clear dose-response analgesic effects in patients with neuropathic pain, while others suggested that opioids were ineffective.[14,21,23] There have also been a number of randomised trials that have specifically evaluated the long-term efficacy of opioids in patients with chronic non-cancer pain (reviewed by Dickinson et al.[21]).[24-28] These studies have uniformly shown that opioids are effective in relieving pain, but effects of opioid treatment on disability, emotional distress, quality of life, and psychological or functional improvements have been variable.[21] For example, one study in patients with back pain found that patients reported significantly less pain and improved mood, but few differences were found in activity or hours asleep.[26]

Despite these mixed findings, there are subgroups of patients with chronic non-cancer pain who benefit from regular administration of opioid drugs.[27] Overall, studies have suggested that patients with nociceptive pain are the most responsive to opioids and derive the most benefit from long-term treatment. Moreover, although patients with neuropathic pain are less likely to respond, there is a subset of patients that do gain pain relief without intolerable adverse effects.[21] Therefore, the diagnosis of neuropathic pain does not preclude opioid therapy. Although the inferred pathophysiology might suggest the likelihood of a response, opioid responsiveness cannot be reliably predicted in individual patients. Indeed, it has been suggested that opioid responsiveness represents a continuum with extensive overlap in the responsiveness of pain that is mediated by neuropathic, nociceptive and mixed pain mechanisms. A trial of opioid therapy will identify patients with chronic non-cancer pain who may gain substantial clinical benefit.[29] Further controlled clinical trials clearly are needed to better define the role of long-term opioid therapy in chronic non-cancer pain, and to establish criteria for patient selection and specific treatment algorithms.

4.2 Treatment Based on Pain Severity: the WHO Analgesic Ladder

A patient's report of pain is the most important factor in determining the degree of pain relief needed. The WHO has established a stepwise algorithm (the 'WHO Analgesic Ladder') for analgesic therapy for cancer pain based on severity.[30] Step 1 of the ladder recommends treatment for mild pain: paracetamol (acetaminophen), aspirin (acetylsalicylic acid) or other non-steroidal anti-inflammatory drugs (NSAIDs). If pain persists or increases, the addition of opioids, such as codeine, hydrocodone and oxycodone, is recommended as step 2. Step 2 opioids are frequently administered in fixed-dose combinations with paracetamol (acetaminophen) or aspirin. Step 3 opioids are prescribed when moderate-to-severe pain control is needed. Step 3 opioids include morphine, oxycodone, hydromorphone, methadone and fentanyl. Adjuvant agents may be added at any step to enhance analgesic efficacy, treat concurrent symptoms that exacerbate pain and produce analgesic activity for specific types of pain.[31]

The WHO approach includes a framework for administering analgesics, which consists of the following five elements.

- By mouth: oral administration is effective, inexpensive and easy to titrate.
- By the clock: analgesics should be administered throughout the day using routine administration of immediate-release (IR) formulations or sustained-release (SR) preparations so that continuous pain relief is achieved.
- By the ladder: pain medication should be changed according to the severity of pain, as specified by the analgesic ladder.
- For the individual: because response to pain medication may differ, individualised treatment is required so that adequate pain relief is obtained for each patient.
- With attention to detail: patients must be closely monitored; pain assessment and frequent reassessment are cornerstones of effective pain management.

The WHO three-step analgesic ladder has been extensively validated in numerous studies and shown to be highly effective in managing cancer pain. For example, in a 10-year prospective study involving over 2 000 patients, 76% of patients reported good pain relief using analgesics prescribed according to the WHO guidelines, with a low rate of analgesia-associated complications.[32] In a second study involving 174 patients, oral drug therapy was successful in managing pain in 89% of patients. More than 80% described their pain as ranging between 'none' and 'moderate' when WHO guidelines were followed.[33]

The WHO ladder has been validated in patients with cancer pain, but it has not been validated in non-cancer settings. Several guidelines have recently been proposed for the use of opioids in chronic non-cancer pain.[21,34-36] These guidelines note the substantial personal and societal costs of chronic non-cancer pain and recognise that opioid therapy may provide benefits for some patients. Overall, these guidelines acknowledge that good medical practice should guide prescribing of opioids and that treatment should be tailored to the individual patient. Several suggest that opioids should be considered only after adequate trials of other alternative agents.[21] Common elements in these guidelines include: a thorough evaluation of the patient; generation of a clear treatment plan and objectives; a periodic review of treatment to assess safety, efficacy, compliance, misuse and to reassess pain; consultation or referral to other specialists in the case of comorbid psychiatric disorders or when there is a high index of suspicion for abuse; and detailed documentation of treatment (table II). However, empirical studies must yet be performed to substantiate these guidelines. Furthermore, minimal guidance is provided regarding the key issue of patient selection.[21]

The recent experience with prescription opioid drug abuse has heightened the need for good clinical judgement and increased attention to guideline recommendations. In a bulletin from the American Pain Society, it was stressed that 'opioids alone are rarely effective in the treatment of chronic pain. However, opioids can be effective in some patients as part of an interdisciplinary approach to diagnosis and treatment of chronic pain'. A balanced approach is now advocated, one that is able to address concerns of drug abuse and misuse, while preserving access for appropriate use.[37]

4.3 Route of Administration

The route of administration selected should be the safest and least invasive method that will provide effective analgesia.[18] For most patients, the oral route of administration is preferred because it is the most convenient, inexpensive and easy to titrate.[30,31] Other routes of administration are available if oral administration is not possible. For patients who cannot swallow or who have gastrointestinal obstruction, the rectal and transdermal routes provide alternatives that are less invasive than parenteral injection. Parenteral routes are preferred when patients require rapid onset of analgesia or need very high doses of opioids which cannot otherwise be conveniently administered.[18]

Table II. Common elements of guidelines for the use of opioids to treat patients with chronic non-cancer pain

Patient evaluation
Obtain a pain history and assess the impact of pain on social, occupational, physical and psychological function
Review previous diagnostic studies, other consultations and opinions, and previous surgical and medical interventions
Review medical, psychiatric and substance abuse history, and assess coexisting diseases or conditions
Conduct a directed physical examination
Treatment plan and objectives
Establish a working diagnosis and medical indication for treatment with opioids
Outline measurable outcome objectives (e.g., pain control, improvement in activities of daily living, functional improvement, sleep)
Provide informed consent on the risks and benefits associated with opioids
Need copy of informed consent
Discuss the conditions under which opioids will be prescribed and discontinued
Periodic review
Assess the safety and efficacy of treatment (e.g., subjective pain ratings, functional changes, quality of life, adverse effects, improvement in mood)
Assess for compliance and evidence of possible misuse (e.g., through use of screening tools, urine toxicology)
Reassess the nature of the pain complaint to confirm that opioid treatment is still warranted
Consultation
Referral to a specialist in pain medicine may be warranted depending on the level of prescribing comfort, expertise of the practitioner and the complexity of the problem
Referral to an addiction specialist is often indicated for patients with a history of addiction or substance use disorder
Referral to a psychiatrist or psychologist may be indicated for patients with significant psychiatric comorbidity
Documentation on the following areas should be maintained and updated on a regular basis
Evaluation
Diagnosis (including the reason for prescribing opioids if not obvious from the diagnosis)
All prescriptions
Overall plan to manage pain
Consultations received
Written instructions to the patient, the patient's consent and agreements with the patient

4.4 Dose Administration Regimens

Opioids should be administered around-the-clock for patients with chronic pain so that pain relief is continuous.[15,18] When this type of regimen is employed using a conventional IR formulation of morphine, however, administration every 3–4 hours is required. This may result in interruption of sleep, inconvenience to the patient, adverse effects leading to non-compliance and the potential for medical errors.[38] Over the past decade, several long-acting formulations have been developed for twice or once daily administration, including morphine-containing formulations with recommended dosage intervals of 8–12 hours (for a comprehensive listing of the trade names associated with morphine solutions, see *Martindale: The Complete Drug Reference*[39]). One oral morphine formulation is recommended for once daily administration (Kadian®/Kapanol®**1**).[40] The efficacy and safety of the once daily formulation has been directly compared with a formulation indicated for twice daily administration (MS Contin®) in a double-blind study in 152 patients with cancer pain.[38] The once daily and twice daily formulations provided similar pain control. The incidence of breakthrough pain, measured by the number of patients who required rescue medication, also was comparable between the two formulations. There were no significant differences between the formulations in the frequency or severity of adverse events. Pa-

1 Use of trade names is for product identification purposes only and does not imply endorsement.

tient global assessment of pain control significantly favoured the once daily formulation.[38]

Oxycodone is available in a SR formulation indicated for twice daily administration. The efficacy of this formulation in the treatment of chronic cancer pain has been compared with IR oxycodone in a multicentre, randomised, double-blind, parallel-group study in 111 patients.[41] Patients were treated with IR oxycodone 15mg four times daily or SR oxycodone 30mg every 12 hours for 5 days. The 5-day mean pain intensity scores were 1.1 ± 0.1 for the IR preparation and 1.4 ± 0.1 for the SR preparation. Furthermore, adverse events and discontinuation rates for the two treated groups were similar, indicating that patients can be equally well treated whether they are administered IR or SR oxycodone.[41]

Fentanyl is available in a transdermal formulation. The usual dosage interval is 72 hours, although some patients require a dosage interval of 48 hours to maintain adequate analgesia.[18,42] The efficacy of transdermal fentanyl and a twice daily oral SR morphine preparation (MS Contin®) were compared in 202 patients with cancer in a randomised, open, two-period, crossover study. Both treatments were equally effective for pain control as assessed by the Memorial Pain Assessment Card and European Organisation for Research and Treatment of Cancer (EORTC) pain scores. Regarding adverse effects, fentanyl was associated with significantly less constipation and daytime drowsiness, but greater sleep disturbance and shorter sleep duration than the morphine formulation.[43] In a recent study, quality of life assessment and patient preference favoured transdermal fentanyl.[44]

All patients with cancer who receive an around-the-clock regimen should be supplied with rescue medication to be used on an as-needed basis should breakthrough pain occur. A limited supply of a short-acting rescue medication should also be made available for patients with chronic non-cancer pain.

4.5 Dosage Initiation and Titration

Treatment in opioid-naïve patients is often initiated using a conventional formulation. Recommended starting doses and schedules are provided in table III. Opioids with short half-lives such as morphine, hydromorphone, fentanyl or oxycodone are preferred because they are easy to titrate. Titration is necessary to establish the optimal balance between analgesia and adverse effects; titration starting with low doses also is necessary to avoid severe adverse effects. The rate of titration should be guided by the patient's report of pain intensity.[18]

Table III. Dose administration data for opioid analgesics in patients with moderate to severe chronic pain[15]

Drug	Approximate equianalgesic oral dose	Approximate equianalgesic parenteral dose	Recommended starting dose (adults >50kg bodyweight)	
			Oral	Parenteral
Morphine	20–60mg/day initial starting dose; then 30mg q3–4h (IR)	10mg q3–4h	30mg q3–4h[a]	10mg q3–4h (use of IV route is preferable)
Fentanyl		0.1[b]		
Oxycodone	30mg q3–4h (IR)	NA	10mg q3–4h	NA
Hydromorphone[c]	7.5mg q3–4h	1.5mg q3–4h	6mg q3–4h	1.5mg q3–4h
Methadone	5–10mg q6–8h	5–10mg q6–8h	5–10mg q6–8h	2.5–5mg q6–8h

a Starting dose of 20 to 60mg/day may be used to avoid adverse effects such as vomiting.

b Transdermal fentanyl 100 μg/hr is approximately equivalent to 2–4 mg/hr of IV morphine. A conversion factor for transdermal fentanyl that can be used for equianalegesic calculation is 17 μg/hr. Roughly, the dose of transdermal fentanyl in μg/hr is approximately one-half of the 24-hour dose of oral morphine.[45]

c For morphine and hydromorphone, rectal administration is an alternate route for patients unable to take oral medication, but equianalgesic doses may differ from oral and parenteral doses because of pharmacokinetic differences.

IR = immediate release; **IV** = intravenous; **NA** = not available; **qXh** = every X hours.

Under certain circumstances, it is necessary to switch to an alternative opioid. For instance, a patient may experience dose-limiting adverse effects without achieving adequate pain control. An equianalgesic dose table should be used to determine the starting dose of the new drug (table III). When switching to a different opioid, it is recommended that only one-third to one-half of the calculated equianalgesic dose should be administered initially.[45]

4.6 Adverse Effects of Opioid Therapy

4.6.1 Constipation

Constipation is a common adverse effect of long-term opioid therapy.[18,31] Because it is so common, laxative medications should be used concurrently in most patients. Mild constipation may be managed with increased fibre consumption and mild laxatives. Severe constipation can be treated with stimulating cathartic drugs such as bisacodyl, senna or phenolphthalein. Stool softeners in combination with a stimulant laxative also may be helpful.[18,31]

4.6.2 Nausea and Vomiting

Nausea and vomiting are common upon initiation of opioid therapy, occurring in approximately 30–60% of patients.[46,47] A majority of patients will habituate to nausea and vomiting over the first week of treatment. Three mechanisms are responsible for these adverse effects: opioid activation of a chemoreceptor trigger zone for emesis, reduced gastrointestinal motility, or increased vestibular sensitivity.[48]

Treatment consists of concurrent use of antiemetic agents, which include metoclopramide, antihistamines, haloperidol, chlorpromazine, prochlorperazine, scopolamine, or 5-HT_3 receptor antagonists (ondansetron, tropisetron). Metoclopramide is generally recommended as first-line therapy because it improves gastrointestinal motility and acts at the chemoreceptor trigger zone. Antihistamines may be used in patients when vestibular sensitivity is suspected or in the case of bowel obstruction. Haloperidol also may be used in patients with bowel obstruction. Chlorpromazine, an agent with modest antiemetic activity, is another option, although it is associated with a high incidence of sedation, postural hypotension, and anticholinergic adverse events. Prochlorperazine is a stronger antiemetic but causes greater extrapyramidal effects. Scopolamine may be used, but this agent often is limited by anticholinergic side effects. The role of the 5-HT_3 receptor antagonists in patients with opioid-induced emesis remains to be better established.[48]

4.6.3 Sedation and Cognitive Impairment

Somnolence or cognitive impairment may occur when opioid administration is initiated or during significant dose escalation. It is generally transitory, as tolerance usually develops rapidly.[31] Several research groups have sought to assess the impact of long-term opioid use on psychomotor performance using measures of driving ability.[49,50] In one study, psychological and neurological tests originally designed for professional motor vehicle drivers were conducted in 24 patients on continuous morphine for cancer pain and 25 patients with cancer who were pain-free and did not require analgesia. Although results were slightly worse in patients taking morphine, there were significant between-group differences in only one measure. The authors concluded that long-term morphine treatment had only a slight and selective effect on functions related to driving.[50] Galski and colleagues used several off-road tests, including pre-driver evaluation (PDE), a simulator evaluation (SDE), and behavioural observation during simulator performance to assess driving ability in a small pilot study involving 16 patients with chronic non-cancer pain who were being treated with long-term opioid therapy.[49] These 16 patients were compared with a historical control group of cerebrally compromised patients who had taken similar tests as well as an on-road test. Patients who were receiving long-term opioid therapy generally performed better than the historical controls. While the results of this small pilot study remain to be confirmed, it suggested that long-term opioid therapy did not significantly impair perception, cognition, coordination and behaviour

measured in off-road tests.[49] However, it must be noted that the issue of driving ability in patients receiving long-term opioid treatment for chronic pain is an important one that requires further clinical research.

4.6.4 Respiratory Depression

Respiratory depression is the most dangerous adverse effect of opioid therapy. However, respiratory depression is rare when the opioid dose is carefully titrated[18] and patients receiving long-term opioid therapy usually develop tolerance to respiratory-depressant effects.[31] Physical stimulation of a symptomatic patient may be enough to prevent significant hypoventilation. Because of the risk of withdrawal syndrome and return of pain in patients who are receiving opioids on a long-term basis, opioid antagonists should be used with caution.[31]

4.6.5 Tolerance and Physical Dependence

Tolerance to the pain-relieving effects of opioids describes the need to increase the dose over an extended period of time to maintain pain relief. Patients also develop tolerance to the adverse effects of an opioid, the exception being constipation.[31] Physical dependence manifests as a withdrawal syndrome when dosage is abruptly reduced or an opioid antagonist is administered.[18] Symptoms of physical dependence can also manifest after tapering the dose gradually and, particularly, after stopping the opioid. Typical signs are anxiety, irritability, chills and hot flashes, joint pain, lacrimation, rhinorrhoea, diaphoresis, sleep disturbances, nausea, vomiting, and abdominal cramps and diarrhoea.[31] It is not a manifestation of addiction nor is it a clinical problem if patients are warned not to abruptly discontinue drug therapy. If treatment discontinuation is indicated, the withdrawal syndrome can generally be avoided using a tapering regimen.[18]

Physical dependence and addiction are not interchangeable terms. Addiction is psychological dependence on the use of substances for their psychic effects. It is characterised by a core group of aberrant drug-related behaviours, including loss of control over drug use, compulsive drug use and continued use despite harm.[20] Selling prescription drugs, prescription forgery, stealing drugs from others and obtaining prescription drugs from non-medical sources are clear indicators of addiction and/or abuse. On the other hand, less overt behaviours, such as aggressive complaining about the need for more drugs or drug hoarding during periods of reduced symptoms, may be more difficult to assess.[20] Other signs of concern include repeated lost prescriptions, multiple requests for early refills and a desire to continue excessive use of short-acting opioids. If there are multiple episodes of less obvious behaviours, further assessments may be necessary. Increased attention to the issue of addiction and problematic prescription opioid use has led to the development of specific screening tools to assess addictive disease in patients with chronic pain, agreements for patients that clearly specify conditions for opioid treatment and urine toxicology to monitor use.[36,51,52]

Clinicians should be alert to the signs of addiction, particularly when treating patients with existing alcoholism or drug abuse/addiction history. It is important to note that exposure of patients to opioids does not necessarily cause addiction. Rates of drug abuse and addiction in patients with chronic non-cancer pain have been estimated to be between 3.2 and 18.9%.[21] A recent retrospective survey of medical records assessed the medical use of commonly used opioid agents in relationship to hospital emergency department admissions resulting from drug abuse.[53] Between 1990 and 1996, the medical use of morphine, fentanyl, oxycodone and hydromorphone to treat pain increased substantially. Over the same period, reports of opioid abuse relative to total drug abuse decreased from 5.1 to 3.8%. Therefore, the trend of increasing medical use of opioids was not associated with proportional increases in opioid abuse. The results of this survey address an important barrier to effective pain management by overturning the notion that increased medical use of opioids leads to abuse.[53]

5. Opioids for Treating Chronic Pain

Commonly available opioid agents are described in this section. All of these agents are strong opioids and full agonist drugs. They are discussed here based on their formulation, and are subdivided into short-acting opioids, opioids with an intermediate duration of action, long-acting opioids, and those with actions of a variable length. New formulations and delivery systems are responsible for the decreased dose administration intervals and greater convenience afforded by longer-acting preparations.

5.1 Short-Acting Opioids

5.1.1 Morphine

IR morphine is the most widely used opioid and the standard against which new agents are measured.[15] By convention, the relative potency of commonly used opioids is based upon a comparison with 10mg parenteral morphine.[18] The elimination half-life of IR morphine in patients with normal renal function is 2 hours, and the duration of action is 3–6 hours. IR morphine is available in a wide variety of preparations, including oral capsules, solution and tablets; parenteral injection for intramuscular, intravenous, subcutaneous, epidural and intrathecal use; and by rectal suppository.

5.1.2 Oxycodone

Oxycodone, combined with paracetamol (acetaminophen) or aspirin, is a step 2 analgesic used to control moderate pain. As a single agent, it is used to manage severe pain.[18] It has a higher oral bioavailability than morphine and comparable analgesic potency.[18] The half-life after single-dose administration of oral oxycodone has been shown to be approximately 3.5 hours,[54] although others have found a slower elimination half-life in the range of 5 hours.[55] These differences may in part be explained by individual variations in metabolism, highlighting the need for careful monitoring during the initial titration phase.

5.1.3 Hydromorphone

Hydromorphone has an elimination half-life of 2–3 hours and a duration of action of 2–4 hours.[18] It is available in a variety of formulations for oral, parenteral and rectal administration. Because of its high solubility, it can be prepared at a high concentration for parenteral injection. It therefore can be used in patients who require large doses of opioids for adequate pain relief and it is commonly used for continuous subcutaneous infusion.[18,56]

5.2 Opioids with an Intermediate Duration of Action

5.2.1 Morphine

Several SR morphine preparations are available for twice-daily administration (eg, MS Contin®, Oramorph SR®). It is important to note that the pharmacokinetic profiles of twice-daily formulations are quite different from IR preparations. An IR dose of morphine reaches a peak plasma concentration within the first hour and has an elimination half-life of 2–4 hours. Twice-daily formulations have an approximate 3- to 6-hour elimination half-life, the peak is attenuated in comparison to IR formulations and the plasma concentrations are sustained over a 12-hour period.[18] The recommended dosage interval is every 12 hours, although the dose administration regimen should be adjusted on the basis of individual patient needs.[57]

5.2.2 Oxycodone

An SR oxycodone formulation for twice-daily administration is available (Oxycontin®). It displays a biphasic pharmacokinetic profile, with an initial half time of absorption of 0.6 hours and a second half time of absorption of 6.9 hours. This represents an initial release of oxycodone from the tablet, followed by a prolonged release. The half-life of elimination of SR oxycodone is 4.5 hours.[58]

Although package inserts for SR oxycodone suggest an equivalency ratio of 2 : 1 for oral morphine to oral oxycodone, others recommend a milligram-to-milligram conversion (1 : 1) in the opioid-tolerant patient. Ratios of 1 : 1 and 1.3 : 1

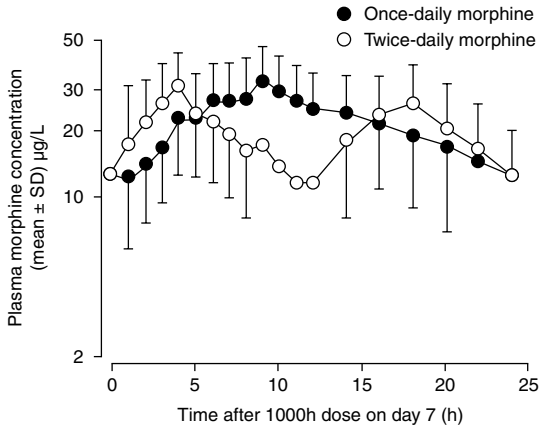

Fig. 1. Mean (±SD) plasma morphine concentration as a function of time at steady state for a once-daily morphine formulation (Kadian®/Kapanol®, closed circles) and a twice-daily morphine formulation (MS Contin®, open circles) [reproduced with permission from Gourlay[40]].

(oral oxycodone to oral morphine) have been found to be effective and safely used in chronic cancer pain.[44]

5.3 Long-Acting Opioids

5.3.1 Once-Daily Morphine

One oral morphine formulation is recommended for once-daily administration (Kadian®/Kapanol®).[40] In contrast to SR morphine for twice-daily administration, the once-daily SR morphine preparation has an elimination half-life of approximately 10 hours.[40] As noted earlier, the safety and efficacy of once daily administration has been established.[38] Figure 1 shows the mean plasma concentrations of morphine as a function of time at steady state for the once-daily formulation administered every 24 hours and a twice-daily morphine formulation (MS Contin®) administered every 12 hours.[59] The once-daily formulation demonstrated a less variable pharmacokinetic profile compared with the twice-daily formulation even though the dose administration interval for the once-daily formulation was twice that of the twice-daily formulation.[59] Both formulations provided excellent pain control.[40]

The once-daily formulation also is effective and can be safely used for twice-daily administration.[38] Figure 2 shows plasma morphine concentrations at steady state following administration of an IR morphine solution every 4 hours, and a twice-daily and a once-daily formulation administered every 12 hours.[60] Comparison with the once-daily formulation, the twice-daily formulation released proportionally more morphine in the first 4-hour time interval, equivalent amounts between 4–8 hours, and significantly less morphine in the 8- to 12-hour time interval. These results are consistent with clinical experience, which indicates that the twice-a-day formulation, in a percentage of patients, requires administration every 8 hours. In contrast, the relatively flat plasma morphine concentration-time profile for the once-daily formulation indicates that it can be administered at 12-hour intervals.[60]

5.3.2 Transdermal Fentanyl

Fentanyl is a semisynthetic opioid that is approximately 100 times more potent than morphine.[15] Fentanyl, available in a transdermal for-

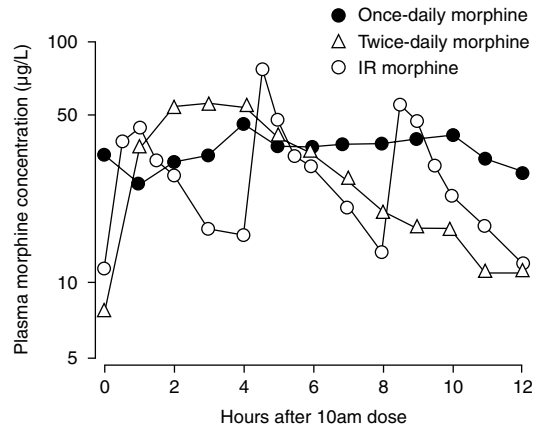

Fig. 2. Plasma morphine concentrations in a representative patient as a function of time at steady state following the administration of the same morphine dose (120mg/24h). A long-acting morphine formulation (Kadian®/Kapanol®, closed circles) and a twice-daily formulation (MS Contin®, open triangles) were administered twice daily. Immediate-release (IR) morphine solution (open circles) was administered every 4 hours (reproduced with permission from Gourlay[60]).

Table IV. Barriers to cancer pain management

Problems related to healthcare professionals	Inadequate knowledge of pain management	
	Poor assessment of pain	
	Concern about regulation of controlled substances	
	Fear of patient addiction	
	Concern about adverse effects of analgesia	
	Concern about patients becoming tolerant to analgesics	
Problems related to patients	Reluctance to report pain	Concern about distracting physicians from treatment of underlying disease
		Fear that pain means disease is worse
		Concern about not being a 'good' patient
	Reluctance to take pain medication	Fear of addiction or of being thought of as an addict
		Worries about unmanageable adverse effects
		Concern about becoming tolerant to pain medications
Problems related to the healthcare system	Low priority given specifically to cancer pain treatment	Inadequate reimbursement
		The most appropriate treatment may not be reimbursed or may be too costly for families
	Restrictive regulation of controlled substances	
	Problems of availability of or access to treatment	

mulation, is released from the transdermal reservoir at a nearly constant rate; serum concentrations increase gradually after application, level off at 12–24 hours and then decline gradually.[18] When the patch is removed, the mean apparent half-life is approximately 17 hours (range: 13–22 hours). There is significant interindividual variability in fentanyl bioavailability.[18,42] One limitation to its use is poor adhesion to the skin of some patients.[18]

5.4 Opioids with a Variable Duration of Action

5.4.1 Methadone

Methadone is used to control pain, and to treat opioid abstinence syndromes and heroin users.[15] It has a higher oral bioavailability than morphine, a comparable duration of action of 4–8 hours and a much longer elimination half-life of 15–48 hours.[18] Methadone has non-competitive antagonistic activity at N-methyl-D-aspartate (NMDA) receptors, which suggests that it may have clinical utility in treating patients with neuropathic pain.[61] Methadone is a difficult drug to titrate because of its variable half-life and because plasma concentrations tend to rise with repeated dose administration. Methadone and morphine have been shown to be equipotent in single-dose studies but methadone is several times more potent than morphine with repeated administration.[18] This enables either lower dosage or longer dosage intervals. Both oral and parenteral routes are available; the subcutaneous route is not recommended because it causes local skin irritation.[18] An advantage to the use of methadone is that it is relatively inexpensive.

6. Challenges in Chronic Pain Management

Despite published guidelines for pain management, patients experiencing chronic pain – even chronic cancer pain – may not receive adequate analgesia. Cleeland and colleagues surveyed 1 308 outpatients with metastatic cancer, of whom 65% had reported pain or had taken analgesic drugs daily during the week preceding the study. Over one-third of patients described their pain as severe enough to impair their ability to function. Among these patients, 42% of patients with pain were not given adequate analgesic therapy, as assessed by guidelines developed by the WHO.[62] Important barriers to pain management still exist. Jacox et al. found barriers to pain management in the AHCPR cancer pain management guidelines related to healthcare professionals, patients and the healthcare system itself (table IV).[31]

While there is no 'perfect' opioid analgesic that is capable of providing complete pain relief in all patients without any negative consequences, successful pain relief without intolerable adverse effects is an attainable goal for many patients with chronic pain.

The recognition that disabling pain is still under-recognised and under-treated has led to the development of standards that are explicit about the need for improved pain assessment and management. For example, the JCAHO recently developed evidence-based standards for pain assessment that call for healthcare organisations to:

- recognise patients' rights to pain control
- screen for pain
- perform a complete assessment when pain is present
- record the assessment in a way that facilitates regular reassessment and follow-up
- set a standard for monitoring and intervention
- educate providers and assure staff competency
- establish policies that support appropriate prescription or ordering of pain medicines
- educate patients and families
- include pain needs for symptom control in discharge planning and
- collect data to monitor the effectiveness and appropriateness of pain management.

The JCAHO pain management standards are a formal mandate to incorporate principles of pain management into the patterns of daily medical practice in order to address institutional barriers to adequate pain control.

7. Conclusions

It is essential that all clinicians who treat patients with chronic pain recognise that it is their responsibility to provide effective pain management. In order to do so, physicians must be knowledgeable in general principles of pain management, analgesic pharmacology, special issues related to opioid therapy and the use of commonly available agents. Opioid analgesics are the standard of care for patients with moderate-to-severe chronic cancer pain. How opioids should be used in patients with chronic non-cancer pain is still a matter of debate. Further controlled clinical trials are needed to better define the role of long-term opioid therapy in patients with chronic non-cancer pain, and to establish criteria for patient selection and specific treatment algorithms. Given the large personal and socioeconomic burdens of chronic non-cancer pain, there is an increasing consensus of opinion that opioid treatment should be considered in selected patients after reasonable trials of other agents have failed. In addition, it is recognised that careful attention must be paid to treating the whole patient and not just the pain. A balanced, multidisciplinary approach that takes into account the individual needs of each patient is advocated. The ultimate imperative for all clinicians is to relieve unnecessary pain.

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