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Comprehensive Review

Chronic Opioid Therapy for Chronic Non-Cancer Pain: A Review and Comparison of Treatment Guidelines

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Background: Long-term opioid use for chronic non-cancer pain has increased substantially in recent years despite the paucity of strong supporting scientific data and concerns regarding adverse effects and potential misuse.

Study Design: Review and summary of practice guidelines available on PubMed and Cochrane databases as well as on the Internet on chronic opioid therapy from June 2004 to June 2013.

Objective: To review expert-developed practice guidelines on chronic opioid therapy, published in different countries over the past decade in order to reveal similar principles of therapy and to provide useful information and references for future development of opioid guidelines to identify adequately supported practice points and areas in need of further scientific evidence.

Method: Seven guidelines were identified as pertaining specifically to the long-term use of opioids for general chronic non-cancer pain from an initial search of the PubMed/Medline and Cochrane databases using combinations of the search terms "opioid," "chronic opioid therapy," "chronic pain," "chronic non-cancer pain," "chronic non-malignant pain," "guidelines," "practice guidelines," and "clinical practice guidelines," filtered to include only articles on humans published in the English language over the past 10 years.

Results: All guidelines espouse an individual approach to management, beginning with a comprehensive patient evaluation, with particular focus on eliciting factors that may indicate potential drug misuse and abuse, and a trial of therapy to determine the course of treatment. Goals of treatment should be adequately discussed with and consented to by the patient. Opioids are generally not recommended as first-line therapy but, when used, clinicians should closely monitor patients for loss of response, adverse effects or aberrant behavior, and revise the treatment plan accordingly. Urine drug testing (UDT) may be used as a tool to monitor for aberrant behavior or drug misuse; opioid rotation may be considered when loss of response or adverse effects are a concern, at a starting dose lower than the calculated equianalgesic dose.

Limitations: Information on some African nations, countries in the Middle-East, and Pacific Islands is not available and therefore was not included in this review.

Conclusion: There is a growing body of scientific evidence to support opioid use in chronic pain. Future work should focus on continuing to generate good-quality evidence on the long-term benefits of opioid therapy, as well as scientific data to guide drug choice and dosing for specific conditions, populations, and situations.

Key words: Chronic pain, opioid, non-cancer pain, guidelines, opioid rotation, pain management, opioid therapy

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Despite the limited availability of strong scientific evidence to support long-term opioid therapy for chronic non-cancer pain (1), use of opioids has increased substantially through the years, with a corresponding increase in drug-related deaths and misuse (2-8). The addictive nature of opioids, in addition to their psychotropic effects, makes them particularly vulnerable to misuse and abuse (9). By 2007, abuse of prescription drugs in the United States had already surpassed that of traditionally abused drugs such as cocaine, methamphetamine, and heroin (10). Prescription drug abuse is also being increasingly reported in other parts of the world, including parts of Africa, South Asia, and Europe (10). Global data indicate that the average opioid/morphine equivalent consumption increased from 1.82 mg/person in 1980 to 61.66 mg/person in 2011 (11).

Although various risk factors have been identified for opioid misuse, environmental exposure appears to be the most important contributor to the increase in illicit use (12,13). In addition to the inherent risks of opioid tolerance, opioid-induced hyperalgesia, and other side effects (14) associated with chronic opioid therapy, including opioid induced respiratory depression and death, unsupervised use can lead to addiction and its attendant physical, social, and economic adverse consequences, including increased suicide rate, robbery, counterfeit drugs, and increased health care costs due to suicide, overdose, and drug abuse treatment (10,15,16).

In the face of the growing concerns associated with chronic opioid therapy, care must be taken to not deprive patients with a legitimate need for pain relief afforded by opioid analgesics. This has led to the development of documents aimed at providing guidance for the responsible and appropriate use of opioids in chronic non-cancer pain. This article aims to provide useful information and references for future development of opioid guidelines by reviewing expert-developed practice guidelines on chronic opioid therapy for non-cancer pain, to identify adequately supported practice points and areas in need of further scientific evidence.

Methods

Seven guidelines were identified as pertaining specifically to the long-term use of opioids for general chronic non-cancer pain from an initial search of the PubMed/Medline and Cochrane databases using combinations of the search terms "opioid," "chronic opioid therapy," "chronic pain," "chronic non-cancer pain," "chronic non-malignant pain," "guidelines," "practice guidelines," and "clinical practice guidelines," filtered to include only articles on humans published in the English language over the past 10 years, supplemented by a secondary Web search using the same search parameters and a manual search of listed references. In cases where there was more than one edition of the guideline within the specified duration parameters, the most updated version was used. Published guidelines not developed or supported by duly recognized specialty organizations or relevant government agencies were excluded from the discussion.

Results

The clinical practice guidelines included in this review were developed by the following:

- American Pain Society–American Academy of Pain Medicine (APS-AAPM) (17)
- Australian and New Zealand College of Anaesthetists (ANZCA) (18)
- National Opioid Use Guideline Group (NOUGG, Canada) (19)
- British Pain Society (20)
- American College of Occupational and Environmental Medicine (ACOEM) (21)
- American Society of Interventional Pain Physicians (ASIPP) (22)
- Pain Association of Singapore (23)

In general, the practice guidelines are in agreement with regard to the overarching principles governing the appropriate and responsible long-term use of opioids for chronic non-cancer pain. These include thorough patient evaluation, judicious opioid dosing, and careful patient monitoring to minimize the risks of adverse events and abuse, while providing patients in need with broader options for relief from persistent pain and improved quality of life. Slight variations between guidelines arise mainly from different approaches to the organization and focus of each guideline, which may highlight different aspects of therapy in varying degrees. The highlights of each guidance document are discussed in turn below.

American Pain Society–American Academy of Pain Medicine (APS-AAPM)

Due to the substantial increase in the use of opioid prescription in non-cancer pain despite a lack of support from strong scientific evidence, the APS and

the AAPM commissioned the Oregon Evidence-based Practice Center to review available evidence and develop recommendations on the use of opioid therapy in chronic non-cancer pain. The guidance document was published in 2009 and comprised 25 evidence-based recommendations that provide guidance not only on the evaluation and management of patients in chronic pain, but also on risk mitigation and related public health policies (Table 1).

Recommendations were graded based on methods adapted from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group (24). Each recommendation received a separate grade for the strength of the recommendation (strong

Table 1. *APS-AAPC guideline for the use of chronic opioid therapy (COT) in chronic non-cancer pain (CNCP).*

Area	Recommendation	Strength of recommendation	Quality of evidence
Patient selection and risk stratification	1.1 Before initiating COT, clinicians should conduct a history, physical examination and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction.	Strong	Low
	1.2 Clinicians may consider a trial of COT as an option if CNCP is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms.	Strong	Low
	1.3 A benefit-to-harm evaluation including a history, physical examination, and appropriate diagnostic testing, should be performed and documented before and on an ongoing basis during COT.	Strong	Low
Informed consent and opioid management plans	2.1 When starting COT, informed consent should be obtained. A continuing discussion with the patient regarding COT should include goals, expectations, potential risks, and alternatives to COT.	Strong	Low
	2.2 Clinicians may consider using a written COT management plan to document patient and clinician responsibilities and expectations and assist in patient education.	Weak	Low
Initiation and titration of COT	3.1 Clinicians and patients should regard initial treatment with opioids as a therapeutic trial to determine whether COT is appropriate.	Strong	Low
	3.2 Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. There is insufficient evidence to recommend short-acting versus long-acting opioids, or as-needed versus around-the-clock dosing of opioids.	Strong	Low
Methadone	4.1 Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics and should be initiated and titrated cautiously, by clinicians familiar with its use and risks.	Strong	Moderate
Monitoring	5.1 Clinicians should reassess patients on COT periodically and as warranted by changing circumstances. Monitoring should include documentation of pain intensity and level of functioning, assessments of progress toward achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapies.	Strong	Low
	5.2 In patients on COT who are at high risk or who have engaged in aberrant drug-related behaviours, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the COT plan of care.	Strong	Low
	5.3 In patients on COT not at high risk and not known to have engaged in aberrant drug-related behaviours, clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the COT plan of care.	Weak	Low
High-risk patients	6.1 Clinicians may consider COT for patients with CNCP and history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviours only if they are able to implement more frequent and stringent monitoring parameters. In such situations, clinicians should strongly consider consultation with a mental health or addiction specialist.	Strong	Low
	6.2 Clinicians should evaluate patients engaging in aberrant drug-related behaviours for appropriateness of COT or need for restructuring of therapy, referral for assistance in management, or discontinuation of COT.	Strong	Low

Table 1 (cont.). *APS-AAPC guideline for the use of chronic opioid therapy (COT) in chronic non-cancer pain (CNCP).*

Area	Recommendation	Strength of recommendation	Quality of evidence
Dose escalations, high-dose opioid therapy, opioid rotation, and indications for discontinuation of therapy	7.1 When repeated dose escalations occur in patients on COT, clinicians should evaluate potential causes and reassess benefits relative to harm.	Strong	Low
	7.2 In patients who require relatively high doses of COT, clinicians should evaluate for unique opioid- related adverse effects, changes in health status, and adherence to the COT treatment plan on an ongoing basis, and consider more frequent follow-up visits.	Strong	Low
	7.3 Clinicians should consider opioid rotation when patients on COT experience intolerable adverse effects or inadequate benefit despite dose increases.	Weak	Low
	7.4 Clinicians should taper or wean patients off COT who engage in repeated aberrant drug-related behaviours or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse effects.	Strong	Low
Opioid-related adverse effects	8.1 Clinicians should anticipate, identify, and treat common opioid-associated adverse effects.	Strong	Moderate
Use of psychotherapeutic cointerventions	9.1 As CNCP is often a complex biopsychosocial condition, clinicians who prescribe COT should routinely integrate psychotherapeutic interventions, functional restoration, interdisciplinary therapy, and other adjunctive non-opioid therapies.	Strong	Moderate
Driving and work safety	10.1 Clinicians should counsel patients on COT about transient or lasting cognitive impairment that may affect driving and work safety. Patients should be counselled not to drive or engage in potentially dangerous activities when impaired or if they describe or demonstrate signs of impairment.	Strong	Low
Identifying a medical home and when to obtain consultation	11.1 Patients on COT should identify a clinician who accepts primary responsibility for their overall medical care. This clinician may or may not prescribe COT, but should coordinate consultation and communication among all clinicians involved in the patient's care.	Strong	Low
	11.2 Clinicians should pursue consultation, including interdisciplinary pain management, when patients with CNCP may benefit from additional skills or resources that they cannot provide.	Strong	Moderate
Breakthrough pain	12.1 In patients on around-the-clock COT with breakthrough pain, clinicians may consider as-needed opioids based upon an initial and ongoing analysis of therapeutic benefit versus risk.	Weak	Low
Opioids in pregnancy	13.1 Clinicians should counsel women of childbearing potential about the risks and benefits of COT during pregnancy and after delivery. Clinicians should encourage minimal or no use of COT during pregnancy, unless potential benefits outweigh risks. If COT is used during pregnancy, clinicians should be prepared to anticipate and manage risks to the patient and newborn.	Strong	Low
Opioid policies	14.1 Clinicians should be aware of current federal and state laws, regulatory guidelines, and policy statements that govern the medical use of COT for CNCP.	Strong	Low

CNCP = chronic non-cancer pain; COT = chronic opioid therapy

or weak) and for the quality of evidence (high, moderate, or low). In general, a strong recommendation was based on the assessment that potential benefits of following the recommendation clearly outweigh potential harms and burdens; a weak rating was based on the assessment of a tighter balance of benefits vis-à-vis harms or burdens, or weaker evidence.

Of all the recommendations in the guideline, none were supported by high-quality evidence, and most of the evidence was graded low-quality. Nevertheless, it was determined that the potential benefits of the recommendations outweigh the possible risks, and most of the recommendations were graded as strong.

Australian and New Zealand College of Anaesthetists (ANZCA)

The 2010 guidance from the ANZCA is a brief document outlining recommended principles in prescribing opioid analgesics and managing patients with chronic non-cancer pain based on a review of evidence, outlined as follows:

Comprehensive assessment of the patient.

Non-somatic contributions to the condition, especially the social environment, including work, must be recognized and addressed without ignoring the biological contributions; patient's attitudes regarding prognosis and diagnosis, and impact on daily living, relationships, and life events, must be explored and assessed.

Adequate trial of other therapies.

Drug therapy must be used mainly for symptom control, and as part of a multimodal approach that also includes non-drug therapies (e.g., patient education, exercise programs, sleep hygiene). Paracetamol is preferred over nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line pharmacotherapy, especially when inflammation is not the relevant mechanism; adjuvant analgesics (e.g., tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, anticonvulsants) should be considered before opioids.

Agreement regarding an opioid trial.

A therapeutic contract to define the goals of an opioid trial should be discussed and established between the doctor and patient, including possible discontinuation if the goals are not met. There should be only one prescriber of the patient's opioids, with provision of adequate back-up should the prescriber become unavailable. If possible, only one pharmacy should dispense the opioid.

Conduct of an opioid trial.

Chronic pain should not be treated with short-acting drugs. Long-acting or sustained-release oral or transdermal preparations are preferred. Continuous assessment of the 5As (analgesia, activity, adverse effects, affect, aberrant behavior), with corresponding dose titration, is recommended. Doses requiring 120 mg morphine or equivalent warrant reassessment and possible specialist advice.

Response to difficulty.

In achieving goals of an opioid trial. Opioid rotation may be considered when achieving the 5A assessments proves difficult. Variations in stability of dose and responsiveness warrant comprehensive reassessment – possible actions include recalibration of goals of therapy, tapering of opioid to withdrawal, reconsideration of other modes of therapy, and consultation with colleagues.

The above recommendations are, in the main, consistent with the principles governing the recommendations in the rest of the guidelines discussed in this article, and appear to be a distillation of the South Australian guideline published in 2008 regarding the use of Schedule 8 drugs (25). Schedule 8, or S8, drugs are defined as "substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence" (26). These are also referred to as drugs of addiction or drugs of dependence (27), and include opioids, stimulants (methylphenidate and dexamphetamine), and flunitrazepam in Western Australia.

National Opioid Use Guideline Group (NOUGG, Canada)

The Canadian guideline, published in 2010, was developed by the National Opioid Use Guideline Group in

Table 2. *Recommendations from the Canadian NOUGG guideline.*

Key Words	Recommendation	Grade*
Cluster 1: Deciding to initiate opioid therapy		
Comprehensive assessment	Before initiating opioid therapy, ensure comprehensive documentation of the patient's pain condition, general medical condition and psychosocial history (Grade C), psychiatric status, and substance use history. (Grade B).	B to C
Addiction-risk screening	Before initiating opioid therapy, consider using a screening tool to determine the patient's risk for opioid addiction.	B
Urine drug screening	When using urine drug screening (UDS) to establish a baseline measure of risk or to monitor compliance, be aware of benefits and limitations, appropriate test ordering and interpretation, and have a plan to use results.	C
Opioid efficacy	Before initiating opioid therapy, consider the evidence related to effectiveness in patients with chronic non-cancer pain.	A
Risks, adverse effects, complications	Before initiating opioid therapy, ensure informed consent by explaining potential benefits, adverse effects, complications and risks (Grade B). A treatment agreement may be helpful, particularly for patients not well known to the physician or at higher risk for opioid misuse. (Grade C).	B to C

Table 2 (cont.). *Recommendations from the Canadian NOUGG guideline.*

Key Words	Recommendation	Grade*
Benzodiazepine tapering	For patients taking benzodiazepines, particularly for elderly patients, consider a trial of tapering (Grade B). If a trial of tapering is not indicated or is unsuccessful, opioids should be titrated more slowly and at lower doses. (Grade C).	B to C
Cluster 2: Conducting an opioid trial		
Titration and driving	During dosage titration in a trial of opioid therapy, advise the patient to avoid driving a motor vehicle until a stable dosage is established and it is certain the opioid does not cause sedation (Grade C); and when taking opioids with alcohol, benzodiazepines, or other sedating drugs. (Grade B).	B to C
Stepped opioid selection	During an opioid trial, select the most appropriate opioid for trial therapy using a stepped approach, and consider safety.	C
Optimal doses	When conducting a trial of opioid therapy, start with a low dosage, increase dosage gradually and monitor opioid effectiveness until optimal dose is attained.	C
Watchful dose	Chronic non-cancer pain can be managed effectively in most patients with dosages at or below 200 mg/day of morphine or equivalent (Grade A). Consideration of a higher dosage requires careful reassessment of the pain and of risk for misuse, and frequent monitoring with evidence of improved patient outcomes. (Grade C).	A to C
Risk: opioid misuse	When initiating a trial of opioid therapy for patients at higher risk for misuse, prescribe only for well-defined somatic or neuropathic pain conditions (Grade A), start with lower doses and titrate in small-dose increments (Grade B), and monitor closely for signs of aberrant drug-related behaviours. (Grade C).	A to C
Cluster 3: Monitoring long-term opioid therapy (LTOT)		
Monitoring LTOT	When monitoring a patient on long-term therapy, ask about and observe for opioid effectiveness, adverse effects or medical complications, and aberrant drug-related behaviours.	C
Switching or discontinuing opioids	For patients experiencing unacceptable adverse effects or insufficient opioid effectiveness from one particular opioid, try prescribing a different opioid or discontinuing therapy.	B
LTOT and driving	When assessing safety to drive in patients on long-term opioid therapy, consider factors that could impair cognition and psychomotor ability, such as a consistently severe pain rating, disordered sleep, and concomitant medications that increase sedation.	C
Revisiting opioid trial steps	For patients receiving opioids for a prolonged period who may not have had an appropriate trial of therapy, take steps to ensure that long-term therapy is warranted and dose is optimal.	C
Collaborative care	When referring patients for consultation, communicate and clarify roles and expectations between primary-care physicians and consultants for continuity of care and for effective and safe use of opioids.	C
Cluster 4: Treating specific populations with long-term opioid therapy		
Elderly patients	Opioid therapy for elderly patients can be safe and effective (Grade B) with appropriate precautions, including lower starting doses, slower titration, longer dosing interval, more frequent monitoring, and tapering of benzodiazepines. (Grade C).	B to C
Adolescent patients	Opioids present hazards for adolescents (Grade B). A trial of opioid therapy may be considered for adolescent patients with well-defined somatic or neuropathic pain conditions when non-opioid alternatives have failed, risk of opioid misuse is assessed as low, close monitoring is available, and consultation, if feasible, is included in the treatment plan.	C
Pregnant patients	Pregnant patients taking long-term opioid therapy should be tapered to the lowest effective dose slowly enough to avoid withdrawal symptoms, and then therapy should be discontinued if possible.	B
Co-morbid psychiatric diagnoses	Patients with a psychiatric diagnosis are at greater risk for adverse effects from opioid treatment. Usually in these patients, opioids should be reserved for well-defined somatic or neuropathic pain conditions. Titrate more slowly and monitor closely; seek consultation where feasible.	B
Cluster 5: Managing opioid misuse and addiction in chronic non-cancer pain (CNCP) patients		
Addiction treatment options	For patients with chronic non-cancer pain who are addicted to opioids, three treatment options should be considered: methadone or buprenorphine treatment (Grade A), structured opioid therapy (Grade B), or abstinence-based treatment (Grade C). Consultation or shared care, where available, can assist in selecting and implementing the best treatment option. (Grade C).	A to C
Prescription fraud	To reduce prescription fraud, physicians should take precautions when issuing prescriptions and work collaboratively with pharmacists.	C
Patient unacceptable behaviour	Be prepared with an approach for dealing with patients who disagree with their opioid prescription or exhibit unacceptable behaviour.	C
Acute-care opioid prescribing policy	Acute or urgent health care facilities should develop policies to provide guidance on prescribing opioids for chronic pain to avoid contributing to opioid misuse or diversion.	C

*Recommendation grades: Grade A: consistent high-quality evidence. Grade B: inconsistent or limited evidence. Grade C: lacking direct evidence.

collaboration with various Canadian medical societies, and consists of 24 evidence-based recommendations under 5 clusters (Table 2), each representing an aspect of management, as summarized below. Each recommendation statement is followed by a discussion and a summary of peer-reviewed evidence.

While the document is organized topically rather than in a more step-wise fashion, the overall recommendations nevertheless agree with the broad principles outlined in the APS-AAPM guideline and the rest of the reviewed practice guidelines. Particular features of the Canadian guideline include a detailed discussion on urine drug screening, taken at baseline and used as a monitoring tool.

The Canadian guideline also includes a specific recommendation and discussion on a trial of benzodiazepine tapering for patients with concomitant use of benzodiazepines, particularly in the elderly; the combination of opioids and benzodiazepines increases the risk of sedation, overdose, and diminished function in all patients, especially as age advances (28-30). This was also mentioned in the recommendations for the elderly, under the cluster of long-term therapy for specific populations (elderly, adolescent, pregnant, and psychiatric), which is another notable feature of the Canadian guideline.

British Pain Society

Also in 2010, the British Pain Society published Opioids for Persistent Pain: Good Practice as guidance for opioid use in chronic non-cancer pain. The British guideline is compatible with the recommendations in the American guidelines regarding patient evaluation and risk assessment, use of opioid analgesics, and monitoring for adverse events and aberrant drug-related behavior. However, while the American guidelines placed particular emphasis on public health concerns, the British guideline adopted a more clinical approach in its recommendations, which were organized and discussed in the context of providing safe and appropriate relief from chronic pain. Treatment goals include not only reduction in pain intensity but also improvement in sleep, mood, and physical, vocational, social, and emotional wellbeing.

The recommendations are presented not as a review of scientific evidence, but as a practical guide on the appropriate evaluation and management of the patient in pain. The guidance briefly describes the basic pharmacology of currently available opioid analgesics and discusses the adverse effects of opioid therapy with recommendations for management, including advising patients to avoid driving at the start of opioid therapy and following dose changes.

The document also provides general guidance on when to prescribe opioids and their appropriate choice. In particular, the guideline recommends that drugs with demonstrated efficacy for persistent pain syndromes (e.g., tricyclic antidepressants and antiepileptic drugs for neuropathic pain) should always be prescribed before starting opioids. The guideline further recommends using modified-release opioids administered at regular intervals, where possible; injectable opioids are not recommended except in extraordinary circumstances, and then only after consultation with a specialized multidisciplinary pain management service. As with the APS-AAPM guideline, the British guideline recommends that a trial of opioid therapy be done to aid in the decision-making on whether to initiate long-term opioid therapy.

American College of Occupational and Environmental Medicine (ACOEM)

The American College of Occupational and Environmental Medicine (ACOEM) guideline was published in 2011, in response to emerging evidence of an increased risk of death that appeared to parallel the increase in opioid consumption. It was developed to provide a framework for management of pain that had not been controlled by more conservative means, particularly in injured workers, and includes guidance for the initiation, maintenance, and discontinuation of opioid therapy, as well as criteria to diagnose addiction, substance abuse, and problematic opioid use. As with the guidelines discussed above, it also adopts a biopsychosocial rather than a biomedical perspective, and advocates limiting chronic opioid therapy to patients in whom other proven treatments have failed and for whom opioids show continued clear documented benefit. Table 3 outlines the evidence-based recommendations described in the document.

Similar to the British guideline, goals of treatment are more holistic and focus not only on pain reduction but also on health-related quality of life as measured by physical (disease-specific or generic) and emotional functioning; participant ratings of global improvement, symptoms, and adverse effects; and participant disposition (i.e., adherence to the treatment regimen). However, unlike the British guideline which does not have specific provisions for restricting opioid therapy on any particular patient population, the ACOEM takes a more conservative stance and proposes withholding opioid therapy in

Table 3. *Evidence-based recommendations from the ACOEM guidelines.*

Recommendation	Strength of evidence
Routine use of opioids for chronic pain	Not Recommended, Evidence (C)
Use of opioids for select patients with chronic persistent pain, neuropathic pain, or CRPS	Recommended, Insufficient Evidence (I)
Screening for prior substance abuse and psychological evaluation	Recommended, Insufficient Evidence (I)
Treatment agreement to document patient understanding and agreement with the expectations of opioid use *If literacy is a problem, the physician should read the agreement to the patient and ascertain that they understand it or revise the agreement so they can read and understand its content	Recommended, Insufficient Evidence (I)
Routine use of urine drug screening for patients on chronic opioids	Recommended, Evidence (C)

Recommended, Evidence (C) – The intervention is recommended for appropriate patients. There is limited evidence that the intervention may improve important health and functional benefits.
Recommended, Insufficient Evidence (I) – Consensus-based; The intervention is recommended for appropriate patients and has nominal costs and essentially no potential for harm. The EBPP feels that the intervention constitutes best medical practice to acquire or provide information in order to best diagnose and treat a health condition and restore function in an expeditious manner. The EBPP believes based on the body of evidence, first principles, and/or collective experience that patients are best served by these practices, although the evidence is insufficient for an evidence-based recommendation.
Not Recommended, Evidence (C) – Recommendation against routinely providing the intervention. The EBPP found at least moderate evidence that harms and costs exceed benefits based on limited evidence.

patients with relevant behavioral and emotional issues until psychological evaluation and, if warranted, referral for appropriate psychological, behavioral, and/or rehabilitative interventions are carried out. The guideline also provides recommendations on the evaluation, management, and potential weaning of patients who are already on opioid therapy, especially those who have not reported functional gains despite being maintained on high doses of extended-release opioids.

Potential effects of opioid therapy on driving were discussed in greater detail, based on an evidence-based review to assess opioid-related impairment of driving skills. Results suggest that opioids do not impair driving-related skills in opioid-dependent/tolerant patients. Nevertheless, while each patient should be evaluated individually according to occupational or personal requirements, the guidance cautions health care providers that prescribing opioids to patients who operate a commercial motor vehicle or pilot an aircraft generally precludes them from working, and other workers in safety-sensitive positions in industry (e.g., industrial machinery, construction, heavy equipment operations) who are prescribed opioids may be restricted from returning to their jobs at the discretion of management.

American Society of Interventional Pain Physicians (ASIPP)

The 2012 ASIPP guideline was published in part as an update to the previous ASIPP guideline published in 2008 and presents a comprehensive review of scientific literature, consensus among the panellists, and practice patterns, including references to previous guidelines published by the APS-AAPM, Canadian NOUGG, and British Pain Society. The guideline also features a management algorithm for opioid therapy that outlines the steps from initial patient assessment to treatment tapering or discontinuation, as well as algorithms for risk stratification, adherence monitoring, and urine drug testing (UDT).

Like the British guideline, the ASIPP recommendations demonstrate a clinical approach, tracing a stepwise path from initial patient assessment through final disposition (treatment continuation/ discontinuation/ modification). However, unlike the British guideline, the ASIPP offers evidence-based instead of practical recommendations.

Compared with the 25 recommendations in the APS-AAPM guideline, most of which were strongly recommended despite the lack of strong scientific evidence, a re-evaluation of scientific evidence for the current ASIPP guideline yielded fair to good evidence for the majority of the 27 consensus recommendations that fall under 10 steps of opioid therapy (Table 4). The ASIPP determined that evidence is still limited on the benefits of long-term therapy and the utility of opioid rotation, buprenorphine, or methadone for treatment modification; nevertheless, current evidence does not appear to be in conflict with earlier recommendations.

Table 4. *ASIPP recommendations with evidence levels.*

Step	Recommendation	Evidence
Initial steps of opioid therapy	Comprehensive assessment and documentation before initiating opioid therapy	Good
	Screening for opioid use	Limited
	Implementation of prescription drug monitoring programs (PMDPs)	Good to fair
	Implementation of urine drug testing (UDT) along with subsequent adherence monitoring	Good
Establish diagnosis	Establishment of appropriate physical diagnosis and psychological diagnosis if available prior to initiating opioid therapy	Good
	Caution in ordering imaging and other evaluations, and providing patients only with appropriate relevant clinical information when there is correlation of the symptoms with findings	Good
	Pain management consultation, for non-pain physicians, if high-dose opioid therapy is being utilized	Fair
Establishing medical necessity	Establishment of medical necessity prior to initiation or maintenance of opioid therapy	Good
Establishing treatment goals	Establishment of treatment goals of opioid therapy with regard to pain relief and improvement in function	Good
Assessment of effectiveness of opioid therapy	Understanding the effectiveness and adverse consequences of long-term opioid therapy in chronic non-cancer pain and its limitations	Fair for short-term, limited for long-term
	Use of high doses of long-acting opioids only in specific circumstances with severe intractable pain that is not amenable to short-acting or moderate doses of long-acting opioids	Fair
	Trial of opioid rotation for patients requiring escalating doses	Limited
	Evaluation of contraindications to opioid use in chronic non-cancer pain	Fair to limited
Informed decision-making	Development of a robust agreement which is followed by all parties for initiating and maintaining opioid therapy	Fair
Initial treatment	Once medical necessity is established, initiation of opioid therapy with low doses and short-acting drugs with appropriate monitoring to provide effective relief and avoid side effects	Fair for short-term, limited for long-term effectiveness
	Recommended doses of up to 40 mg of morphine equivalent doses as low dose, 41 to 90 mg of morphine equivalent dose as a moderate dose, and greater than 91 mg of morphine equivalence as high dose	Fair
	Caution in titration of long-acting opioids	Good
	Use of methadone in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses	Limited
Adherence monitoring	Obtaining an electrocardiogram prior to initiation, at 30 days and yearly thereafter for monitoring methadone prescription	Fair
	Adherence monitoring by UDT and PMDPs to identify non-compliant patients or prescription drugs or illicit drug abuse	Fair
Monitoring and managing side effects	Monitoring for and appropriate management of side effects, including discontinuation of opioids if indicated	Fair
	Close monitoring for constipation and initiation of a bowel regimen as soon as deemed necessary	Good
	Development and monitoring of a policy for driving under the influence of drugs during initiation of therapy, changes in the dosages, and addition of other centrally acting agents	Good
The final phase	Continuation of chronic opioid therapy with continuous adherence monitoring, modified at any time during this phase, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse effects.	Fair
	Use of methadone and buprenorphine in late stages after failure of other opioid therapy and only by clinicians with specific training in the risks and uses	Limited
	A trial of opioid rotation for patients requiring escalating doses.	Limited
	Monitoring of chronic opioid therapy for adverse effects, with appropriate management	Good

PMDP = prescription drug monitoring program; UDT = urine drug testing

Pain Association of Singapore

The treatment guideline published by the Pain Association of Singapore is the most recent of the guidelines reviewed in this document. The general recommendations on approach to opioid therapy are consistent with those in the guidelines discussed above: detailed patient evaluation; risk assessment and specialist referral as needed; informed consent; trial of opioid therapy prior to initiation of therapy; use of minimum effective dose with upward titration as needed and as tolerated; patient monitoring for aberrant behavior, adverse effects, or loss of efficacy; and dose tapering and discontinuation, as needed.

In addition to guidance on the approach to overall management, the Singapore guideline also provides specific evidence-based treatment recommendations for low back pain, neck pain, musculoskeletal pain, head/orofacial pain, chronic pelvic pain, persistent post-surgical pain, fibromyalgia, post-herpetic neuralgia, diabetic peripheral neuropathic pain, and peripheral vasculopathy. Review of evidence suggests that opioids may be used for pain relief if other analgesics are ineffective, or as part of a multimodal treatment regimen; however, overall, evidence to support long-term opioid use is still limited. Nonetheless, there is evidence to support the benefits of tramadol in low back pain, fibromyalgia, and post-surgical pain; the short-term benefits of oxycodone in neck pain; and opioid monotherapy in diabetic peripheral neuropathic pain and peripheral vasculopathy. The use of pethidine is not recommended due to its high potential for abuse and risk of neurotoxicity.

Discussion

Guidelines on the use of opioid analgesics for chronic pain were developed for various reasons. The Singapore guideline was developed in response to the increasing incidence of chronic pain in Asia, owing in part to the increasing size of the elderly population (> 65 years). In the UK, Australia, and New Zealand, the majority of chronic pain cases are managed by general practitioners, and the British Pain Society and Australia and New Zealand College of Anaesthetists (ANZCA) guidelines were consequently developed by multidisciplinary panels as a general guide for all health care professionals who manage chronic pain. In an effort to provide more evidence-based guidelines on the rational use of opioids for chronic pain, the APS-AAPM and NOUGG released more comprehensive recommendations in the United States and Canada, respectively. The ACOEM guideline was published especially as a guide for managing injured workers whose pain is not controlled by more conservative therapy. More recently, the ASIPP built on previously published guidelines, including those from the US, UK, and Canada, and updated with new evidence at the time of development. The current document aims to provide a concise review of current expert-developed guidelines, as a useful reference both for current practice and for future development of opioid guidelines in other regions.

While there is some variation in the focus and level of detail of practice guidelines across different countries and specialities, the following general principles governing the approach to initiating opioid therapy were noted across all guidelines (Table 5).

1. A comprehensive evaluation, with particular emphasis on psychological, psychosocial, and other factors that may help identify potential drug misuse and abuse, should be conducted as part of the initial assessment of the patient with chronic non-cancer pain.
2. Prior to initiating therapy, a trial of opioid therapy is recommended to aid decision-making on whether or not to proceed with the opioid treatment regimen.
3. Patients should be adequately informed of the benefits and risks of opioid therapy. Obtaining written and signed informed consent prior to initiating therapy may be appropriate in some cases.
4. Opioids are generally not recommended as first-line therapy, and must be considered only when other evidence-based interventions are unavailable or ineffective.
5. The treatment regimen, including opioid selection and dosage, should be individualized according to patient needs and response.
6. Patients should be started at the minimum dose required to effect relief without significant adverse effects, and the dose subsequently titrated upward according to patient response and safety.
7. Once therapy is initiated, the patient must be closely monitored for loss of response, adverse events, or aberrant drug-related behavior.

Driving while on opioid therapy was discussed with varying levels of detail across guidelines. In general, evidence suggests that opioid therapy does not impair driving skills; however, it may be prudent to avoid driving at the start of therapy or dose adjustment, or when impaired cognitive functioning is noted or suspected. Other principles relevant to long-term opioid therapy, emphasized to varying degrees across different guidelines, are discussed below.

Table 5. *Comparison of recommendations on selected parameters.*

	ANZCA	APS-AAPM	NOUGG	BPS	ACOEM	ASIPP	PAS
Patient evaluation	All guidelines advocate comprehensive patient evaluation, with particular emphasis on identifying risk factors for adverse events and drug misuse						
Informed consent	Yes	Yes	Yes	No mention	Yes; sample treatment agreement form provided	Yes; sample treatment agreement form provided	Yes, preferably with a signed opioid treatment agreement
Trial of opioid therapy	Based on individual assessment	Yes, for several weeks to months	Yes; stepped approach to selecting opioids described in guideline	No specific dosing recommendations	No specific dosing recommendations	No specific discussion	Yes, up to 2 months
Optimal starting dose	No specific dose recommendations	Based on individual assessment	Suggested initial doses provided in Table B-9.1 of the guideline	Not specified	No specific dose recommendations	Suggested doses provided in Table 7 of the guideline	Based on individual assessment
Opioids as first-line therapy	Not recommended	Not recommended	Stepped approach described in Table B-8.1 of the guideline	Not recommended	Not recommended	No specific recommendation	Not generally recommended
Driving while on opioid therapy	No specific recommendation	Caution, especially when initiating or changing doses	Caution, especially at start of opioid trial	Caution, especially at start of opioid therapy and following dose changes	Based on individual evaluation	Caution, especially during dosage titration	No mention
Methadone	No specific recommendation	For experienced clinicians only; use with caution	May consider in opioid addiction	Caution in pregnant women	No specific recommendation; risks mentioned	May consider after failure of opioid therapy; for experienced clinicians only	No specific recommendation
Opioid rotation	May be considered to address inappropriate response to current opioid	Consider for inadequate benefit or intolerable side effects	Start new opioid on lower dose (50%-75% less than previous, converted to morphine equivalent)	No mention	No mention	Consider in patients requiring escalating doses	No specific recommendation
Urine drug testing	May be included as a monitoring tool in the treatment plan	For patients at high risk or who have exhibited aberrant behaviour	To establish baseline, monitor compliance	No mention	Routine screening recommended	Must be implemented from initiation of therapy	Recommended in all high-risk patients
Maximum daily dose	Doses above the equivalent of 120 mg morphine per day require reassessment including specialist advice if possible	No specific recommendation	Exercise particular caution when prescribing doses exceeding 200 mg morphine equivalent	Refer to specialist for doses exceeding 120-180 mg morphine equivalent	No mention	low-dose: ≤ 40 mg; moderate dose: 41-90 mg; high dose: ≥ 91 mg morphine equivalent dosages	Consider discontinuation for doses ≥ 200 mg morphine equivalent

Trial of opioid therapy and optimal starting dose

A trial of opioid therapy is recommended not just to determine whether or not to proceed with opioid therapy; a trial of therapy is also used to determine optimal dose. For this reason, most of the guidelines do not recommend specific starting doses, instead recommending that these be determined based on individual evaluation. The selection of which opioid to use may be based on pain severity, prior exposure to opioids, or even cost. Codeine appears to be an appropriate first-line agent for mild to moderate pain, while morphine is a common initial choice for severe pain, along with oxycodone or hydromorphone (1,19,22,31).

Theoretical considerations can also influence the choice of starting agent; while the Australian and New Zealand guidelines emphatically discourage the use of short-acting opioids as initial therapy and recommend the use of long-acting opioids, the ASIPP believes that long-acting opioids have a greater potential for abuse because they tend to be provided in high-dose formulations and can easily induce immediate-release effects when bitten or crushed; thus, the ASIPP guideline specifically recommends initiating therapy with low doses of short-acting opioids.

Despite apparent differences in the recommendations on opioid initiation and maintenance, all guidelines echo the principles of the WHO analgesic ladder (32), which was developed as a guide for cancer pain but may also apply to chronic non-cancer pain (33). It is also clear that thorough history-taking and patient evaluation is crucial in determining the appropriate agent and dose for each patient. Once initiated, opioid therapy must then be followed by careful patient monitoring for adequacy and appropriateness of response.

Maximum dose

Upper threshold levels for daily doses of morphine or morphine equivalents differ slightly for each guideline, as well as recommended further steps once the threshold is reached. The South Australian guideline sets different maximum doses for different drugs and recommends referral to a pain specialist for unusual dose requirements (27), a recommendation adopted by the ANZCA guideline. Similarly, the British guideline strongly recommends referral to a pain medicine specialist if useful relief from pain symptoms is not achieved at daily doses of 120 – 180 mg morphine equivalent. On the other hand, both the Canadian and Singapore guidelines set a threshold daily morphine or equivalent dose of 200 mg; yet, while the Singapore guideline recommends considering discontinuation if therapeutic goals are not achieved at this dose, the Canadian guideline sets 200 mg daily only as a "watchful dose," above which patients must be monitored more frequently for opioid effectiveness, medical complications, adverse effects, and risks. The American guidelines provided no specific recommendations; at most, the ASIPP guideline assigned daily morphine or equivalent doses below 41 mg as low and above 91 mg as high dose, with in-between doses classified as moderate. In the absence of a clear consensus, 100 to 120 mg morphine equivalent seems to be a prudent reference level for heightened caution (34,35), due to evidence of increased morbidity and mortality at these doses (2,7,36).

Methadone

Methadone is a long-acting synthetic opioid that has been available for more than 50 years. Its widely variable half-life (37) makes universal dosing recommendations difficult; nevertheless, its relatively low cost, powerful effect, and long duration of action have probably contributed to its increased use for chronic pain in recent years (38). This increase has been paralleled by increases in methadone abuse and methadone-related deaths in the United States (39-41), which may account for the more conservative stance of the American guidelines regarding methadone use. American hesitancy notwithstanding, methadone still has a place in pain management, especially in the treatment of opioid addiction, and is still considered an acceptable option for chronic pain. Although non-American guidelines do not actively discourage the use of methadone, particular care in determining appropriate doses for each patient is recommended, taking into consideration the patient's individual response to the drug.

Opioid rotation

Opioid rotation refers to a switch from one opioid to another. It is a common strategy to address tolerance, achieve increased analgesic response, and help manage side effects during opioid therapy (42), usually with the use of an equianalgesic dose table as basis for determining the dose of the new opioid (27). However, a recent review of opioid rotation practices has revealed an increase in fatal or near-fatal overdoses that could be due to errors in prescribing, such as inappropriate dose conversion ratios in equianalgesic tables (43). To minimize risk of overdosing, a starting dose lower than the calculated equianalgesic dose is recommended, with subsequent titration to optimize the balance between pain relief and side effects. The Canadian guideline recommends starting the new opioid on 50% to 75% less than the previous morphine equivalent dose; the APS-AAPM and ASIPP guidelines likewise allow opioid rotation as an option in cases of inadequate response or intolerable adverse effects, but provide no specific dosing recommendations.

Urine drug testing

UDT is useful in identifying aberrant behavior or drug misuse, and may be conducted to establish a baseline measure and to monitor compliance. The Canadian guideline suggests that there may be a role for UDT to establish a baseline measure of risk or to monitor compliance. Nevertheless, the ASIPP guide-

line takes a firmer position on UDT, recommending routine UDT not only to identify patients taking illicit substances but also to de-stigmatize drug testing. In fact, there is no compelling evidence to guide physicians on identifying which patients should have UDT or how often. Clinicians are advised to consider the patient's risk for opioid misuse and addiction, aberrant drug-related behaviors, and availability of UDT. Instituting routine UDT may circumvent the need to identify candidates for and frequency of UDT; further, routine UDT may ease the perceived lack of trust in the patient when a UDT is requested, and can help de-stigmatize drug testing while providing a complement to self-reporting and behavioral monitoring to detect drug abuse and misuse (19,22,44). Regardless of the decision on whether to request UDT for all or selected patients, clinicians are cautioned to be aware of the benefits and limitations of UDT as well as appropriate test ordering and interpretation, and have a plan in place on how to use the results.

Conclusion

The substantial increase in the use of opioids for pain not associated with malignant disease or end-of-life care has encouraged the development of a wealth of information on the appropriate use of opioids for chronic non-cancer pain. Experts and specialty organizations from several countries have developed guidance documents to help patients and health care providers navigate the benefits and risks associated with opioid analgesic therapy. This review of recently published guidelines revealed a broad commonality across guidelines in the basic principles governing the responsible use of opioid analgesics, which include careful patient evaluation, gradual dose titration, and close monitoring. Taken individually, each guideline presents a different perspective that provides additional details to complement the general principles. The 2012 ASIPP guidelines suggest that scientific evidence to support general recommendations has become more robust recently, compared with the scientific data available during the development of the 2009 APS-AAPM guidelines. Future directions should focus on continuing to generate good-quality evidence on the benefits of long-term opioid therapy, as well as scientific data to guide drug choice and dosing for specific conditions, populations, and situations.

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