Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain

Part A: Executive Summary and Background
Part B: Recommendations for Practice

PART B

— Recommendations for Practice —

Published by the
National Opioid Use Guideline Group (NOUGG)
a collaboration of:

Federation of Medical Regulatory Authorities of Canada
College of Physicians & Surgeons of British Columbia
College of Physicians & Surgeons of Alberta
College of Physicians and Surgeons of Saskatchewan
College of Physicians & Surgeons of Manitoba
College of Physicians and Surgeons of Ontario
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College of Physicians and Surgeons of Nova Scotia
College of Physicians and Surgeons of Prince Edward Island
College of Physicians and Surgeons of Newfoundland and Labrador
Government of Nunavut
Yukon Medical Council

April 30 2010 Version 5.6

http://nationalpaincentre.mcmaster.ca/opioid/

Acknowledgements

The following individuals are gratefully acknowledged for their contribution to the inception, development, review, revision, and publication of the *Canadian Guideline*.

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Part B: Table of Contents

List of Figures and Tables

NOTES:

- Numbering of Tables and Figures
  Tables and Figures are numbered to correspond with the associated section in Part A, and the associated recommendation in Part B, e.g.,
  - Table A-11.1 is located in Part A, section 11.1.
  - Table B-12.1 is located in Part B, under Recommendation 12.

- Individual Recommendations
  For Part B, the recommendations are organized into three sections: Recommendation Statement, Discussion, and Summary of Peer-Reviewed Evidence. For recommendations with Grade-C only support, the "Summary of Peer-Reviewed Evidence" is omitted.

- Acronyms used in Part B:
  CNCP = chronic non-cancer pain
  CPG = clinical practice guideline
  CR = controlled release
  FDA = Food and Drug Administration
  IR = immediate release
  LTOT = long-term opioid therapy
  MEQ = morphine equivalent
  NA = not applicable
  NRS = numeric rating scale
  OIH = Opioid-induced Hyperalgesia
  ORT = Opioid Risk Tool
  PDI = pain disability index
  RCT = randomized controlled trial
  UDS = urine drug screening

SUMMARY of RECOMMENDATIONS

Cluster 1: Deciding to Initiate Opioid Therapy

No.	Recommendation	Keyword
R01	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).	*Comprehensive assessment*
R02	Before initiating opioid therapy, consider using a screening tool to determine the patient's risk for opioid addiction. (Grade B).	*Addiction-risk screening*
R03	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. (Grade C).	*Urine drug screening*
R04	Before initiating opioid therapy, consider the evidence related to effectiveness in patients with chronic non-cancer pain. (Grade A).	*Opioid efficacy*
R05	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).	*Risks, adverse effects, complications*
R06	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).	*Benzodiazepine tapering*

Cluster 2: Conducting an Opioid Trial

R07	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).	*Titration and driving*
R08	During an opioid trial, select the most appropriate opioid for trial therapy using a stepped approach, and consider safety. (Grade C).	*Stepped opioid selection*
R09	When conducting a trial of opioid therapy, start with a low dosage, increase dosage gradually and monitor opioid effectiveness until optimal dose is attained. (Grade C).	*Optimal dose*
R10	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).	*Watchful dose*
R11	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 behaviors. (Grade C).	*Risk: opioid misuse*

Cluster 3: Monitoring Long-Term Opioid Therapy (LTOT)

No.	Recommendation	Keyword
R12	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. (Grade C).	*Monitoring LTOT*
R13	For patients experiencing unacceptable adverse effects or insufficient opioid effectiveness from one particular opioid, try prescribing a different opioid or discontinuing therapy. (Grade B).	*Switching or discontinuing opioids*
R14	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. (Grade C).	*LTOT and driving*
R15	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. (Grade C).	*Revisiting opioid trial steps*
R16	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. (Grade C).	*Collaborative care*

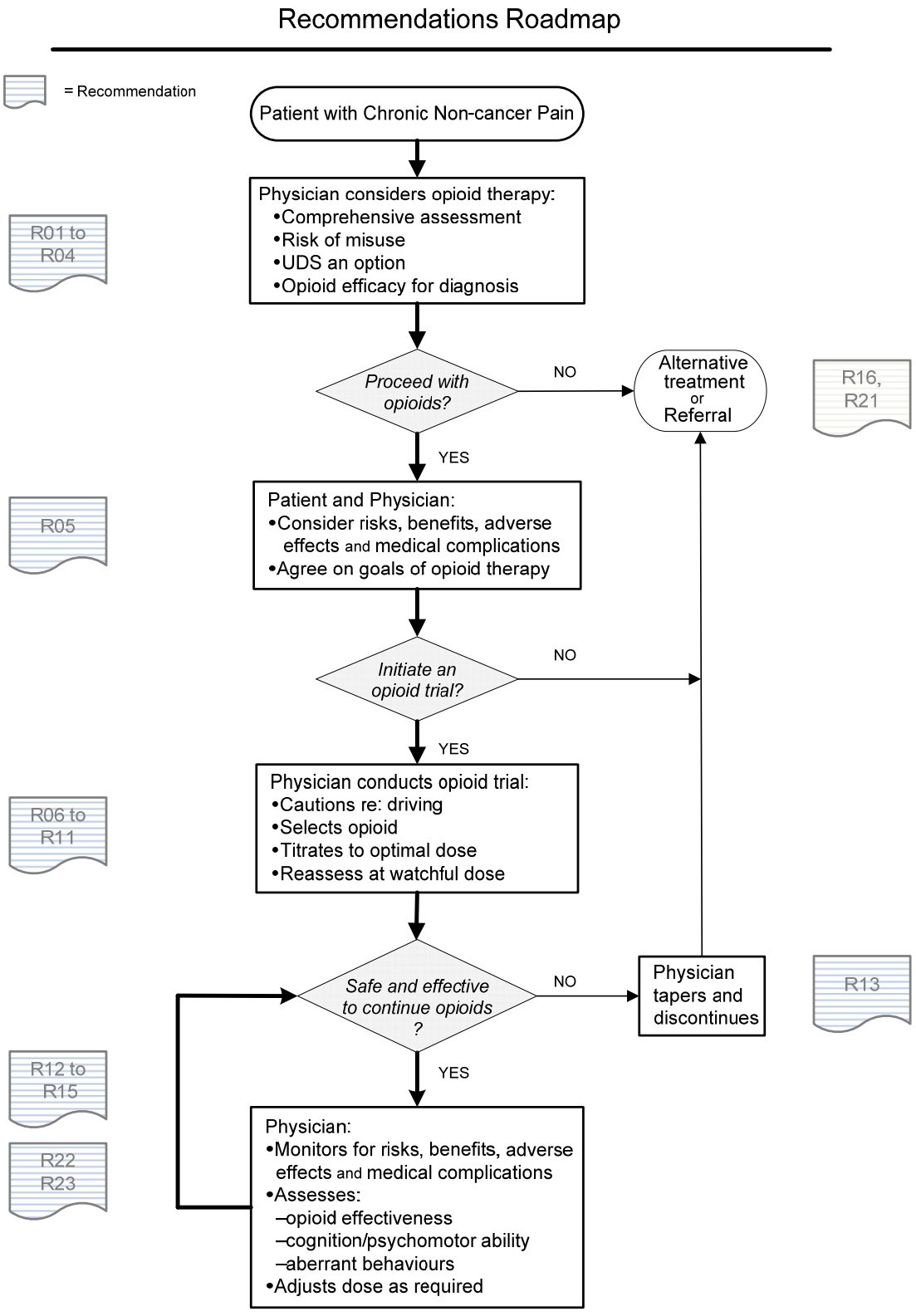
Cluster 4: Treating Specific Populations with Long-Term Opioid Therapy

R17	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).	*Elderly patients*
R18	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. (Grade C).	*Adolescent patients*
R19	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. (Grade B).	*Pregnant patients*
R20	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. (Grade B).	*Co-morbid psychiatric diagnoses*

Cluster 5: Managing Opioid Misuse and Addiction in CNCP Patients

No.	Recommendation	Keyword
R21	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).	*Addiction treatment options*
R22	To reduce prescription fraud, physicians should take precautions when issuing prescriptions and work collaboratively with pharmacists. (Grade C).	*Prescription fraud*
R23	Be prepared with an approach for dealing with patients who disagree with their opioid prescription or exhibit unacceptable behaviour. (Grade C).	*Patient unacceptable behaviour*
R24	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. (Grade C).	*Acute care opioid prescribing policy*

Figure 01. Recommendations Roadmap



Canadian Guideline RECOMMENDATIONS

Cluster 1: Deciding to Initiate Opioid Therapy

R01 Recommendation Statement

R01	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).	*Comprehensive assessment*

R01 Discussion

1. Comprehensive Knowledge of the Patient

1.1 Pain Condition

Comprehensive knowledge of the patient's pain condition includes:

- thorough history and physical examination to determine the type, cause and nature of the pain, including questions about past investigations and interventions for pain including medication trials
- estimate of the pain intensity and the functional impairment that arises from it (impact of pain on work, school, home and leisure activities)
- diagnosis.

1.2 General Medical and Psychosocial History

- General medical history includes questions about general physical health, emotional health, and medication use.
- Psychosocial history includes information regarding: living arrangements, family/social support, family obligations, work status.

1.3 Psychiatric Status

Psychiatric status includes information regarding:

- the patient's current and past history of psychiatric disorders and treatments; (also see Recommendation 20 for more details about prescribing options for patients with psychiatric disorders)
- family history of psychiatric disorders.

1.4 Substance Use History

Substance use history includes questions about:

- current, past, and family history of substance use, abuse, and addiction (alcohol, marijuana, tobacco, benzodiazepines, opioids, cocaine, amphetamines, barbiturates, hallucinogens, and solvents), and
- any attendance at a treatment program for addiction. (See Appendix B-1 for tools and interview guides to assist in taking a substance use history.)

2. Documentation

Maintain detailed records documenting the assessment of the patient, treatment plan, discussion of risks and benefits, informed consent, opioids prescribed, and outcomes.

...continued

R01 Summary of Peer-Reviewed Evidence

1. Opioid addiction is estimated to have an overall prevalence of 3.3% in patients receiving opioids for CNCP, with a wide variation between clinics and regions. Aberrant drug-related behaviours have a much higher prevalence. The major risk factor for addiction is a current or past history of addiction.

The prevalence of aberrant drug-related behaviours and addiction among patients on LTOT is not certain. In a recent systematic review of 67 studies (Fishbain 2008), the prevalence of clinically diagnosed opioid abuse or addiction was reported as 3.3% in those studies that included patients with a history of substance abuse. The prevalence of aberrant drug-related behaviours was 11.5% (range 0–44%). The percent of urine drug screens with illicit drugs present was 14.5%, while the percent of urine drug screens with a non-prescribed opioid or no opioid present (suggesting possibly diversion) was 20.4%.

The corresponding figures were much lower for studies that excluded patients with a history of substance abuse, confirming that a past history is an important risk factor for the development of abuse or addiction. Other risk factors have been identified in individual studies, such as anxiety disorders, post-traumatic stress disorder and personality disorders (Wilsey 2008).

This review (Fishbain 2008) and the studies on which it is based have several limitations. There was no breakdown of the types of clinics studied or the dates of the study (evidence suggests the incidence of opioid addiction is increasing). The diagnosis of addiction is dependent on the clinician's judgment—aberrant drug-related behaviours and urine drug screen results are only a proxy measure of addiction. Aberrant drug-related behaviours could indicate opioid addiction but they also might reflect inadequately treated pain, or abuse of non-opioid drugs, e.g., cocaine.

The prevalence of aberrant drug-related behaviours appears to vary widely between regions and clinics. One study of two primary-care clinics found a prevalence of opioid aberrant drug-related behaviours of 24% and 31% (Reid 2002), while another found a prevalence of 7% among depressed primary-care patients (Roeloffs 2002). Specialty medical or surgical clinics, which tend to follow older patients with organic pain conditions, have found low rates of opioid aberrant drug-related behaviours (Mahowald 2005). There are also striking regional variations.

It is difficult to generalize from these studies, as they 1) were usually based in a specific clinic setting, 2) are limited by selection biases, and 3) often used proxy measures for addiction (drug-seeking behaviours) rather than comprehensive patient assessment.

2. The prevalence of problematic substance use, including opioids, non-opioid substances and alcohol, is higher among patients on long-term opioid therapy for CNCP than in the general population.

One large nationally representative cross-sectional survey of over 9,000 subjects found that the prevalence of problematic substance use was higher among those on prescribed opioids than among non-opioid users (Edlund 2007). This included problematic use of alcohol and non-opioid substances as well as opioids. Controlling for co-morbid mental disorders, the association with non-opioid substances disappeared, suggesting that the higher prevalence of mental disorders in opioid users mediates their higher risk for problematic substance use.

R02	Before initiating opioid therapy, consider using a screening tool to determine the patient's risk for opioid addiction. (Grade B).

Addiction-risk screening

R02 Discussion

A comprehensive history when considering opioids for CNCP includes a thorough review of the patient's alcohol and other substance use. This history is important in assessing the patient's risk for opioid misuse or addiction and various screening tools can help with this determination. Most of the screening tools have not been studied in depth, validated, or been compared to each other but the Opioid Risk Tool (ORT) is widely used (see Appendix B-2: ORT).

The ORT provides a scoring mechanism that translates the patient's responses into a low, moderate or high risk categorization. It relies on identifying personal or family history of alcohol and substance abuse as well as personal psychiatric history.

See Appendix B-1 for examples of interview guides and assessment tools that may be used to supplement a comprehensive history of alcohol and substance use.

R02 Summary of Peer-Reviewed Evidence

1. Some screening questionnaires for risk of opioid misuse and abuse have demonstrated high sensitivity and specificity. However, samples used were small and unrepresentative.

The Opioid Risk Tool, in a preliminary study (Webster 2005), demonstrated high sensitivity and specificity for predicting individuals presenting to a pain clinic who were at risk for developing aberrant behaviors related to their opioid use. The ORT assessed personal and family history of substance abuse, age, history of preadolescent sexual abuse, depression, and other psychiatric history and categorized patients as low, moderate or high risk.

A systematic review of predictors for opioid misuse concluded that none of the screening tools can be recommended with confidence, because the samples were small and unrepresentative (Turk 2008). A personal history of abuse of illicit drugs or alcohol remains the strongest predictor of opioid misuse and abuse.

R03 Recommendation Statement

R03	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. (Grade C).	*Urine drug screening*

R03 Discussion

In the context of using opioids for treating CNCP, UDS can be used to as a tool for: 1) setting a baseline measure of substance use that may help assess risk for addiction, and 2) ongoing monitoring of the patient's compliance with opioids prescribed. However, opinions regarding UDS utility vary.

1. Types of Urine Drug Screening (UDS)

1.1 Point-of-care Testing

For point-of-care (POC) testing, the urine sample is collected and tested at the physician's office/clinic.

- POC test kits are available for purchase; urine dipsticks are required.
- Results are immediate, but it tends to be less sensitive and specific than laboratory tests.

1.2 Laboratory Testing

For laboratory testing, the urine sample is collected at physician's office/clinic and sent to a laboratory for testing.

There are two types of laboratory tests: immunoassay and chromatography (see Appendix B-3 for a comparison and overview of detection time).

- Province health plans vary in funding UDS; some provide immunoassays for classes of drugs (opioids, cocaine, benzodiazepines, cannabis) or one single drug at a time (e.g., oxycodone, methadone)
- Immunoassay detects drugs for a longer time than chromatography (5–7 days compared to 1–2 days) but does not distinguish between different types of opioids and often misses semi-synthetic or synthetic opioids such as oxycodone or meperidine.
- Chromatography is more expensive and requires specification of the drug(s) to be identified e.g., oxycodone, morphine, codeine, hydromorphone (alternatively can indicate: "full screen" or "broad spectrum screen").

2. Clinical Usefulness of UDS

2.1 Baseline Measure of Risk

UDS can be helpful in establishing the reliability of a patient's reported substance use. Some clinicians believe that UDS should be used routinely to establish baseline information regardless how well the patient is known to the prescriber. They believe a universal approach will eventually "de-stigmatize" UDS and increase prescriber confidence in using opioids. Other clinicians point out that UDS, whether point-of-care or laboratory-completed, is costly, not available in all parts of Canada, and that routine use adds an unnecessary burden to the system. These clinicians believe that UDS should be used selectively with patients who may be at risk for misuse.

...continued

R03 Discussion...continued

2.2 Monitoring for Compliance

During an opioid trial or after a patient is established on LTOT, UDS can be useful in detecting unauthorized drug use, non-compliance, and diversion (Adams 2001, Brown 2006). There is evidence that urine drug screening reduces substance use in LTOT patients (Manchikanti 2004, Manchikanti 2006.)

There is no compelling evidence to guide physicians on identifying CNCP patients who should have UDS or how often. In deciding whether to order a baseline UDS, and how often to use screening to monitor patients, consider:

- patient's risk for opioid misuse and addiction
- aberrant drug-related behaviours
- availability of UDS.

3. Conducting Urine Drug Screening

3.1 Prior to Ordering the Test

- Take a detailed history of the patient's medication use for the preceding 7 days.
- Inform patients that the UDS is not meant to "catch" or punish patients but to improve the safety and effectiveness of LTOT.
- Tell the patient what results are expected from appropriate opioid use and ask the patient if anything else might show up. (This gives the patient the opportunity to inform the prescriber about changes in their use of the prescribed drug or illicit drug use).
- If using a treatment agreement, add the requirement of UDS to the treatment agreement (see Recommendation 5).

3.2 Sample Collection and Preventing Tampering

3.2.1. Sample Dilution

The most common and easiest form of tampering is diluting the urine sample with water. Supervised sample collection makes tampering more difficult, but is a costly use of staff time and patients may find it demeaning. Use supervision if the patient is known to have tampered with a sample.

3.2.2 Sample Temperature

The temperature of the sample can be used to detect tampering because water added to a sample usually varies from body temperature. Temperature-test strips can be used, but they are costly, and must be read within minutes because the sample cools rapidly.

3.2.3. Creatinine Level

A urine creatinine of less than 2–3 mmol/liter is non-physiologic and suggests dilution. Most laboratories can test creatinine level.

4. Interpreting Unexpected Results of UDS

UDS can assist clinical decision-making but should not be considered definitive. Two examples illustrate this: 1) a patient who is diverting prescribed opioids might take a small amount of the prescribed drug so the UDS will be positive; 2) for cocaine there is a relatively short window of detection, so binge cocaine use could be missed.

R03 Discussion...continued

Table B-3.1 reviews some common unexpected results and provides a range of possible reasons and some potential actions. In some cases the physician may find it useful to review unexpected results with the laboratory or a physician experienced in interpreting UDS. Prescribers who are unfamiliar with using UDS should take steps to increase knowledge and skill by seeking out an appropriate educational resource or observership.

Table B-3.1 Interpreting Unexpected Results of Urine Drug Screens

	Unexpected Result	Possible Explanations	Actions for the Physician
1	UDS *negative* for prescribed opioid.	• False negative. • Non-compliance. • Diversion.	• Repeat test using chromatography; specify the drug of interest (e.g. oxycodone often missed by immunoassay). • Take a detailed history of the patient's medication use for the preceding 7 days (e.g., could learn that patient ran out several days prior to test) • Ask patient if they've given the drug to others. • Monitor compliance with pill counts.
2	UDS *positive* for non-prescribed opioid or benzodiazepines.	• False positive. • Patient acquired opioids from other sources (double-doctoring, "street").	• Repeat UDS regularly. • Ask the patient if they accessed opioids from other sources. • Assess for opioid misuse/addiction (See Recommendation 12). • Review/revise treatment agreement
3	UDS *positive* for illicit drugs (e.g., cocaine, cannabis).	• False positive. • Patient is occasional user or addicted to the illicit drug. • Cannabis is positive for patients taking dronabinol (Marinol®), THC:CBD (Sativex®) or using medical marijuana.	• Repeat UDS regularly. • Assess for abuse/addiction and refer for addiction treatment as appropriate • Ask about medical prescription of dronabinol, THC:CBD or medical marijuana access program.
4	Urine creatinine is lower than 2-3 mmol/liter.	• Patient added water to sample.	• Repeat UDS • Consider supervised collection or temperature testing • Take a detailed history of the patient's medication use for the preceding 7 days • Review/revise treatment agreement.
5	Urine sample is cold.	• Delay in handling sample (urine cools within minutes). • Patient added water to sample.	• Repeat UDS, consider supervised collection or temperature testing • Take a detailed history of the patient's medication use for the preceding 7 days • Review/revise treatment agreement.

R03 Summary of Peer-Reviewed Evidence

1. Urine drug screening and other forms of adherence monitoring may reduce rates of substance abuse.

Urine drug screens are an important but underutilized therapeutic tool. Currently, only a small percentage of physicians prescribing opioids for pain are utilizing UDS as a clinical tool: in one study only 8% of physicians utilized UDS (Adams 2001). Another study found only 7% used UDS before initiating opioids and 15% used UDS once patients were on long-term treatment (Bhamb 2006).

Yet, UDS can have value in both detecting substance abuse and in reducing it. In one study (Manchikanti 2004) of patients on stable doses of opioids, 16% were found to have evidence of illicit drug use, and the use of random UDS was found to decrease the amount of illicit drug use. Another evaluation of the same group of patients (Manchikanti 2006) found that a combination of UDS, treatment agreements, pill counts, and education reduced substance abuse by 50%.

R04 Recommendation Statement

R04 Before initiating opioid therapy, consider the evidence related to effectiveness in patients with chronic non-cancer pain. (Grade A).

Opioid efficacy

R04 Discussion

The systematic review update (see Part A, 10: Literature Search Methods) completed to support this guideline examined the effectiveness of opioids for CNCP. A summary of findings includes:

- Opioids were more effective than placebo for pain and function, irrespective of the type of opioid (strong or weak) or mechanism of pain (nociceptive or neuropathic).
- The effect sizes of opioids over placebo were medium[1] for pain and small for function. In other words, opioids work better for pain than for function.
- One opioid (tramadol) was effective for fibromyalgia for pain and function; however there were only two randomized trials, and the effects sizes were small for both pain and function.

Table B-4.1 Evidence of Opioid Efficacy

Examples of CNCP conditions for which opioids *were shown to be effective* in placebo-controlled trials*		Examples of CNCP conditions that *have NOT been studied* in placebo-controlled trials
Tramadol only	**Weak or strong opioid**	
Fibromyalgia	• Diabetic neuropathy • Peripheral neuropathy • Postherpetic neuralgia • Phantom limb pain • Spinal cord injury with pain below the level of injury • Lumbar radiculopathy • Osteoarthritis • Rheumatoid arthritis • Low-back pain • Neck pain	• Headache • Irritable bowel syndrome • Pelvic pain • Temporomandibular joint dysfunction • Atypical facial pain • Non-cardiac chest pain • Lyme disease • Whiplash • Repetitive strain Injury

*A limitation of these trials was that the duration of opioid therapy was a maximum of three months.

1. **Nociceptive pain of musculoskeletal origin (e.g., osteoarthritis, low-back pain, neck pain)**
Opioids showed only small to moderate benefits for nociceptive pain in improving function and relieving pain (Furlan 2006, Furlan unpublished 2010, Nuesch 2009). If opioids are required, patients generally respond to moderate doses. Acetaminophen, NSAIDs and non-pharmacological treatments are often effective for patients with low back pain and other common musculoskeletal problems.

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[1] For effect size, most authors use Cohen's three levels, (REF Cohen, & REF 2009 Updated Method Guideline)
Small: • Mean difference less than 10% of the scale (e.g., <10mm on a 100 mm VAS).
• ES <0.5.
Medium: • Mean difference 10 to 20% of the scale.
• ES from 0.5 to <0.8.
Large • Mean difference >20% of the scale.
• ES ≥ 0.8.

R04 Discussion… continued

2. Neuropathic pain

Opioids showed only small to moderate benefits for neuropathic pain (Furlan 2006, Furlan 2009, Eisenberg 2005). Patients with neuropathic pain may require higher opioid doses, in combination with tricyclic antidepressants (Khoromi 2007) or anticonvulsants (Gilron 2005).

3. Migraine, tension headache, functional GI problems

Opioids are usually not indicated for migraine or tension headaches, or for patients with functional gastro-intestinal problems such as irritable bowel syndrome (Bigal 2009).

4. Widespread soft tissue pain

The benefit of the weak opioid tramadol for fibromyalgia was small. Other pain-relief options should be considered.

R04 Summary of Peer-Reviewed Evidence

The updated systematic review of opioids for CNCP included 62 randomized trials (see Appendix B-13). Opioids were compared to placebos in 47 randomized trials. The effect size for improvement in pain was medium (0.58 95% confidence interval [CI]: 0.48 to 0.67, extracted from 47 RCTs). For functional outcomes, the effect size was small (0.34 95% CI: 0.25 to 0.43, extracted from 31 RCTs) (Furlan unpublished 2010).

1. Nociceptive pain and osteoarthritis.

The meta-analysis of 31 randomized trials of opioids for nociceptive pain showed a medium-effect size for pain relief outcomes (0.60 95% CI: 0.49 to 0.72, extracted from 31 trials), and small for functional outcomes (0.38 95% CI: 0.26 to 0.49, extracted from 21 trials) (Furlan unpublished 2010).

A recently published Cochrane review of opioids for osteoarthritis showed that the small-to-moderate beneficial effects of non-tramadol opioids are outweighed by large increases in the risk of adverse events. They concluded that non-tramadol opioids should therefore not be routinely used, even if osteoarthritic pain is severe (Nuesch 2009).

2. Neuropathic pain.

The meta-analysis of 13 randomized trials of opioids for neuropathic pain showed a medium effect size for pain relief outcomes (0.56 95% CI: 0.38 to 0.73, extracted from 13 trials), and small for functional outcomes (0.24 95% CI: 0.09 to 0.39, extracted from 7 trials) (Furlan unpublished 2010).

A fixed-effects model meta-analysis of 6 randomized trials of opioids for neuropathic pain showed mean post-treatment visual analog scale scores of pain intensity after opioids to be 14 units lower on a scale from 0 to 100 than after placebo (95% CI: −18 to −10; P<.001) (Eisenberg 2005).

3. Widespread soft tissue pain.

There are no randomized trials of strong opioids for fibromyalgia. There are two randomized trials of the weak opioid, tramadol for fibromyalgia. They showed small benefits in reducing pain (Russell 2000, Bennett 2003). The EULAR (European League Against Rheumatism) guidelines for the treatment of fibromyalgia recommend tramadol but not strong opioids (Carville 2008).

R05 Recommendation Statement

R05	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).	***Risks, adverse effects, complications***

R05 Discussion

1. Informed Consent

A discussion about potential benefits, adverse effects, complications, and risks helps the physician and patient make a joint decision on whether to proceed with opioid therapy. (See Appendix B-4 for opioid information for patients).

1.1 Goal Setting: Potential Benefits and Patient Expectations

Before starting opioids, the physician should ensure the patient's expectations are realistic. The goal of opioid therapy for *chronic* non-cancer pain is rarely the elimination of pain, but rather an improvement in function or a reduction of pain intensity by at least 30%. Before starting opioids, a discussion with the patient about specific goals related to pain reduction and functional improvement should address any unrealistic expectations. These agreed-on goals should be documented in the patient's record; they are critical in determining that opioids are effective and should be monitored over time.

1.2 Adverse Effects

The most common adverse effects are listed in Table B-5.1.

Table B-5.1 Adverse Effects of Opioids

Note: From randomized trials, excluding enrichment design trials, results show a clinically important difference (Diff>10%) and are statistically significant (P<0.05).

Adverse effect	Number of Studies	Incidence in Opioid Group	Incidence in Placebo Group	Difference (95% CI)
Nausea	38	28%	9%	17% (13% to 21%) P<0.00001
Constipation	37	26%	7%	20% (15% to 25%) P<0.00001
Somnolence/drowsiness	30	24%	7%	14% (10% to 18%) P<0.00001
Dizziness/vertigo	33	18%	5%	12% (9% to 16%) P<0.00001
Dry-skin/ itching/ pruritus	25	15%	2%	10% (5% to 15%) P<0.0001
Vomiting	23	15%	3%	11% (7% to 16%) P<0.00001

Adverse effects where the difference was not clinically important (Diff <10%) and/or not statistically significant (P>=0.05) include: dry-mouth, headache, sexual dysfunction, hot flushes, loss of appetite, abdominal pain, fatigue, sleeplessness/insomnia, sweating, blurred vision/confusion, muscle contractions, diarrhea, ataxia, edema, difficulty urinating, restless legs, application site reaction, heart burn, anxiety, weakness.

…continued

R05 Discussion… continued

1.3 Medical Complications

Information about medical complications associated with LTOT is reported in *non-randomized* trials (RCTs are short-term: 3 months). There is no evidence regarding the frequency of medical complications, the relationship between length of time on opioids and occurrence of medical complications, or whether the complications are permanent or transient. Patients should be informed about potential long-term use medical complications such as **neuroendocrine** (hypogonadism and amenorrhea), **sleep apnea** (central sleep apnea or worsening of obstructive sleep apnea), and **opioid-induced hyperalgesia**.

1.3.1 Neuroendocrine Abnormalities

Neuroendocrine abnormalities and **erectile dysfunction** can be experienced with LTOT (Ballantyne 2003, Daniell 2006). One recently published randomized trial found that the incidence of sexual dysfunction after morphine happened in 11% (Khoromi 2007). However, two other randomized trials suggested that patients taking opioid medications reported better sexual function, which was likely an improvement of well-being (Arkinstall 1995, Watson 2003). In summary, in the short term, the patient may notice improvement in sexual function (as a consequence of improved analgesia), but in the long term, opioids may cause neuroendocrine dysfunction.

1.3.2 Sleep Apnea

Opioids can aggravate not just **central sleep apnea**, but frequently also significantly aggravate **obstructive sleep apnea**. High opioid doses may contribute to sleep movement disorders including myoclonus and sometimes choreiform movement, and in combination with benzodiazepines and other drugs may significantly contribute to oxygen desaturation (Zgierska 2007, Mogri 2008, Farney 2003). Consider a sleep study for patients using high-dose opioids, opioid in combination with other sedating drugs, elderly patients, obese patients, and patients with somnolence.

1.3.3 Opioid-induced Hyperalgesia (OIH)

OIH is a paradoxical hyperalgesia resulting from LTOT. It is characterized by pain sensitivity (hyperalgesia and allodynia) in the absence of overt opioid withdrawal. It is distinct from tolerance in that pain extends beyond the area of initial complaint. It is also known as opioid neurotoxicity or opioid-induced pain sensitivity (OIPS) (Chu 2006, Ballantyne 2003).

1.4 Risks

Explain the potential risks of opioid therapy and provide reassurance on how the risks can be managed. See Table B-5.2.

…continued

Table B-5.2 Opioid Risks

	Actions for the Physician	Information for the Patient	Directions for the Patient and Family
1. Risk: OVERDOSE	• Start with a low dose, titrate gradually, and monitor frequently. See Table B-9.1: Opioid Suggested Initial Dose and Titration. • Be cautious when prescribing benzodiazepines (see Recommendation 06). • For patients at higher risk of overdose*, —initial dose should not exceed 50% of the suggested initial dose, and dose increments should be more gradual (See Table B-9.1). —consider a 3-day "tolerance check:" contact the patient 3 days after starting the opioid to check for signs of oversedation.	• Opioids are safe over the long term, BUT can be dangerous when starting or increasing a dose. • Overdose means thinking and breathing slows down — this could result in brain damage, trauma, and death. • Mixing opioids with alcohol or sedating drugs greatly increases the risk of overdose.	• *Contact a physician on early signs of overdose: slurred or drawling speech, emotional lability, ataxia, "nodding off" during conversation or activity.* • *Avoid mixing prescribed opioids with alcohol or sedating drugs.* • *Avoid driving a vehicle or operating equipment/heavy machinery until a stable dose is reached.* • *If you interrupt your medication schedule for three days or more for any reason, do not resume taking it without consulting a physician.*
2. Risk: DIVERSION	Ask questions about the following to determine risk of opioid diversion: • History of alcohol or substance abuse (patient and/or household member) • Transient or unstable housing • Vulnerability and dependence on caregivers	• Sharing prescribed medication with others is illegal, and could harm the other person. • While the patient's opioid dose is safe, it may be dangerous for other people. • Adolescents may abuse prescription opioids and sometimes pilfer drugs from the family medicine cabinet	• *Do not give your prescribed medication to any other person: This is illegal, and the drug could harm the other person.* • *Store your medication in a secure place with limited access to guard against others' (e.g., adolescents) illicit use.* • *Inform your physician if you feel your medication is insecure, or if you feel any pressure about sharing.*

Table B-5.2 Opioid Risks... *continued*

	Actions for the Physician	Information for the Patient	Directions for the Patient and Family
3. Risk: ADDICTION	Use appropriate screening tools to determine risk of addiction.	• Addiction means that a person uses the drug to "get high," and cannot control the urge to take the drug. • However, most patients do not get high from taking opioids, and addiction is unlikely if addiction risk factors are low: those at greatest risk have a history of addiction. • Withdrawal symptoms can occur in any patient taking opioids regularly: they do not indicate addiction.	*Do not let unfounded fears of addiction stop you from taking your medication. Take your medication strictly as prescribed and do not stop the medication without informing a doctor.*
4. Risk: WITHDRAWAL	If a decision is made to discontinue opioid therapy, the opioids should be tapered under medical supervision (see Appendix B-12).	• Opioid withdrawal symptoms are flu-like, e.g., nausea, diarrhea, and chills. • Withdrawal is not dangerous but it can be very uncomfortable. • Withdrawal can occur in any patient who takes opioids regularly, and it does not mean that the patient is addicted.	*Do not abruptly discontinue your medication, as this can cause uncomfortable withdrawal symptoms.*

* Patients at higher risk of opioid overdose are those with:

1. **Renal or hepatic impairment***:* Caution is advised, because opioids are metabolized in the liver and excreted through the renal system (Tegeder 1999, Foral 2007). Morphine is contraindicated in renal insufficiency.
2. **Chronic obstructive pulmonary disease (COPD) and sleep apnea***:* Opioid use may be a risk factor for central sleep apnea (Mogri 2008). Tolerance to the respiratory depressant effects of opioids develops slowly and incompletely, putting COPD patients at risk for respiratory depression with a higher dose increase.
3. **Sleep disorders***:* Sleep disorders, including insomnia and daytime sleepiness, are common among opioid users (Zgierska 2007). They may reflect the effects of pain, or the sedating effects of opioids, or concurrent depression.
4. **Cognitive impairment***:* Opioids should be avoided in cognitively impaired patients who live alone, unless ongoing medication supervision can be arranged.

R05 Discussion... continued

2. Treatment Agreement / Contract

Contracts are widely used in the long-term administration of potentially abusable substances. These agreements are intended to improve adherence and to enhance the therapeutic relationship by initiating an alliance between the patient and the physician. A contract is defined as an "explicit bilateral commitment to a well-defined course of action." Responsible parties in the contract usually have a clearly stated understanding of their individual obligations.

Contracts attempt to improve treatment through disseminating information, facilitating an agreed-on course, and enhancing adherence. The treatment agreement often includes clear descriptions of medication use and abuse, as well as the consequences for violating the contract.

2.1 Treatments Agreements: Oral or Written

- Written treatment agreements are chosen particularly for patients the physician does not know well, or who are at higher risk for misuse. A written agreement is usually signed by both patient and physician, with a copy provided to the patient.
- Oral treatment agreements should be documented in the patient's chart.

2.2 Treatments Agreement Contents

The agreement usually outlines responsibilities and boundaries for both the patient and physician. (See Appendix B-5 for an example of a treatment agreement.) For example, a treatment agreement typically includes the following:

- states that the patient:
  - —will not give opioids to others
  - —will not receive opioids from other sources
  - —will store the medication in a safe place
  - —will comply with scheduled visits and consultations
  - —will provide urine samples for drug screens when requested
- states that the physician:
  - —will not normally refill the prescription ahead of schedule if the patient runs out
  - —may cease opioid prescribing if the patient does not abide by the agreement.
- identifies one single prescribing physician: All physicians involved in the patient's care should agree on a designated prescribing physician, and whenever possible, identify an alternate physician to continue prescribing a patient's medication in the event that the primary prescribing physician is unavailable.
- identifies one dispensing pharmacy.

R05 Summary of Peer-Reviewed Evidence

1. Non-randomized trials describe medical complications.

1.1 Hypogonadism

Opioids influence the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis. Morphine has been reported to cause a strong, progressive decline in the plasma cortisol level in adults. Opioids interfere with the modulation of hormonal release, including an increase in prolactin and a decrease in luteinizing hormone, follicle-stimulating hormone, testosterone, and estrogen. Testosterone depletion has been demonstrated in heroin addicts and in patients receiving methadone maintenance therapy. The collective effects of the hormonal changes may lead to decreased libido, aggression, and drive; amenorrhea or irregular menses; and galactorrhea (Ballantyne 2003).

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R05 Summary of Peer-Reviewed Evidence…continued

Most randomized trials reviewed did not inquire about sexual dysfunction. The few studies that did so were of too short duration to allow for the development of any endocrinological abnormalities. In these studies, the authors inquired about sexual activity by using the Pain Disability Index (PDI). This index consists of 7 self-reported disability subscales, one of which refers to sexual activity; each scale is graded from 0 to 10, where 0 = no disability and 10 = total disability. This scale is not adequate to validly identify sexual dysfunction. Only two studies give a specific score on the dimension of sexual activity. In the first study using this measure (Arkinstall 1995), with 46 patients randomly assigned to receive CR codeine or placebo, the PDI score for the "sexual activity" subscale was 4.1 and 6.3, respectively. In the other (Watson 2003), which involved 45 patients, the score was 3.4 for controlled-release oxycodone and 4.5 for placebo. Both studies, therefore, suggested that patients taking opioid medications reported better sexual function than those taking placebo.

However, the PDI is a patient-rated global rating of function, does not measure variables such as libido, sexual dysfunction or gonadal function, or opportunity for sexual activity, and by itself cannot be used to estimate risk of hypogonadism. It is more likely that improvement of well-being secondary to better pain control by the use of opioids, accounted for this reported positive result in those studies.

One recently published trial (Khoromi 2007) found that the incidence of sexual dysfunction after morphine happened in 11% (of 28 completers of the study, out of 55 randomized), 0% in the nortriptyline group, 4% in the combination (morphine plus nortryptiline) and 0% in the placebo group. It is not possible to draw conclusions about the differences among these four groups because 1) this information is drawn from the completers of the study, and 2) these subgroup analyses do not have statistical power to detect any meaningful difference. Nevertheless, it was interesting to note that most recent studies are starting to ask participants about sexual dysfunction as a possible adverse event from opioids.

1.2 Sleep apnea

Patients on long-term sustained-release opioids show a distinctive pattern of sleep-disordered breathing that is different from the disturbances usually observed in subjects with obstructive sleep apnea (OSA). The oxygen desaturation is more severe and respiratory disturbances are long during NREM sleep (Farney 2003). In another study, even a short-term ingestion of opioid analgesic precipitated central sleep apnea in patients with chronic pain receiving long-term opioid therapy (Mogri 2008). There is also evidence that opioids may complicate underlying sleep apnea and make continuous positive airway pressure (CPAP) therapy less effective (Mogri 2008).

1.3 Opioid-induced hyperalgesia

Many studies were conducted in healthy volunteers with experimental pain, opioid addicts on methadone program and on perioperative exposures to opioids. There is one prospective study conducted on chronic pain patients (low-back pain) after one month of oral morphine therapy (Chu 2006). These authors showed evidence for the development of analgesic tolerance and OIH using a cold pressor test and experimental heat pain to measure pain sensitivity.

…continued

R05 Summary of Peer-Reviewed Evidence…continued

2. Evidence for Treatment Agreements

Overall, there is evidence to support the use of treatment agreements, although from non-randomized studies (Arnold 2006). One small study found that treatment agreements improve compliance (Fishman 2000), while another found that primary-care physicians were more willing to prescribe opioids to patients if the pain-medicine physician also signed an agreement ("trilateral contract") (Fishman 2002).

R06	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).

Benzodiazepine tapering

R06 Discussion

The combination of opioids and benzodiazepines increases the risk of sedation, overdose, and diminished function in all patients, especially as age advances. (See also Recommendation 17 for prescribing cautions for the elderly). Opioids should be prescribed more slowly and at lower doses for patients on benzodiazepine treatment.

A successful trial of **benzodiazepine tapering** can mean either a dose reduction or elimination of benzodiazepines. (See Appendix B-6 for a description of benzodiazepine tapering approach.) Benzodiazepine tapering is feasible in a primary-care setting, and it is associated with improved health outcomes. Tapering benzodiazepines may not be indicated in situations such as moderate to severe anxiety, panic disorder, seizures, and spasticity.

R06 Summary of Peer-Reviewed Evidence

1. There is evidence that benzodiazepines increase opioid toxicity and risk of overdose.

Concurrent prescribing of opioids and benzodiazepines is common. Cross-sectional studies suggest that pain patients may be more likely to be prescribed opioids and to receive higher doses if they abuse alcohol, are on benzodiazepines, or are depressed (Hermos 2004, Sullivan 2005). Most opioid overdoses involve multiple drugs in addition to opioids (Mirakbari 2003); benzodiazepines and alcohol are most commonly implicated. The serum concentration of opioids is lower in mixed overdoses than in pure overdoses, suggesting that other drugs significantly lower the lethal opioid dose (Cone 2004).

2. There is evidence that benzodiazepines can be successfully tapered in a primary-care setting, with improved health outcomes.

Several controlled trials have demonstrated that benzodiazepine tapering can be done in a primary-care setting. Tapering has been shown to be successful both in patients with anxiety disorders and with insomnia (Baillargeon 2003, Gosselin 2006). An observational study documented reduced symptoms of depression in methadone patients who were tapered off benzodiazepines and started on antidepressant therapy (Schreiber 2008). Tapering is more effective when combined with cognitive-behavioural therapy, but can be successful without formal CBT (Baillargeon 2003, Gosselin 2006, Vicens 2006). A significant number of older patients are willing to attempt benzodiazepine tapering (Cook 2007). Patients being tapered for insomnia have decreased sleep time but improved quality of sleep post-taper (Morin 2004). Controlled trials have found that psychiatric symptoms (panic disorder, GAD) do not worsen with tapering, and may improve (Moroz 1999, Gosselin 2006). For an approach to benzodiazepine tapering, see Appendix B-6.

Cluster 2: Conducting an Opioid Trial

R07	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).

Titration and driving

R07 Discussion

During an opioid trial titration, patients should be advised that opioids could cause cognitive effects that could impair their ability to drive. This caution is even more important in patients taking alcohol, benzodiazepines, or other sedating drugs with their opioids. For more details about opioids and driving, see Recommendation 14.

A "pharmacologically stable dose" is one that produces a fairly steady plasma level; it is established when the *total daily dose* is fixed for at least two weeks *and*:

1) frequency is scheduled and spread throughout the day
   AND/OR
2) at least 70% of the prescribed opioid is controlled release.

R07 Summary of Peer-Reviewed Evidence

1. Patients who undergo a significant increase in the dose of narcotic experience significant cognitive impairment.

Bruera et al. reported on 40 patients with cancer pain: 20 had no change in narcotic dose (stable dose) and 20 had undergone an increase of more than 30% in dose (increased dose group). Cognitive changes were observed only in the increased dose group (Bruera 1989).

2. In a population receiving both narcotics and benzodiazepines, the cognitive impairment noted was found to be more likely due to benzodiazepines than to narcotics.

Hendler et al. compared three groups of patients: benzodiazepines alone, narcotics alone, and both benzodiazepine and narcotics. They found that narcotics did not impair cognitive functioning, memory or performance on visual and motor-perceptual tasks, however, cognitive impairment was much more apparent in patients receiving benzodiazepines (Hendler 1980).

R08 Recommendation Statement

R08	During an opioid trial, select the most appropriate opioid for trial therapy using a stepped approach, and consider safety. (Grade C).	***Stepped opioid selection***

R08 Discussion

The most appropriate drug for an opioid trial depends on the patient's clinical profile and individual circumstances. The following tables have been prepared to assist prescribers in selecting the most appropriate opioid.

Table B-8.1 Stepped Approach to Opioid Selection

Mild-to-Moderate Pain	**Severe Pain**
First-line for Mild-to-Moderate Pain: codeine or tramadol	
Second-line for Mild-to-Moderate Pain: morphine, oxycodone or hydromorphone	*First-line for Severe Pain*: morphine, oxycodone or hydromorphone
	Second-line for Severe Pain: fentanyl
	Third-line for Severe Pain: methadone

…continued

Table B-8.2 Safety Issues to Consider When Selecting Opioids

Note: This table highlights safety issues for specific agents; for comprehensive information, prescribers should consult the individual drug monographs.

Agent	Safety Issues
Codeine	1) Use with caution for breast-feeding women: some rapidly convert codeine to morphine, placing the infant at risk of morphine toxicity. (See Recommendation 19.) 2) Lower risk of overdose and addiction than stronger opioids. (See Supporting Evidence item 1.)
Tramadol	1) Associated with seizures in patients at high seizure risk, or when combined with medications that increase serotonin levels, e.g., SSRIs. 2) Lower risk of overdose and addiction than stronger opioids. (See Supporting Evidence item 1.)
Morphine	Avoid for patients with renal dysfunction: an active metabolite of morphine (M-6 glucoronide) can accumulate to toxic levels in patients with renal impairment. (See Supporting Evidence item 2.)
Oxycodone, Hydromorphone, Hydrocodone	Use with caution for patients at higher risk for opioid misuse and addiction: experimental studies and surveys of drug users suggest that oxycodone, hydromorphone and hydrocodone may have a higher abuse liability than morphine. (See Supporting Evidence item 3.)
Fentanyl	1) Before starting fentanyl, obtain a complete history of-opioid use within the last 2 weeks to ensure the patient is fully opioid tolerant. Tolerance can be assumed if the patient is on a moderate, stable dose of a strong opioid, i.e., a total daily dose of at least 60–90 mg/day morphine equivalence daily for at least 2 weeks. This dose should be scheduled rather than p.r.n. (at least b.i.d. for CR or q.i.d. for IR). See Supporting Evidence item 4.) 2) Do not switch from codeine to fentanyl regardless of the codeine dose, as some codeine users may have little or no opioid tolerance. 3) Maintain the initial dose for at least 6 days: use extra caution with patients at higher risk for overdose, e.g., elderly, patients on benzodiazepines. 4) Advise the patient as follows: • Be alert for signs of overdose: (e.g. slurred or drawling speech, emotionally labile, ataxia, nodding off during conversation or activity) if detected, remove the patch and seek medical attention. • Apply as prescribed: do not apply more than one patch at a time or change more often than directed. • Avoid heat sources such as heating pads, electric blankets, saunas, heated waterbeds, hot baths, sunbathing. • Dispose of patches securely: a used patch contains large amount of fentanyl and could be dangerous to others. e.g., children or abusers could "recycle" by cutting into small pieces and sucking the pieces.
Methadone	Use methadone to treat pain only if holding a written Health Canada exemption. Titration is hazardous due to its very long half life leading to bio-accumulation. (See Supporting Evidence item 5.)

...continued

Table B-8.2 Safety Issues to Consider When Selecting Opioids… continued

Agent	Safety Issues
Meperidine (Demerol®)	Not recommended for use in CNCP: a) oral meperidine has poor bioavailability and is less effective than codeine, and b) normeperidine can accumulate with frequent use of parenteral doses of meperidine, causing seizures and delirium. (See Supporting Evidence item 6.)
Acetaminophen-opioid combinations	Use with caution to avoid acetaminophen toxicity. FDA (U.S.) recommends a maximum daily dose of 3.2 grams acetaminophen for adults = 10 tablets/day for opioid/ acetaminophen combinations. The manufacturer recommends a lower dose for tramadol/acetaminophen (8 tablets/day). (See Supporting Evidence item 7.) Heavy drinkers should be advised to use acetaminophen with extra caution.

Table B-8.3 Other Formulations and Preparations

Formulation/ Preparation	Safety Issues
CR formulations	Titrate with caution to avoid overdose and misuse: each CR tablet can contain a much higher opioid dose than IR formulations, and can easily be converted to IR by biting or crushing the tablet. (See Supporting Evidence item 8.)
Parenteral opioids	Parenteral opioids are not recommended for use in CNCP: parenteral route has higher risk of overdose, abuse and addiction, and infection.

R08 Supporting Evidence

1. Codeine and Tramadol

1.1 Codeine and tramadol may have a lower abuse risk than more potent opioids.

Codeine has a lower risk of abuse and addiction than stronger opioids. For example, one national U.S. study found that codeine and other low potency opioids have low ratios of abuse to prescription use, relative to oxycodone, hydromorphone and hydrocodone. Abuse rates were measured from Drug Abuse Warning Network data (Dasgupta 2006). Tramadol also has a low risk of addiction, and experimental studies suggest that it has fewer psychoactive effects than other opioids (Preston 1991, Cicero 2005).

2. Morphine

2.1 Morphine can cause toxicity in patients with renal dysfunction.

For example, one cross-sectional study demonstrated that M-6 glucoronide, an active metabolite of morphine, accumulated in the serum of patients with renal dysfunction when morphine was administered orally or subcutaneously. The degree of accumulation was related to the morphine dose and the extent of renal impairment (Peterson 1990).

3. Oxycodone, Hydromorphone and Hydrocodone

3.1 There is evidence that oxycodone and hydromorphone have a higher abuse liability than other opioids. This is based on phase-2 studies, patient surveys, and studies of treatment programs.

One study found that prescription opioid misusers ranked controlled-release oxycodone, and immediate-release hydromorphone and oxycodone as the most desirable of 14 different opioid formulations. The study used a validated opioid attractiveness scale (Butler 2006). A national surveillance study of addiction experts, law enforcement agencies and poison control centers identified hydrocodone and both immediate-release and controlled-release oxycodone as by far the most commonly abused opioids in the United States (Cicero 2007).

Only a few controlled studies have been conducted comparing opioids on their abuse liability. Two placebo-controlled studies compared the psychoactive effects of oral morphine to oral oxycodone in non-drug abusing volunteers. The studies found that oxycodone had greater reinforcing effects at equi-analgesic doses to morphine (Zacny 2003, Zacny 2007). Another controlled trial found that oxycodone, hydromorphone and hydrocodone had equivalent abuse liability (Walsh 2008). The clinical significance of these studies for chronic pain patients is not certain because volunteers may experience different psychoactive effects than actual pain patients (Lamb 1991).

It is also possible that the prevalence of oxycodone abuse may simply reflect its popularity as an opioid analgesic. In an analysis of data from the Drug Abuse Warning Network, oxycodone, hydromorphone and morphine had similar rates of overdoses and other events after controlling for the potency of the opioid and the amounts prescribed in kg (Dasgupta 2006).

4. Fentanyl

4.1 Fentanyl can cause significant cognitive impairment in non-tolerant opioid patients.

Experimental studies in volunteers have found that cognitive impairment caused by acute intravenous fentanyl administration was greater than that caused by moderate doses of alcohol (Zacny 1992, Schneider 1999).

…continued

R08 Supporting Evidence, 4. Fentanyl…continued

4.2 Fentanyl has contributed to numerous overdose deaths.

Fentanyl was a contributing cause in 100 overdose deaths in Ontario between 2002 and 2004. In 54 of the deaths, fentanyl intoxication was the sole cause of death. Deaths occurred from both therapeutic and illicit use (Martin 2006).

Fentanyl-laced heroin appeared simultaneously in various parts of the United States, beginning in 2005. In Chicago, in the first half of 2006, 55 drug overdose cases (resulting in 12 deaths) have been attributed to fentanyl-laced heroin (Fodale 2008). Fentanyl toxicity is related in 92% of fentanyl-related deaths and is attributed partially due to cytochrome P450 3A4*1B and 3A5*3 variant alleles, resulting in variable fentanyl metabolism: the homozygous CYP3A5*3 have impaired metabolism of fentanyl (Fodale 2008). In July 2005, the FDA issued a public health advisory calling attention to an increase in the number of fentanyl patch-related overdoses and deaths, particularly among patients ignoring the product's boxed warnings and instruction for use (Federal Drug Administration 2007).

4.3 CNCP patients on codeine at risk for overdose when switched to fentanyl.

Up to 10% of Caucasians lack the enzyme CYP450 2D6 that converts codeine to morphine and therefore when switching from codeine to fentanyl, regardless of the codeine dose, caution is required as patients may have little or no opioid tolerance (Tyndale 1997, Romach 2000, Howard 2002).

5. Methadone

5.1 Methadone for pain is more effective than placebo, but has not been shown to be more effective than other opioids.

Sandoval (2005) conducted a systematic review of methadone for CNCP. The review included 21 studies (1 small randomized trial, 13 case reports, and 7 case series) and concluded that pain improvements were meaningful in 59% of the patients in the uncontrolled studies. The randomized trial demonstrated a statistically significant improvement in pain for methadone (20 mg/day) compared to placebo. Side effects were considered minor. One controlled trial found no difference in analgesic efficacy between morphine and methadone in cancer patients with respect to pain management (Bruera 2004). A similar trial found no difference between methadone, oral morphine and transdermal fentanyl 25 ucg/hour, although methadone titration was more difficult (Mercadante 2005).

5.2 Physicians must hold an exemption from Health Canada before prescribing methadone for pain.

Methadone has been associated with numerous overdose deaths in pain patients. Methadone analgesic use has increased sharply in the US, with a seven-fold rise from 1997 to 2004 (Sims 2007). This has been accompanied by a 17-fold increase in methadone overdose deaths (Shields 2007, Sims, 2007). Federal law requires that a physician hold a written exemption from Health Canada before prescribing methadone for analgesia. The specific process to apply for a methadone exemption varies by jurisdiction, and may include submission of a letter of support from the applicable medical regulatory authority before Health Canada will provide a methadone exemption. A physician may be able to receive an exemption to prescribe methadone under various circumstances, including if "mentored" by an experienced methadone prescriber. Physicians should confirm the methadone prescribing requirements of the jurisdiction where they practice.

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R08 Supporting Evidence…continued

6. Meperidine (Demerol®)

6.1 Repeated parenteral doses of meperidine are associated with adverse neurological events.

In one study of hospitalized patients receiving parenteral meperidine, 14% had neurological adverse events such as confusion or seizures. The risk of an adverse event was associated with the cumulative meperidine dose, renal insufficiency, and benzodiazepine use (Seifert 2004).

7. Acetaminophen-opioid Combinations

7.1 Acetaminophen is a common cause of hepatotoxicity; risk increases with alcohol use.

Acetaminophen toxicity causes the majority of cases of acute liver failure in the U.S., (Krenzelok 2009, Amar 2007). Sub-clinical liver toxicity has been shown to occur even with doses below 4 gm/day (Krenzelok 2009, Arundel and Lewis 244-54). To reduce toxicity, the FDA in the U.S. revised their maximum daily acetaminophen dose downward, from 4 gm/day to 3.2 gm/day. Alcohol competes for the same metabolic pathway as acetaminophen so heavy drinkers are at higher risk for toxicity. Chronic alcohol use is an independent risk factor for mortality in acetaminophen poisoning (Schmidt 2002).

8. CR Formulations

8.1 CR opioids are available in high-dose formulations which increase their risk of abuse and overdose.

CR opioids contain much higher opioid doses than acetaminophen-opioid combinations (e.g., one OxyContin® 80 mg tab = 16 Percocet® tablets). This increases the risk of both overdose and addiction. Controlled experimental studies indicate that the psychoactive effects of an opioid are dose related (Lamas 1994). Studies using non-drug-abusing volunteers have found dose-related reinforcing psychoactive effects with oral doses of 5, 10, and 20 mg of hydrocodone, and 10, 20, and 30 mg of oxycodone (Zacny 2003, 2005).

CR opioids can easily be converted to IR by crushing or biting the tablet. The outer layer of the OxyContin® tablet (but not other Contin tablets) is an IR formulation, containing 1/3 of the total dose.

R09 Recommendation Statement

R09	When conducting a trial of opioid therapy, start with a low dosage, increase dosage gradually and monitor opioid effectiveness until optimal dose is attained. (Grade C).	***Optimal dose***

R09 Discussion

1. Optimal Dose

1.1 Dose: Initial and Incremental

The object of the trial is to determine the optimal dose, i.e., a dose that will improve function or reduce pain intensity by at least 30% without causing major adverse effects or complications. It is recommended to start the opioid trial with a low dose and increase the dose in small quantities. Opioids produce a graded analgesic response: the patient experiences the greatest benefits at lower doses and a plateauing of analgesic response at higher doses. Therefore, slow titration 1) avoids unnecessarily high doses, and 2) reduces the risk of sedation and overdose as it ensures that a dose increase does not exceed the patient's tolerance. (Consider a three-day "tolerance check" for elderly and other high-risk patients: the nurse, physician, or pharmacist calls the patient/family three days after starting the prescription to check for any signs of sedation.) See Table B-9.1 for opioid suggested initial dose and titration.

1.2 Attaining Optimal Dose

The **optimal dose** is reached with a BALANCE of three factors:
1) **effectiveness**: improved function or at least 30% reduction in pain intensity
2) **plateauing**: effectiveness plateaus—increasing the dose yields negligible benefit, and
3) **adverse effects/complications**: adverse effects or complications are manageable.

1.3 Watchful Dose

Watchful Dose = morphine or equivalent dose exceeding 200 mg/day. See Recommendation 10 for guidance on a watchful dose.

2. Measuring Opioid Effectiveness

Opioid effectiveness = improved function or at least 30% reduction in pain intensity.

During an opioid trial, schedule patient visits frequently (e.g., 2–4 weeks) to assess for changes in pain intensity and function.

2.1 Assessing Function Change

The patient's progress in reaching agreed-on goals is an important indicator of function change. Self-report can be prompted by asking about work, household activity, mood, walking ability, sleep, and social activities. For an example of a structured assessment tool frequently used in trials, see Appendix B-9: Brief Pain Inventory©.

2.2 Assessing Pain Change

A 30% or greater reduction in pain intensity is considered clinically significant (Farrar 2001).

Change in pain intensity can be assessed using an 11-point (0–10) numeric rating scale (NRS). With each dose increase, the patient should be asked to estimate the pain intensity: a desirable response is a reduction in pain intensity (e.g., from 9/10 [baseline] to 6/10 [endpoint]) and a longer duration of analgesia per dose.

…continued

R09 Discussion, Assessing Pain Change… continued

Example of assessing change in pain intensity:

1. Determine the ***raw change*** in the NRS score:
   baseline – endpoint, e.g., 9 – 6 = 3

2. Determine the ***percent change***:
   $\frac{\text{raw change}}{\text{baseline}}$ x 100, e.g., $\frac{3}{9}$ x 100 = 33%

3. Monitoring for Adverse Effects, Medical Complications, Compliance, and Risks

3.1 Adverse Effects and Medical Complications

See Recommendation 5 for potential adverse effects, medical complications, and risks.

3.2 Compliance

Compliance is indicated when the patient takes the opioids as prescribed and shows no signs of misuse or aberrant drug-related behaviours.

4. Ending Titration

Titration ends when 1) the optimal dose is attained, or the 2) trial is considered a "failed trial."

The following circumstances could indicate a failed trial:

1) The patient experiences insufficient analgesia after two or three dose increases and/or unacceptable adverse effects and/or medical complications (see Recommendation 13).
2) There are indications of misuse or addiction (see Recommendation 12).

5. Documenting the Trial

It is important to record all aspects of the opioid trial in the patient's chart. Details regarding dose, frequency, opioid effectiveness, adverse effects, medical complications, goal attainment, and compliance are crucial in evaluating the opioid trial outcome.

For documentation templates, see Appendix B-7.

R09 Summary of Peer-Reviewed Evidence

1. Clinically important change for numerical pain scale (NRS)

"On average, a reduction of approximately two points or a reduction of approximately 30% in the PI-NRS represented a clinically important difference. The relationship between percent change and the PGIC was also consistent regardless of baseline pain, while higher baseline scores required larger raw changes to represent a clinically important difference" (Farrar 2001).

Table B-9.1 Opioid Suggested Initial Dose and Titration

Modified from Weaver 2007 with information from the e-CPS (Canadian Pharmacists Association, 2008)

Note: The table is based on oral dosing for chronic non-cancer pain. Brand names are shown if there are some distinct features about specific formulations. Reference to brand names as examples does not imply endorsement of any of these products.

ASA: acetylsalicylic acid, CR = controlled release, IR = immediate release, NA = not applicable

Opioid	Initial dose	Minimum time interval for increase	Suggested dose increase	Minimum daily dose before converting IR to CR
Codeine (alone or in combination with acetaminophen or ASA)	15-30 mg q.4 h. as required	7 days	15-30 mg/day up to maximum of 600 mg/day (acetaminophen dose should not exceed 3.2 grams/day)	100 mg daily
CR Codeine	50 mg q.12 h.	2 days	50 mg/day up to maximum of 300 mg q.12 h.	NA
Tramadol (37.5 mg) + acetaminophen (325 mg)	1 tablet q.4-6 h. as needed up to 4/day	7 days	1-2 tab q. 4-6 h. as needed up to maximum 8 tablets/day	3 tablets
CR Tramadol	a) Zytram XL®: 150 mg q. 24 h. b) Tridural™: 100 mg q. 24 h. c) Ralivia™: 100 mg q. 24 h.	a) 7 days b) 2 days c) 5 days	Maximum doses: a) 400 mg/day b) 300 mg/day c) 300 mg/day	NA
IR Morphine	• 5-10 mg q. 4 h. as needed • maximum 40 mg/day	7 days	5-10 mg/day	20-30 mg
CR Morphine	• 10-30 mg q.12 h. • Kadian®: q. 24 h. Kadian® should not be started in opioid-naïve patients	Minimum 2 days, recommended: 14 days	5-10 mg/day	NA
IR Oxycodone	• 5-10 mg q. 6 h. as needed • maximum 30 mg/day	7 days	5 mg/day	20 mg
CR Oxycodone	• 10-20 mg q.12 h. • maximum 30 mg/day	Minimum 2 days, recommended: 14 days	10 mg/day	NA
IR Hydromorphone	• 1-2 mg q. 4-6 h. as needed • maximum 8 mg/day	7 days	1-2 mg/day	6 mg
CR Hydromorphone	• 3 mg q. 12 h. • maximum 9 mg/day	Minimum 2 days, recommended: 14 days	2-4 mg/day	NA

R10 Recommendation Statement

R10	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).	*Watchful dose*

R10 Discussion

Watchful Dose = morphine or equivalent dose exceeding 200 mg/day.

Some patients may require higher doses of opioids (e.g., patients who are benefiting from opioids but have developed tolerance), but based on existing RCTs, the majority of patients with CNCP will respond at doses up to the equivalent of 200 mg/day of morphine.

1. Considerations before Dose Exceeds 200 mg/day

Before prescribing over 200 mg/day, consider:

1. Reassessment of the pain problem:
   - Is diagnosis(es) accurate?
   - Is opioid effective for the patient's diagnosis(es)? (See Recommendation 4 for an overview of evidence of opioid efficacy.)
   - Is further investigation and/or consultation required?
   - Are non-opioid treatment options available?
   - Is there an inadequately treated mental health disorder?
2. Patient's response to opioids:
   - Has the patient shown appropriate opioid effectiveness (i.e., improved function or at least 30% reduction in pain intensity) in response to the dose increases to date? (Opioids have a graded response with the greatest benefit at the lowest doses.) If response has been insignificant, continuing to increase the dose will be futile. Switching or discontinuing the opioid could be considered.
   - Are there indications of increased medical complications and adverse effects? Some complications, i.e., opioid-induced hyperalgesia, cognitive impairment (attentional performance) and hypogonadism occur more frequently with higher doses (also see Recommendation 5).
3. Risk of misuse:
   - Is there any indication of aberrant drug-related behaviours?

2. Monitoring Doses Exceeding 200 mg/day

If prescribing over 200 mg/day, monitor patients more frequently for opioid effectiveness, medical complications, adverse effects and risks.

R10 Summary of Peer-Reviewed Evidence

1. Evidence of effectiveness and adverse effects from randomized controlled trials.

The systematic review update described in Part A: Literature Search Methods included 62 randomized trials, of which 25 employed a titration or fixed scheme to achieve optimal analgesia (Furlan unpublished 2010). The maximum, minimum, and average daily doses of morphine equivalents are shown in Table B-10.1 below.

Randomized trials of tramadol or codeine are not shown Table B-10.1 because there is a maximum pre-established daily dose of 400 and 600 mg respectively. Elderly patients (>75 years of age) should receive maximum of 300 mg of tramadol per day (Pascual 2007). Trials of transdermal fentanyl are not shown because they are not recommended for opioid-naïve patients, and it is commonly used as a second-line opioid; therefore the usual doses of transdermal fentanyl are dependent on the doses of the first-line opioid. In many cases patients with extremely high doses of other opioids are switched to transdermal fentanyl in an attempt to decrease the adverse effects and improve analgesia. Trials of transdermal buprenorphine were excluded because the conversion rate to morphine equivalent is not well established.

Table B-10.1 Morphine Equivalents for Strong Opioids used in Randomized Controlled Trials

MEQ= morphine equivalent, NR = not reported.

Drug	Pain type	MEQ Minimum	MEQ Average	MEQ Maximum	N studies
CR oxycodone	Nociceptive	20	65.7	146.7	6
	Neuropathic	40	81.3	173.3	3
Dihydrocodeine	Nociceptive	No Studies	No Studies	No Studies	0
	Neuropathic	NR	24	NR	1
CR morphine	Nociceptive	25	56.8	120	2
	Neuropathic	28.75	91.7	202.5	5
Oxymorphone	Nociceptive	30	219.2	420	3
	Neuropathic	No Studies	No Studies	No Studies	0

2. Concerns regarding high daily dose of opioids from observational studies.

The potential for adverse psychological and physical effects, the potential for misuse, and questionable efficacy are all factors that should be considered in limiting the dose and increasing the frequency of follow-up visits. Some studies reported safety concerns or questionable efficacy of higher daily doses of opioids.

Rowbotham and Lindsey reported on a long-term open label study where study patients were discouraged from exceeding a total of 360 mg/day MEQ. Twenty-nine patients entered the study, and interestingly there was a sex difference with men reaching both a higher dose (282 compared to 150 mg/day), and showing greater dose escalation (Rowbotham 2007).

2.1. Hypogonadism related to higher daily dose.

In 2003, Rajagopal and Bruera studied 20 male patients with cancer-related chronic pain who were disease-free for at least one year and all patients were consuming at least 200 mg/day MEQ. They found marked central hypogonadism and sexual dysfunction in this population (Rajagopal 2003). They reported on a case of a cancer survivor who showed improvement in sexual function after reduction of chronic high-dose MEQ daily dose from 690 mg to 20 mg (Rajagopal 2003).

…continued

R10 Summary of Peer-Reviewed Evidence…continued

2.2. Poor outcomes in population receiving higher daily dose.

Rome et al. reported the outcomes of a chronic non-cancer pain rehabilitation program according to opioid use status at admission (Rome 2004). They stratified the participants into non-opioid group (n=221), low dose (<41 mg/day) opioid users (n=71), and high dose (>41 mg/day, average 137.48 mg/day) opioid users (n=64). The outcomes at discharge showed that patients taking higher doses reported significantly greater catastrophizing and greater pain severity than the non-opioid group. There were no significant pre-treatment differences between the groups regarding demographics, pain duration, treatment completion or all outcome variables including pain severity.

Two recently published studies conducted in the workers' compensation population showed similar results. Webster et al. showed that mean disability duration, mean medical costs, risk of surgery and late opioid use increased with higher MEQ amounts. Those who received more than 450 mg were on average disabled 69 days longer than those who received no opioids (Webster 2007). Franklin et al. showed a statistically significant correlation that the receipt of more than 150 mg/day of morphine equivalent doses was associated with doubling of one-year disability risk (Franklin 2008).

2.3 Adverse events more commonly observed at higher daily doses.

Pascual et al. reported on an open-label study of the safety and effectiveness of long-term therapy with extended-release tramadol in the management of 919 patients with non-malignant pain (Pascual 2007). Adverse events were noted to begin more commonly at average daily doses of 300–399 mg/day or > 400 mg, than at lower doses. Two patients experienced seizures during the study (one serious and one non-serious), and both events occurred at a dose of 400 mg/day.

In a randomized trial of morphine compared to placebo for patients with neuropathic pain, attentional performance was assessed with the "d2-test", measuring vigilance over a 20-minute time period. The dose of morphine was titrated to at least 70 mg/day and at highest 300 mg/day. The results showed that the reduction of attention during morphine compared to placebo was more pronounced when a high dosage was taken (attentional deficit and dose: r = 0:73, P <0:05) (Huse 2001).

2.4 Conflicting evidence regarding the dose relationship between opioids and sleep apnea.

Walker et al. report on a retrospective study comparing 60 patients taking chronic opioids with 60 patients not taking opioids to determine the effect of opioid dose on breathing patterns during sleep. After controlling for BMI, age, sex, there was a dose-response relationship between morphine-equivalent dose and apnea-hypopnea, obstructive apnea, hypopnea and central apnea indexes. They concluded that there is a dose-dependent relationship between chronic opioid use and the development of a peculiar pattern of respiration consisting of central sleep apnea and ataxic breathing (Walker 2007).

One observational study of chronic pain patients on opioid therapy was designed to assess whether a dose relationship exists between methadone, non-methadone opioids, benzodiazepines and the indices measuring sleep apnea. They included all consecutive (392) patients on around-the-clock opioid therapy for at least 6 months with a stable dose for at least 4 weeks. Available data were analyzed on 140 patients. The apnea-hypopnea index was abnormal (≥5 per hour) in 75% of patients (39% had obstructive sleep apnea, 4% had sleep apnea of indeterminate type, 24% had central sleep apnea, and 8% had both central and obstructive sleep apnea); 25% had no sleep apnea. They found a direct relationship between the apnea-hypopnea index and the daily dosage of methadone (P = 0.002) but not to other around-the-clock opioids. They concluded that sleep-disordered breathing was common in chronic pain patients on opioids. The dose-response relationship of sleep apnea to methadone and benzodiazepines calls for increased vigilance (Webster 2008). …*continued*

R10 Summary of Peer-Reviewed Evidence…continued

Another study reported on 6 cases of patients receiving opioids for CNCP for more than 6 months referred to a sleep study because of excessive daytime sleepiness (Allatar 2009). All six cases had a diagnosis of central sleep apnea. Three patients also had obstructive sleep apnea. The opioid doses were 120, 230, 262, 300 (two) and 420 MEQ per day.

2.5 Opioid-induced hyperalgesia related to higher daily doses.

Cohen conducted a study on 355 patients on a steady regimen of opioids who volunteered to receive a standardized subcutaneous injection of lidocaine prior to a full dose of local anesthetic for a scheduled interventional procedure. Before and after the injection, they were asked to rate pain and unpleasantness. Subjects were stratified into 6 groups based on the dose of opioids they were taking. A group of 27 volunteers who had no pain and no analgesics were also injected. Both opioid dose and duration of treatment directly correlated with pain intensity and unpleasantness scores. Baseline pain intensity and female genders were also predictive of responses. The results of this study are in agreement with experimental studies of enhanced pain perception in subjects receiving opioid therapy (Cohen 2008).

3. Evidence from other systematic reviews, opinion papers, and clinical practice guidelines.

In a recent review, Ballantyne and Mao indicated that doses higher than 180 mg of MEQ/day have not been validated in clinical trials and should be considered excessive (Ballantyne 2003).

In a recent editorial in JAMA, McLellan and Turner call for physician responsibility in prescribing opioids because of the direct relationship between amount of prescriptions and public health threats from prescription diversion. They advise physicians that opioid doses should be re-evaluated regularly because analgesic response has been shown to wane at longer intervals (McLellan 2008).

The 2009 "Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain" (The American Pain Society and American Academy of Pain Medicine) proposed by panel consensus, a reasonable definition for high-dose opioid therapy as >200 mg daily of oral morphine (Chou 2009).

4. Opioid-receptor genotype associated with higher opioid dose required to achieve pain relief.

Analgesic efficacy of mu-acting drugs has been linked to the 118>G single nucleotide polymorphism (SNP) of OPRM1, the gene encoding the mu-1 receptor. The frequency of the variant G allele varies from 10% to 48% depending on the population studied. Studies conducted in cancer pain show that patients carrying the GG (homozygous variant) genotype require much higher opioid doses to achieve pain relief. In AA patients the daily morphine dose was 112 mg, in AG patients the dose was 132 mg and in GG patients the dose was 216 mg. All three groups achieved the same pain relief (Reynolds 2008.).

R11 Recommendation Statement

R11	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 behaviors. (Grade C).

Risk: opioid misuse

R11 Discussion

1. Indicators of Patients at Higher Risk of Opioid Misuse

The following factors could indicate patients at higher risk of opioid misuse:

1) history of alcohol or substance abuse (patient and/or family)
2) uncertain security in the home (e.g., living in a boarding home with minimal protection for possessions), and
3) past aberrant drug-related behaviours (see Recommendation 12).

For patients at higher risk of misuse, ensure that:

1) opioids have shown to be effective for the patient's diagnosis(es) (See Recommendation 4 for an overview of evidence of opioid efficacy), and
2) all other available treatment options have been exhausted.

2. Titration for Patients with Higher Risk of Opioid Misuse

In these higher-risk cases, start the titration at lower doses, increase in smaller quantities, and monitor more frequently. Careful opioid prescribing will limit both diversion and misuse of prescribed medications. Also, since the euphoric effects of opioids are dose-related, minimizing the dose may reduce the risk of opioid misuse by reducing patients' exposure to the reinforcing psychoactive effects of opioids.

A further precaution could include prescribing at frequent dispensing intervals, e.g., daily, alternate days, twice per week, or every 1–2 weeks.

3. Monitoring Patients with Higher Risk of Opioid Misuse

Extra cautions could include:

1) asking the patient to bring their medication for pill counts and to explain any discrepancies, and
2) using screening tools to check for aberrant drug-related behaviours (see Appendix B-10).

R11 Summary of Peer-Reviewed Evidence

1. Prescribing strong opioids has increased substantially in many regions throughout North America. This has been accompanied by a major increase in prescription opioid misuse and addiction.

Evidence from multiple sources suggests that North America is witnessing a major increase in prescription opioid misuse and addiction. For example, the Drug Abuse Warning Network in the United States has documented a seven-fold increase in emergency department visits and overdose deaths related to oxycodone (Gilson 2004, Paulozzi 2006). Increases in opioid abuse were also documented by the Purdue-sponsored RADARS system using addiction experts as key informants (Cicero 2005). A prospective Canadian study found that illicit opioid users are more likely to use prescription opioids than heroin (Fischer 2006). In the United States, the number of prescription opioid users entering addiction treatment rose from 14,000 in 1994 to 60,000 in 2004 (Maxwell 2006).

2. Physicians' prescriptions are a significant source of abused opioids.

Hall et al. conducted a population-based, observational study of unintended pharmaceutical overdose fatalities in West Virginia. Of the 295 decedents, opioid analgesics were taken by 275 (93.2%), of whom only 122 (44.4%) had ever been prescribed these drugs. Pharmaceutical diversion was associated with 186 (63.1%) deaths, while 63 (21.4%) were accompanied by evidence of doctor shopping (Hall 2008).

In studies of patients admitted to a treatment program for prescription opioid addiction, physicians' prescriptions were a common source of opioids (Brands 2004, Passik 2004, Rosenblum 2007). Most had also received opioids from friends, family or dealers, although it is not known how many of these non-medical sources had received their opioids from physicians' prescriptions.

In 2006, Dasgupta et al. published a study using national data from the Drug Abuse Warning Network (DAWN). They showed that the non-medical use of prescription analgesics was directly associated with the potency-adjusted total amount of opioids in prescriptive use. This data suggests that non-medical use of opioids is predictable based on potency and extent of prescriptive use (Dasgupta 2006).

3. The reinforcing psychoactive effects of opioids are dose-related.

In a retrospective case-control study, opioid-dependent patients had much higher ratings of euphoria on their first exposure to opioids for chronic pain than controls who were not opioid dependent (Bieber 2008). This suggests that a subgroup of patients experience euphoria when prescribed opioids and this group is at greater risk for becoming dependent on them. Controlled studies in healthy volunteers have demonstrated that the cognitive and euphoric effects of opioids are dose related, both in non-drug using volunteers and in former opioid addicts (Zacny 2003, Lamb 1991).

Cluster 3: Monitoring Long-Term Opioid Therapy (LTOT)

R12 Recommendation Statement

R12	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. (Grade C).	*Monitoring LTOT*

R12 Discussion

1. Opioid Effectiveness (improved function or at least 30% reduction in pain intensity)

1.1 Evaluate change in pain intensity; see Recommendation 9.

1.2 Ask about progress in reaching agreed-on goals, an important indicator of function change. Self-report can be prompted by asking about work, household activity, mood, walking ability, sleep, and social activities. For an example of a structured assessment tool frequently used in trials, see Appendix B-9: Brief Pain Inventory©.

1.3 If opioid therapy is not effective consider switching opioids or discontinuing (see Recommendation 13).

2. Adverse Effects and Medical Complications

2.1 More common adverse effects include nausea, constipation, drowsiness, dizziness/vertigo, dry-skin/itching/pruritus, and vomiting.

2.2 Medical complications include neuroendocrine abnormalities and erectile dysfunction, sleep apnea and opioid-induced hyperalgesia.

2.3 See Recommendation 5 for detailed information about adverse effects and medical complications.

3. Aberrant Drug-related Behaviours

3.1 Aberrant drug-related behaviours have been divided into three groups (Passik 2004):
- escalating the dose (e.g., requesting higher doses, running out early)
- altering the route of delivery (e.g., biting, crushing controlled-release tablets, snorting or injecting oral tablets), and
- engaging in illegal activities (e.g., multiple doctoring, prescription fraud, buying, selling and stealing drugs). See Appendix B-10 for more information on detecting aberrant drug-related behaviours.

3.2 Tools designed to recognize aberrant drug-related behaviours may be useful in determining a patient's misuse of opioids. See Appendix B-11 for available tools including two examples, SOAPP®-R and COMM®.

4. Physician-Pharmacist Collaboration

4.1 A complete prescription history in one location can facilitate monitoring and support physician-pharmacist collaboration. Physicians can enable this by encouraging patients to select a single pharmacy to have prescriptions filled.

4.2 Pharmacists, through their multiple interactions with the patient, can:
- reinforce patient education about safe, appropriate use of opioids
- observe for behaviours or adverse effects that should be communicated to the physician (Also see Recommendation 14, LTOT and driving.)
- alert physicians to concerns about potential misuse (Also see Recommendation 22, Prescription fraud.).

R13 Recommendation Statement

R13 For patients experiencing unacceptable adverse effects or insufficient opioid effectiveness from one particular opioid, try prescribing a different opioid or discontinuing therapy. (Grade B).

Switching or discontinuing opioids

R13 Discussion

1. Switching Opioids

Because of unpredictable and incomplete cross-tolerance from one opioid to another, **suggested** initial doses of the new opioid are as follows:

If previous opioid dose was:	Then, **SUGGESTED** new opioid dose is:
• High	50% or less of previous opioid (converted to morphine equivalent)
• Moderate or low	60–75% of the previous opioid (converted to morphine equivalent)

If switching to fentanyl, see Appendix B-8.1: Oral Opioid Analgesic Conversion Table.
There is no evidence to support the practice of combining different types of opioids.

2. Discontinuing Opioids

Opioids should be tapered and discontinued if the patient's pain remains unresponsive after a trial of several different opioids. Patients who receive high opioid doses and remain incapacitated by pain should be considered treatment failures, even if the opioid "takes the edge off" the pain.

Patients sometimes report improvements in mood and pain reduction with tapering. The reason for this is not fully understood. With higher opioid doses, patients might experience withdrawal at the end of a dosing interval, which could heighten pain perception ("withdrawal-mediated pain"). Opioid tapering might relieve these withdrawal symptoms, thus decreasing pain perception. LTOT is known to cause hyperalgesia or pain sensitization, and lowering the opioid dose could reset the patient's pain threshold (Baron 2006) — or it could be that patients' mood and energy level improve with opioid tapering, so they do not focus on their pain as much.

The opioid should be tapered rather than abruptly discontinued. See Appendix B-12 for an opioid tapering protocol.

R13 Summary of Peer-Reviewed Evidence

1. Observational and uncontrolled studies have demonstrated that patients who have not responded to one opioid will sometimes respond when switched to a different opioid.

In 2004, Quigley conducted a Cochrane review on opioid switching to improve pain relief and drug tolerability. They found no randomized control trials. They included 23 case reports, 15 retrospective studies/audits and 14 prospective uncontrolled studies. The majority of the reports used morphine as first-line opioid and methadone as the most frequently used second-line opioid. All reports, apart from one, concluded that opioid switching is a useful clinical maneuver for improving pain control and/or reducing opioid-related side effects.

Quigley also concluded that more studies are needed to determine which opioid should be used first-line or second-line, and more research is needed to standardize conversion ratios when switching from one opioid to another.

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R13 Summary of Peer-Reviewed Evidence…continued

2. Several observational studies have demonstrated that for patients with severe pain on high opioid doses, tapering results in improved reduced pain and improved mood.

Baron reported on a retrospective study of patients undergoing detoxification from high-dose opioids prescribed to treat an underlying chronic pain condition that had not resolved in the year prior. All patients were converted to ibuprofen to manage pain, with a subgroup treated with buprenorphine during detoxification. Self-reports for pain scores were taken at first evaluation, follow-up visits, and termination. Twenty-one of 23 patients reported a significant decrease in pain after detoxification, suggesting that high-dose opioids may contribute to pain sensitization via opioid-induced hyperalgesia, decreasing patient pain threshold and potentially masking resolution of the pre-existing pain condition (Baron 2006).

One study was conducted on over 356 patients with persistent pain and disability who attended a three-week cognitive behavioural program. Patients on opioids were tapered off. Pain decreased, and mood and functioning improved from baseline to discharge; the degree of improvement was the same in patients tapered off opioids as in patients who were not on opioids at baseline (Rome 2004).

One randomized trial demonstrated that patients attending an outpatient multidisciplinary pain program had improved pain ratings, psychological well-being, sleep and functioning, while their need for immediate-release opioid was also reduced (Becker 2000). Another study found that after a brief detoxification period, patients with both chronic pain and opioid dependence also report improved pain scores (Miller 2006).

Another trial reported success with opioid tapering, whether the tapering schedule was patient controlled reduction or staff controlled cocktail (Ralphs 1994). In both groups, 55% of the sample remained abstinent from opioids at six months.

One study demonstrated that multidisciplinary pain rehabilitation treatment incorporating analgesic medication withdrawal is associated with significant clinical improvements in physical and emotional functioning (Crisostomo 2008). A study on patients with fibromyalgia had similar results (Hooten 2007).

There are several limitations to these studies. The length of follow-up was short, up to six months. It is not known whether the outcomes were due to the tapering or to the psychological interventions the patients received. Nor is it known why tapering might improve pain perception.

R14	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. (Grade C).	*LTOT and driving*

R14 Discussion

Physicians should assess cognitive and psychomotor ability because these functions are essential for driving a motor vehicle. Some factors, **in combination with opioids**, threaten these functions, e.g.,

- consistent severe pain rating (i.e., >7/10 most of the time)
- sleep disorder (chronic poor sleep, sleep apnea) and/or daytime somnolence
- pre-existing medical conditions that result in cognitive decline
- concomitant medications that increase sedation, such as benzodiazepines and anticholinergics, tricyclic antidepressants, anticonvulsants, antihistamines, breakthrough pain medication.

Requirements regarding a physician's duty to report a patient as unsafe to drive vary by province. Prescribers have an obligation to be aware of their provincial legislation about reporting concerns regarding the patient's ability to drive safely. A useful resource is "Determining Medical Fitness to Operate Motor Vehicles." (Canadian Medical Association 2009).

Also see Recommendation 7 for titration and driving.

R14 Summary of Peer-Reviewed Evidence

1. Pain itself affects cognitive function.

A recent review by Seminowicz and Davis showed that there is evidence that chronic pain can impair cognitive abilities. One possible mechanism for this effect is based on cortical plasticity and involves impairment of brain function. Another possible mechanism, not exclusive of the first, is based on the concept of limited processing capacity, whereby ongoing pain demands attention and limits the amount of resources available for task performance. Several studies have reported an association between chronic pain and hypervigilance (Seminowicz 2007).

Eccleston suggested that there is competition for attentional resources, reflected in attenuated task performance when a task is very demanding and pain is high (Eccleston 1996).

2. Associations between opioid use and impaired driving.

The evidence for association between opioid use and impaired driving is sparse, heterogeneous, and of poor quality. Some authors attempted to summarize this literature; however, no firm conclusions can be made because of the problems with the primary studies, and because of flaws in the reviews themselves.

Fishbain et al. conducted a systematic review of epidemiological evidence of an association of opioid use and intoxicated driving (6 studies), motor vehicle accidents (MVA) (9 studies) and MVA fatalities (10 studies). The authors concluded that opioids do not appear to be associated with intoxicated driving, MVA, and MVA fatalities (Fishbain 2003). However, there were many flaws in the studies included in this review; also the methods to compare the prevalence rates among the various studies were subject to bias.

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R14 Summary of Peer-reviewed Evidence…continued

Another systematic review by the same author included 41 studies of opioid dependent/tolerant patients and evaluated the following outcomes: psychomotor abilities; cognitive function; effect of opioid dosing on psychomotor abilities; motor vehicle driving violations and MVAs; and driving impairment as measured in driving simulators and off/on road driving. This review concluded that opioids do not impair driving-related skills. However, the majority of the studies included in this review included populations on methadone for addiction, or healthy volunteers. Only five studies were conducted in a population with CNCP. It is known that pain itself interferes with psychomotor and cognitive function; therefore it is difficult to generalize the results of this review to the population for which this guideline is recommended (Fishbain 2003).

R15 Recommendation Statement

R15 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. (Grade C).

Revisiting opioid trial steps

R15 Discussion

Not all patients on opioid therapy have progressed through the recommended steps of an opioid trial to determine an optimal dose (see Recommendation 9 for optimal dose). This situation can arise from various circumstances, e.g., when a patient on LTOT transfers from one doctor to another, or when a patient has inadvertently transitioned from receiving opioids for an acute condition to prolonged use. For these patients, the prescribing physician should review steps for an appropriate opioid trial and schedule follow-up visits to ensure all of the following have been addressed and documented:

1) pain condition diagnosis
2) risk screening
3) goal setting
4) informed consent
5) appropriateness of opioid selected and dose, and
6) opioid effectiveness.

1. Diagnosis

- Confirm the patient has a pain condition for which opioids have been shown to be effective (see Recommendation 4).

2. Screening

- Ensure that the patient's risk for misuse, overdose and addiction has been determined (see Recommendations 1 and 2).
- Screen for aberrant drug-related behaviours (see Recommendation 12).
- Consider usefulness of urine drug screening (see Recommendation 3).

3. Goal Setting

- Ensure the patient's expectations are realistic.
- Discuss specific goals related to pain reduction and function improvement.
- Document agreed-on goals in the patient's record; (they are critical in determining that opioids are effective)

4. Informed Consent

- Review potential benefits, potential adverse effects, medical complications, and risks (see Recommendation 5).
- Consider using a treatment agreement (see Recommendation 5).

5. Opioid Selection and Dose

- Confirm the most appropriate opioid has been selected (see Recommendation 8).
- Review dose — if above daily 200 mg of morphine equivalent, confirm that the patient's pain condition warrants the dose (see Recommendation 10).
- Taper or switch opioid as required.

6. Opioid Effectiveness

- Confirm that LTOT is providing significant benefit, i.e., the patient is experiencing an improvement in function or a reduction of pain intensity by at least 30% (see Recommendation 9).
- Taper or switch opioid as required.

R16 Recommendation Statement

R16	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. (Grade C).	*Collaborative care*

R16 Discussion

Options for external assistance include consultation with physicians with expertise in pain management or addiction, referral for treatment intervention, and shared-care models. Once a primary-care physician seeks outside help, successful management of the CNCP patient depends on clear detailed communication and collaboration between all healthcare providers.

1. Referral for Consultation

1.1 Expertise in Pain Management

1. Primary-care physicians seek consultation with physicians experienced in pain management for a variety of reasons, e.g.,
   - co-morbid conditions
   - uncertain diagnosis
   - uncertainty about the need for opioids or the dose
   - problematic adverse effects and/or medical complications
   - significant risk of overdose.
2. Clear communications *from* the primary-care physician *to* the consultant include:
   - details describing the patient's pain condition
   - actions undertaken to manage the pain and results, and
   - specific requested action(s) for the consultant (e.g., confirm diagnosis, screen for risks or misuse, review and advise on need for opioids and dose).
3. Clear communications *from* the consultant *to* the primary-care physician include:
   - specific details in response to the request(s) for action
   - clarification of any continuing role in directing care, e.g., if consultant initiates opioids, specification of responsibility for continued prescribing and monitoring the trial.

1.2 Expertise in Addictions

1. Primary-care physicians seek consultation with physicians experienced in addictions when one or more of the following are present:
   - The patient has exhibited aberrant drug-related behaviours.
   - The physician has concerns regarding illicit drug use.
   - There is apparent addiction to opioids.
2. Clear communications *from* the primary-care physician *to* the consultant include:
   - details describing the patient's pain condition
   - concerns regarding opioid misuse and/or addiction, and
   - specific requested action(s) for the consultant (e.g., confirm misuse or addiction and advise on treatment options.)
3. Clear communications *from* the consultant *to* the primary-care physician include:
   - recommended treatment
   - clarification of respective continuing roles in directing ongoing care.

2. Referral for Treatment Intervention

2.1 Multidisciplinary Pain Program

Patients on opioids who continue to have severe pain and pain-related disability appear to have better outcomes when managed by a multidisciplinary pain clinic. There are, however, significant variations in multidisciplinary pain programs: different treatment modalities, diagnostic approaches, healthcare providers, and diverse treatment philosophies regarding the use of opioids for CNCP. In addition, access to multidisciplinary pain programs is very limited in most parts of Canada, and many are not publicly funded.

The referring physician should understand the program's goals and postdischarge support available. Ideally, these programs would support primary-care physicians through:

- regular written and telephone communication during the treatment phase
- ongoing follow-up
- facilitation of referrals for counseling and addiction treatment as warranted.

2.2 Addiction Treatment Program

Addiction physicians and psychiatrists usually work in formal inpatient or outpatient treatment programs, or in community or hospital-based clinics. In most cases they directly provide detoxification or methadone treatment when appropriate.

3. Shared-Care Models

Examples of shared-care models vary but they do represent another form of information and knowledge sharing. These models could benefit primary-care physicians and their CNCP patients, and also use specialty expertise to the best advantage. Two examples are:

- Collaboration between primary-care physicians in developing and delivering a care plan for a particular patient seen by both physicians.
- A mentorship approach where primary-care physicians can access specialty opinion about case management, often with the goal of increasing the primary-care physician's knowledge, skills, and expertise in managing particular patient groups.

R16 Summary of Peer-Reviewed Evidence

1. Primary-care management of complex-pain patients on opioids is not as effective as ongoing involvement by a multidisciplinary clinic, even when the primary-care physician has been advised by a pain medicine physician.

In one randomized trial, CNCP patients managed by a multidisciplinary pain clinic had reduced pain intensity and decreased short-acting opioid use, whereas patients managed by their primary-care physician with a consultant's recommendations had no reduced pain intensity and a slight decrease in opioid use. Waiting-list controls actually deteriorated (Becker 2000).

2. Access to multidisciplinary pain programs is very limited.

Pain clinics in Canada vary widely in the types of care providers available, methods, funding, location, and waiting lists (Peng 2007).

Clinics located in academic science centres or publically funded facilities have much longer waiting lists than pain clinics funded by third parties (e.g., workers compensation systems or motor vehicle insurers). The types of patients may vary: hospital-based clinics see more complex patients with significant co-morbidities and more patients with cancer or neuropathic pains (Catchlove 1988), while non-hospital pain clinics and third-party funded clinics may see more musculoskeletal problems (facial pains, headaches, back and neck pain). Access to multidisciplinary pain programs is also variable based on funding, as some of the more intense pain programs are accessible only to those with third-party funding (Peng 2007).

Cluster 4: Treating Specific Populations with LTOT

R17 Recommendation Statement

R17	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).	***Elderly patients***

R17 Discussion

1. Opioids Safe and Effective for the Elderly

Opioid therapy may be underutilized in the elderly. Older patients may be less likely than younger patients to complain of pain or to accept opioid analgesics because they fear addiction; they associate opioids (particularly morphine) with severe or terminal illness, and they fear that complaining about pain may lead to investigations or hospitalization (Robinson 2007). Also, some physicians are reluctant to prescribe opioids for elderly patients.

While older patients are less likely to complain about pain, they appear to have the same pain thresholds as younger patients. It is known that elderly patients have comparable pain levels to younger ones, and that the dose of morphine necessary to achieve pain VAS[2] <4 is not significantly affected by age (Wilder-Smith 2005).

Opioids are generally safe in the elderly if carefully titrated. As a class, opioids cause less organ toxicity than NSAIDs, and in single-dose studies, they appear to cause less cognitive impairment than benzodiazepines (Hanks 1995). Clinics caring for elderly patients with well-defined pain conditions have found very low rates of abuse and addiction (Ytterberg 1998, Mahowald 2005).

2. Risks for the Elderly

2.1 Risks for the Elderly

1. Overdose**:** Several pharmacokinetic factors put the elderly at higher risk for opioid overdose than younger patients, including lower serum binding, lower stroke volume (slows liver metabolism), and greater sensitivity to the psychoactive and respiratory effects of opioids; (Freye 2004, Wilder-Smith 2005).
2. Oversedation: A high proportion of elderly patients on opioids are also on benzodiazepines and other psychotropic medications (Hartikainen 2005), increasing the risk of sedation.

2.2 Reducing Risks for the Elderly

1. Educate the patient and caregiver about signs of overdose, e.g., slurred or drawling speech, emotional lability, ataxia, "nodding off" during conversation or activity (see Table B-5.2: Opioid Risks).
2. Avoid opioids in cognitively impaired patients living alone, unless ongoing medication supervision can be organized.
3. Consider a three-day "tolerance check:" contact the patient three days after starting the prescription to check for any signs of sedation.
4. Monitor renal function (creatinine and creatinine clearance) (Pergolizzi 2008).

…continued

[2] Visual Analog Scale

R17 Discussion… continued

3. Prescribing Cautions for the Elderly

Suggested prescribing recommendations for the elderly are as follows:

1. Start initial titration at no more than 50% of the suggested initial dose for adults, and lengthen the time interval between dose increases. (See Table B-9.1: Opioid Suggested Initial Dose and Titration.)
2. Among strong opioids, oxycodone and hydromorphone may be preferred over oral morphine for the elderly because they are less likely to cause constipation and sedation (Clark 2004).
3. Controlled-release (CR) formulations are recommended for the elderly for reasons of compliance even though there is no evidence CR formulations are more effective than immediate-release (IR) formulations. However, for breakthrough pain or activity-related pain, IR formulations can be used (Pergolizzi 2008).
4. Morphine solutions are preferable to tablets in some situations, e.g., patients with swallowing problems, or patients requiring less than 5 mg morphine per tablet (Pergolizzi 2008).
5. For elderly patients on benzodiazepines, try to taper the benzodiazepine dose to reduce the risk of falls and cognitive impairment.

R17 Summary of Peer-Reviewed Evidence

1. Evidence suggests that many elderly patients who might benefit from opioid therapy are not receiving it.

A national Canadian survey documented that 29% of Canadian adults experienced chronic pain, with increasing frequency in elderly patients (Moulin 2002). Although most of these patients had moderate to severe pain that interfered with function, only 7% were receiving opioids stronger than codeine. In a study of 83,000 patients in 12 primary-care clinics in Wisconsin, only 201 patients were receiving opioid therapy for chronic pain (Adams 2001). Another survey found that up to 35% of primary-care physicians in Canada would never prescribe opioids even for moderate to severe chronic pain (Morley-Forster 2003). Solomon et al. described prescription opioid use among elderly with arthritis and low back pain. They found that elderly patients most commonly receive weak opioids, and rarely strong opioids (Solomon 2006).

2. Controlled-release opioids are preferred for the elderly for reasons of compliance.

"Consensus Statement of an International Expert Panel with Focus on the Six Clinically Most Often Used World Health Organization Step III Opioids" recommends a preference for sustained-release preparations because they increase patient compliance, as dosing frequency can be reduced. Patients should also be prescribed short-acting analgesics for the treatment of breakthrough pain. This recommendation is despite the fact that there is no evidence to support the use of long-acting analgesics over short-acting analgesics (Pergolizzi 2008).

3. Morphine solutions may be used in some situations.

The consensus statement of the International Expert Panel recommends that morphine solutions are a better option than tablets for p.r.n. (as needed) use. If the patient is frail and/or elderly, a low dose, e.g., 5 mg 4-hourly (or less), will help to reduce the likelihood of drowsiness, confusion or unsteadiness (Pergolizzi 2008).

R18	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. (Grade C).

Adolescent patients

R18 Discussion

1. Opioids Hazardous for Adolescents

Non-medical use (misuse) of opioids is more common among adolescents, and may be a risk factor for future opioid addiction. Among adolescents, risk factors for opioid misuse include poor academic performance; higher risk-taking levels; major depression; and regular use of alcohol, cannabis, and nicotine (Schepis 2008).

Misuse and overdose are the greatest risks for adolescents. To reduce these risks:

1. Educate the patient and family: Explain the risks of abuse and overdose carefully to the patient and (if feasible) the family. Emphasize the risks of taking extra doses or giving opioids to friends.
2. Whenever feasible, seek consultation with a healthcare provider experienced in treating adolescents (e.g., social worker, pediatrician, psychiatrist, psychologist, physician with expertise in pain management and/or addictions) before placing an adolescent on LTOT.

2. Prescribing Cautions for Adolescents

1. Titrate more slowly; try to avoid opioids that are commonly abused in the local community.
2. Avoid benzodiazepines if possible.
3. Use structured opioid therapy (see Recommendation 21), with a specific treatment agreement, conservative dosing, frequent dispensing, monitoring for aberrant behaviours, and urine drug screening.
4. Consider tapering the opioid if the patient does not experience opioid effectiveness: improved function or at least 30% reduction in pain intensity. See Appendix B-12 for a tapering protocol.

R18 Summary of Peer-Reviewed Evidence

1. Non-medical use of opioids is common among adolescents, and may be a risk factor for future opioid addiction.

In 2007, researchers from the Centre for Addiction and Mental Health in Toronto ON released the "Ontario Student Drug Use and Health Survey." They found that 21% of Ontario students in grades 7 to 12 report using prescription opioid pain relievers such as Tylenol® No. 3 and Percocet® for non-medical purposes; almost 72% report obtaining the drugs from home. In addition, among all drugs asked about, OxyContin® was the only drug to show a significant, but small, increase in non-medical use since the last survey (2% of students reported using it in 2007, representing about 18,100 students, compared to 1% in 2005) (Adlaf 2006).

One study from Michigan documented that 12% of high-school students had used opioids in the past year (Boyd 2006). Another study documented that the risk of developing prescription drug abuse and dependence later is correlated with the age of first exposure to opioids (McCabe 2007).

Among adolescents, risk factors for opioid misuse include poor academic performance; higher risk-taking levels; major depression; and regular use of alcohol, cannabis, and nicotine (Schepis 2008).

R19 Recommendation Statement

R19	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. (Grade B).	*Pregnant patients*

R19 Discussion

In general, pregnant patients are advised to discontinue all medications because drug effects on the fetus are often unknown.

1. Opioids During Pregnancy

Pregnant patients with CNCP on LTOT should be tapered to the lowest effective dose and discontinued if possible. Slow tapering is essential, as opioid withdrawal can cause uterine smooth muscle irritability, and is associated with premature labour and spontaneous abortion.

- If the patient has CNCP and is also addicted to prescription opioids, methadone treatment is recommended.
- During pregnancy and lactation:
  —Tramadol is not recommended
  —Safety of fentanyl has not been established.
- Where feasible, the treating physician should consider seeking consultation with a physician with expertise in pain, addictions, and pregnancy.

2. Delivery and Postpartum Cautions

Babies born to mothers who used daily opioids during their pregnancy should be delivered in a hospital with appropriate resources to deliver and care for the infant postpartum.

2.1 Neonatal Abstinence Syndrome (NAS)

Regular opioid use for CNCP during pregnancy is associated with a neonatal abstinence syndrome. These babies should be delivered in a hospital prepared to identify and treat the syndrome. NAS:

- usually begins 1–3 days after delivery, and can last for several weeks
- is characterized by poor feeding, irritability, sweating, and vomiting
- has a clinical presentation similar to other neonatal illnesses such as sepsis, hypoglycemia, and hypocalcemia
- is treated with comfort measures and with small doses of morphine, and
- has no long-term sequelae.

2.2 Codeine and Breast Feeding

Some women rapidly metabolize codeine to morphine, placing the neonate at risk for fatal opioid toxicity.

- If prescribing codeine for postoperative pain for women who are breast feeding:
  —Use small doses and limit the prescription to four days supply.
  —Advise the mother to:
  - Watch for signs of CNS depression in the baby, e.g., poor feeding and limpness
  - Contact a physician if she notes any signs of opioid toxicity (e.g., sedation); this should prompt an urgent assessment of the baby.
- NSAIDS and acetaminophen-oxycodone medications are alternatives to codeine.

...continued

R19 Summary of Peer-Reviewed Evidence

1. There is evidence that regular, scheduled opioid use for CNCP during pregnancy is associated with a neonatal abstinence syndrome.

In a study on 13 pregnant women on opioids for chronic pain, 5 of the neonates had neonatal abstinence syndrome (Hadi 2006).

2. Codeine use in breast-feeding women has been associated with fatal opioid toxicity in the neonate.

Codeine is converted to morphine by the cytochrome P450 system. Some patients are rapid converters, resulting in accumulation of morphine in the breast milk (Madadi 2008). There have been several case reports of neonatal toxicity due to morphine accumulation. The key clinical features were: for the baby, not waking up to feed and limpness; and for the mother, signs of sedation and other signs of toxicity. Symptoms were worse by the fourth day (Madadi 2009).

3. Pregnant women addicted to opioids have improved obstetrical and neonatal outcomes when on methadone treatment.

A number of studies have demonstrated that methadone treatment reduces the risk of premature labour, low birth weight and neonatal mortality in heroin-dependent pregnant women (Blinick 1976, Kaltenbach 1998, Kandall 1999, Wang 1999).

R20 Recommendation Statement

R20	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. (Grade B).	***Co-morbid psychiatric diagnoses***

R20 Discussion

1. Extra Considerations for CNCP Patients with Co-morbid Psychiatric Conditions

CNCP patients with psychiatric disorders are more likely to receive opioids than CNCP patients *without* psychiatric disorders (Sullivan 2005, Breckenridge 2003, Fishbain 2004). Yet evidence suggests that patients with depression or anxiety are less likely to benefit from opioids, due to a diminished response to opioids or an enhanced perception of pain, or both (Wasan 2005, Levenson 2008, Riley 2008).

In patients with active psychiatric disorders affecting pain perception, opioids should, in most cases, be reserved for well-defined somatic or neuropathic pain conditions. For example, fibromyalgia patients have a high prevalence of depression and anxiety, and a nociceptive or neuropathic cause for fibromyalgia pain has not been found. Opioids have little effect on functional status of these patients, in particular, strong opioids; (see Recommendation 4).

2. Increased Risks with Co-morbid Psychiatric Conditions

1. Substance Abuse: Patients with psychiatric disorders have a higher prevalence of substance abuse (Becker 2008, Edlund 2007, Sullivan 2006, Manchikanti 2007, Wilsey 2008).
2. Sedation and Falls: Opioids increase the risk of sedation and falls in patients on psychotropic drugs, and they increase the lethality of overdose and suicide attempts (Voaklander 2008).
3. Overdose: Patients with psychiatric disgnoses are frequently on benzodiazepines, and concurrent benzodiazepine use is a common feature in opioid overdoses (White 1999, Cone 2003, Burns 2004, Man 2004).
4. Depression: Opioid use is associated with a higher prevalence of depression.

3. Prescribing Cautions for Co-morbid Psychiatric Conditions

1. Titrate more slowly in CNCP patients with co-morbid psychiatric disorders.
2. Consultation with a psychiatrist might be advisable for patients on LTOT who have a concurrent psychiatric illness, particularly if the illness has not fully responded to treatment. They may be able to comment on a) the role of the illness on the patient's pain perception, and b) the advisability of benzodiazepine tapering.
3. Use structured opioid therapy (see Recommendation 21), with a specific treatment agreement, conservative dosing, frequent dispensing, and monitoring for aberrant drug-related behaviours.
4. Closely monitor the patient's mood and functioning.
5. Consider tapering if opioid effectiveness is inadequate (opioid effectiveness = improved function or at least 30% reduction in pain intensity). Short-term studies have documented improvements in mood and pain with opioid tapering (see Appendix B-12 for a tapering protocol).

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R20 Summary of Peer-Reviewed Evidence

1. Need for careful patient selection, cautious opioid prescribing, and opioid tapering when indicated:

1.1 Patients on chronic opioid therapy have a higher prevalence of depression and other psychiatric conditions than the general population.

A large population-based study found that self-reported regular opioid use was strongly associated with both mood and anxiety disorders (Sullivan 2005).

Another study found that patients with low back pain who were receiving opioids were more likely to be depressed than those receiving only NSAIDs (Breckenridge 2003). Other studies have had similar results (Fishbain 2004).

1.2 Patients with anxiety or depression may have diminished analgesic response to opioid therapy, and/or a heightened perception of pain.

One study found that depressed patients with discogenic back pain had diminished analgesic response to opioids (Wasan 2005).

Another study of patients with sickle cell disease found that the severity of pain, functional disability and use of opioids were correlated with the patient's depression and anxiety. The association held for both crisis days and non-crisis days, and even after controlling for hemoglobin type (Levenson 2008). In a recent review of the literature, the most consistent finding is that depression and anxiety are associated with increased risk for drug abuse and decreased opioid efficacy (Riley 2008).

1.3 Opioid tapering is associated with improved mood and pain intensity.

For more details see Recommendation 13.

In one study, patients attending a multidisciplinary pain program were classified into no opioid, low-dose opioid or high-dose opioid groups. Both opioid groups had higher depression scores than the non-opioid group. The opioid groups were tapered off their medication. By six months, all groups improved in mood and function. Interestingly, all three groups had similar mood ratings at six months, even though the opioid group had more depression at baseline (Townsend 2008).

2. Need for monitoring of substance use and mood:

2.1 Patients on LTOT who have psychiatric disorders are more at risk for substance misuse and dependence than patients on LTOT without psychiatric disorders.

A large national cross-sectional survey (United States) found that depression, panic disorder, social phobia and agoraphobia were associated with non-medical use of prescription opioids (Becker 2008). Another cross-sectional survey found higher rates of opioid misuse and problematic drug use among patients on opioid therapy; these rates were mediated by higher rates of psychiatric disorders (Edlund 2007). An earlier study had similar results (Sullivan 2006). A study of 500 chronic pain patients on opioids documented that anxiety and depression was associated with significantly higher rates of opioid abuse and illicit drug use (Manchikanti 2007). A study of chronic pain patients presenting to the emergency department for prescription refills documented that a) a high proportion (81%) were abusing their opioids, and b) of these, a high proportion had depression and anxiety (Wilsey 2008).

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R20 Summary of Peer-Reviewed Evidence…continued

2.2 Patients on LTOT are at higher risk for completed suicide.

One case control study found that patients on chronic opioid therapy are at greater risk for suicide than control patients (Voaklander 2008). This likely reflects the association between depression and opioid use for chronic pain. Nonetheless, it indicates that physicians should assess their patients for depression and suicidal ideation, and opioids should be dispensed in small amounts for patients at risk.

Cluster 5: Managing Opioid Misuse and Addiction in CNCP Patients

R21 Recommendation Statement

R21	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).	*Addiction treatment options*

R21 Discussion

Where feasible, a physician with expertise in pain management and/or addiction can help select and implement the most appropriate care plan for CNCP patients who are addicted to opioids.

1. Options for Treatment

Three treatment options for the opioid-addicted patient with CNCP are:

1) methadone or buprenorphine treatment
2) structured opioid therapy
3) abstinence-based treatment.

2. Treatment with Methadone and Buprenorphine

2.1. Methadone Treatment

1. Indications for methadone treatment are any of the following:
   - a failed trial of structured opioid therapy
   - using opioids by injection, snorting, or crushing tablets
   - accessing opioids from multiple physicians or from the "street"
   - addiction to opioids and to other drugs/substances, e.g., alcohol, cocaine.
2. Methadone is effective for the treatment of opioid addiction in the presence of CNCP.
   - Methadone maintenance treatment involves daily supervised dispensing, urine drug screening, and counseling.
   - To obtain an exemption to prescribe methadone for opioid addiction, physicians should check with their provincial regulating body for direction.
   - The patient should be expected to consent to open communication between the methadone provider and the primary-care physician (include in treatment agreement).
   - Primary-care physicians and methadone providers should inform each other of newly diagnosed health conditions for the patient and long-term prescribing of other medications, particularly opioids and benzodiazepines.

2.2 Buprenorphine Treatment

1. Indications for buprenorphine treatment are similar to those for methadone treatment; buprenorphine treatment could be preferred over methadone for:
   - patients who are at higher risk of methadone toxicity (e.g., elderly, benzodiazepine users)
   - adolescents and young adults
   - patients in communities where methadone treatment is unavailable.
2. Buprenorphine is a safe and effective treatment for patients with a dual diagnosis of CNCP and opioid addiction.
   - Physicians should be aware of provincial regulatory guidelines regarding buprenorphine prescribing and training requirements.
   - Buprenorphine (buprenorphine and buprenorphine-naloxone are being used interchangeably) is a partial mu opioid agonist with a long duration of action. It is a well-established treatment, with good supporting evidence for the treatment of opioid addiction (West 2000; Mattick 2008).

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R21 Discussion... continued

3. Structured Opioid Therapy (SOT)

Structured opioid therapy has been shown to improve outcomes in patients who have exhibited aberrant drug-related behaviours (see Recommendation 12). SOT is the use of opioids (other than methadone or buprenorphine) to treat CNCP with specific controls in place, including patient education, a written treatment agreement, agreed-on dispensing intervals, and frequent monitoring.

3.1 Indications for a Structured Opioid Therapy Trial

An ideal candidate for a SOT trial would be an opioid-addicted patient with CNCP who:

1) has a well-defined somatic or neuropathic pain condition for which opioids have been shown to be effective. (See Recommendation 4 for a review of evidence of opioid efficacy.)
2) is well-known to the physician
3) is not currently addicted to cocaine, alcohol or other drugs
4) is not, to the physician's knowledge, accessing opioids from other sources, injecting or crushing oral opioids, or diverting the opioid.

3.2 Treatment Agreement Specifications

A written treatment agreement is strongly recommended. It should specify controls relating to prescribing and monitoring, and outline expectations of patient compliance with referral for consultation or treatment programs, e.g., pain management and/or addiction consultation or programs.

3.3 Opioid Selection and Prescribing

1. Selection:
   - It may be advisable to switch patients to a different opioid (see Recommendation 13).
   - Avoid oxycodone and hydromorphone, if possible.
2. Dose: It is advisable to keep below 200 mg morphine equivalent.
3. Dispensing intervals: e.g., daily, bi-weekly or weekly dispensing interval, with no early prescription refills).

3.4 Monitoring Structured Opioid Therapy

Frequent monitoring is required; it could include:

1) urine drug screening (see Recommendation 3)
2) pill and patch count, and
3) evaluation for significant opioid effectiveness (i.e., improved function or at least 30% reduction in pain intensity, see Recommendation 9).

3.5 Failed Trial

If a) opioid effectiveness is not achieved, or b) the patient is not compliant, consider the SOT a failed trial. Taper and refer for opioid agonist treatment or abstinence-based treatment.

4. Abstinence-Based Treatment

- Abstinence-based treatment can be a patient preference or used when methadone or buprenorphine treatment is not available.
- Abstinence-based treatment begins with medically assisted withdrawal management, using clonidine, or tapering doses of methadone, buprenorphine or other opioids.
- This should be immediately followed by formal addiction treatment (inpatient or outpatient).
- Patients should be strongly cautioned that 1) they have lost their tolerance to opioids after as little as a week or two of abstinence, and 2) they are at risk for overdose if they relapse to their original opioid dose (Strang 2003).

R21 Summary of Peer-Reviewed Evidence

1. Structured opioid therapy has been shown to improve outcomes in patients who have exhibited aberrant drug-related behaviours.

Several observational studies have documented improved outcomes in patients receiving structured opioid therapy. In one study, 85 patients on opioids were referred to a primary-care, multidisciplinary disease management program operated by internists, pharmacists and a psychiatrist. Patients received monthly structured assessments, pain contracts, medication titration and monitoring for substance misuse. Twenty-seven patients (32%) were identified as misusers; 15 of these dropped out of the program because they were not prescribed opioids. Those who remained in the program improved pain, depression and disability scores (Chelminski 2005).

Wiedemer (2007) prospectively evaluated a structured opioid renewal clinic operated by a nurse practitioner and clinical pharmacist. About half of the 335 patients referred to the clinic had aberrant drug-related behaviours. The clinic used random urine drug screening, treatment agreements, frequent visits, and pill counts. Only small quantities were dispensed. Of the patients with aberrant baseline behaviours, 45% complied with the treatment agreement and their aberrant behaviours resolved, 38% dropped out of treatment, 13% were referred to addiction treatment, and 4% were weaned off opioids.

A retrospective evaluation of a clinic that performed careful adherence monitoring through urine drug screens and pill counts documented a 50% reduction in cases of opioid abuse (double doctoring or dealing), from 18% to 9% (Manchikanti 2006).

Currie et al. (2003) conducted an evaluation of an outpatient treatment program for 44 chronic pain patients, most of whom had opioid addiction. The clinic provided counseling and close medication supervision, with a tapering protocol using scheduled, long-acting opioids. Half the patients were able to taper completely off opioids and most were able to reduce their opioids (Currie 2003). The patients reported improvements in pain and mood.

These studies suggest that structured opioid therapy can result in increased compliance with the treatment agreement and increased referrals for addiction treatment. These results are promising but the evidence in support of structured opioid therapy is not as strong as the supporting evidence for buprenorphine and methadone therapy for opioid addiction. Also, the clinics using structured opioid therapy were well staffed by nurse practitioners, pharmacists and therapists; it might be difficult for primary-care physicians to undertake this form of treatment. Therefore, we suggest that structured opioid therapy be reserved for patients who meet the criteria listed above – unlikely to be accessing opioids from other sources, altering the route of delivery or diverting.

2. Methadone is effective for the treatment of opioid addiction in patients with CNCP.

Farre et al. conducted a meta-analysis of 13 randomized, double-blinded trials. They showed that higher doses of methadone were more effective than low doses in reduction of illicit opioid use. They concluded that oral methadone at doses of 50 mg/day or higher is the drug of choice for opioid addiction (Farre 2002).

One study found that methadone patients with opioid addiction who also had pain (n=103) had similar substance-related outcomes to those methadone patients in the group without significant pain (n=97). Compared to patients who did not report pain at baseline, patients with pain showed similar reductions in heroin, alcohol, cocaine and illicit prescription sedative use and greater reductions in illicit prescription opioid use. At 1-year follow-up, there was no significant difference in past 30 day use of heroin, cocaine, alcohol, illicit prescription sedative or opioid use between patients with and without pain at baseline (Ilgen 2006).

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R21 Summary of Peer-Reviewed Evidence…continued

3. Patients who "successfully" completed inpatient detoxification were more likely than other patients to have died within a year. The explanation may be loss of tolerance.

Strang et al. followed up patients who received inpatient opiate detoxification, and looked for evidence of increased mortality, and investigated the distinctive characteristics of patients who died. To test whether loss of tolerance increased the risk of overdose, they grouped the patients into three categories, according to their opiate tolerance at the point of leaving treatment: 43 "still tolerant" (ST) patients who failed to complete detoxification; 57 "reduced tolerance" (RT) patients who completed the prescribed phase of detoxification but who prematurely left the treatment program; and 37 "lost tolerance" (LT) patients who completed the detoxification and also completed the inpatient treatment program. The three overdose deaths that occurred within four months after treatment were all from the LT group; the two deaths unrelated to overdose (although both these patients had relapsed) were one LT patient with end stage renal failure and one RT patient with Clostridium welchii infection; no deaths occurred in the ST group (Strang 2003).

4. Buprenorphine is a safe and effective treatment for patients with a dual diagnosis of CNCP and opioid addiction.

A review study found that there was some evidence for the use of buprenorphine in the treatment of CNCP (it largely reviewed trials that used the transdermal preparation) and that it was well tolerated in elderly patients (Johnson 2005).

Myers et al. 2005 state that the "introduction of buprenorphine management has the potential to greatly improve the treatment of chronic pain in patients with a history of addiction to opioids or with a family history of addictive disorders" (Myers 2005).

5. There is evidence from several studies for the safety and effectiveness of buprenorphine use in primary care.

Controlled trials have demonstrated that buprenorphine maintenance treatment is safe and effective when prescribed in primary care settings (O'Connor 1998, Fiellin 2002, Caplehorn 2003, Gibson 2003, Lintzeris 2004, Simoens 2005, Stein 2005, Barry 2007, Mintzer 2007, Moore 2007). Physicians providing office-based opioid agonist treatment report high levels of satisfaction, although they would like better access to counseling and other social services (Becker 2006).

R22 Recommendation Statement

R22	To reduce prescription fraud, physicians should take precautions when issuing prescriptions and work collaboratively with pharmacists. (Grade C).	*Prescription fraud*

R22 Discussion

1. Taking Precautions

In issuing prescriptions, physicians should take the following precautions, which are considered to reduce opioid misuse:

1. Fax prescriptions directly to the pharmacy.
2. If using a paper prescription pad:
    - Use carbon copies or numbered prescription pads.
    - Write the prescription in words and numbers.
    - Draw lines through unused portions of the prescription.
    - Keep blank prescription pads secure.
3. If using desk-top prescription printing, it is especially important to write a clear signature and not use a scribbled initial.
4. If using fax or electronic transmission of the prescription (in jurisdictions that permit it) ensure confidentiality, confirm destination, and retain copies.
5. Promote patient's use of a single dispensing pharmacy.

2. Accessing Drug Databases

If available, physicians and pharmacists should access electronic prescription databases that provide information about patient prescription history.

3. Collaborating

Greater collaboration with other healthcare providers can also contribute to reduction in prescription fraud.

1. Pharmacists are often in a position to alert physicians to possible opioid misuse, e.g., double-doctoring, potential diversion or prescription fraud. Pharmacists are considered part of the patient's "circle of care;" special consent is not required to speak with the pharmacist.
2. If double-doctoring is suspected, expect the patient to consent to a consultation with the "other" prescriber(s), or taper the opioid dose and discontinue. Note: The prescribing physician may contact the "other" physician(s) without the patient's consent if the patient is considered to be at significant risk of overdose.

R23 Recommendation Statement

R23	Be prepared with an approach for dealing with patients who disagree with their opioid prescription or exhibit unacceptable behaviour. (Grade C).	*Patient unacceptable behaviour*

R23 Discussion

1. Patient Disagreement with the Opioid Prescription

Opioid prescribing is a common source of conflict between patients and physicians. Physicians can minimize conflicts through the following actions:

1. Use treatment agreements routinely.
2. Provide explanations for changes in prescribing, e.g.,
   - The prescribing is consistent with existing guidelines.
   - The change is intended to help, not penalize, the patients, e.g., it is meant to reduce the pain and improve mood, activity, and safety.
3. Book a longer appointment to allow for more time to provide education and explanations.
4. Arrange consultations: patients may accept a "team decision" more readily than an individual one.
5. Document verbal agreements and past discussions.

2. Patient Unacceptable Behaviour

Physicians are strongly advised to acquaint themselves with applicable legislation and their provincial regulatory body's policies/guidelines regarding standards and termination of the physician-patient relationship. It is important to know the obligations to the patient, staff, and society if illegal patient activities are suspected.

2.1 Aberrant Drug-related Behaviours

Behaviours that stem from opioid addiction, such as aggressively demanding higher opioid doses or double-doctoring, often resolve when the physician ceases prescribing and refers the patient to addiction treatment. If the patient refuses to accept treatment referral and continues to demand opioids, the physician may consider discharging the patient from the practice.

2.2 Non-violent Offences

If a patient has committed a non-violent offence, such as altering a script, the physician is not obliged to contact the police. The physician should assess the patient for opioid addiction, and (in most instances) cease prescribing opioids and refer the patient for formal treatment.

2.3 Threatened or Actual Violence

The physician could contact the police if the patient has, for example:

- threatened violence and there is perceived danger
- committed violence against clinic staff and other patients, or
- vandalized or stolen property.

R24 Recommendation Statement

R24	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. (Grade C).	*Acute care opioid prescribing policy*

R24 Discussion

Physicians providing care in acute/urgent healthcare facilities need to respond appropriately to patients with pain and to those who are seeking drugs for misuse or diversion. An opioid-prescribing policy, which takes the local community needs into account, could serve to:

1. Provide a framework to facilitate a consistent response from all physicians. (Note: inconsistent policy application can encourage drug seekers "targeting" liberal prescribers.
2. Act as a deterrent for individuals attempting to obtain opioids for diversion or misuse.

Patients with pain are routinely seen in acute/urgent healthcare facilities (e.g., emergency departments and walk-in clinics). Physicians assessing and treating these patients need to distinguish between pain that is acute, originating from an injury or other mechanism, or chronic. This is complicated by various scenarios:

- Some patients have chronic *recurrent* pain and may present in an "acute" episode of a chronic pain condition.
- Patients who are abusing or addicted to opioids or who are drug diverters may visit these settings specifically in an attempt to obtain opioids.
- Patients report they are on LTOT, have run out of their medication, are unable to access their usual care provider, and ask for a temporary prescription: they could be from another area, province, or country.

The following topics are suggested to assist physicians in creating an opioid-prescribing policy:

1. **Development**: Participation by all physicians providing care in the acute/urgent healthcare setting can be useful in addressing the issues and promoting adherence.
2. **Policy Availability**: The policy could be posted in the waiting area of the facility, and/or available as a handout, to provide patients with information in advance of seeing the physician.
3. **Legislation**: The policy should comply with provincial legislation about opioid prescribing, and accessing and sharing patient information.
4. **Opioid Prescribing**: The policy should outline circumstances for prescribing and not prescribing. For example, for patients who report they are established on opioids with another prescriber, but have run out, a policy could include requirements and limits of issuing a prescription, such as:
    - Contact must be made with the prescribing physician or dispensing pharmacist.
    - Number of doses prescribed is limited to last until the next business day.
    - Dose is amount that the physician feels is appropriate, given the patient's underlying pain condition, even if that dose is considerably less than what the patient reports receiving.
    - The facility prescribes once only for patients who have run out.
    - A record of the visit is sent to the primary-care physician.
5. **Suspected Opioid Addiction**: The policy could indicate a response to patients who appear addicted to opioids, e.g., provide information about addiction resources for treatment.

APPENDIX

Appendix B-1: Examples of Tools for Assessing Alcohol and other Substance Use

Appendix B-1.1: Interview Guide for Alcohol Consumption

1. Maximum number of drinks* consumed on any one day in past 1–3 months
2. Number of drinks per week
3. Previous alcohol problem
4. Attendance at treatment program for alcohol
5. Family history of alcohol or drug problem

* Standard drink = 1 bottle beer (12 oz, 5%)
= 5 oz glass wine (5 standard drinks in 750 ml wine bottle)
= 1.5 oz liquor (vodka, scotch) (18 standard drinks in 26 oz bottle 40% alcohol)

Low-Risk Drinking Guidelines[1]

(no more than 2 standard drinks on any one day)
Women: up to 9 standard drinks a week.
Men: up to 14 standard drinks a week.

Patients who exceed the Low-Risk Drinking Guidelines are considered at-risk for acute problems such as trauma, and/or chronic problems such as depression and hypertension.

[1] Source: Centre for Addiction and Mental Health (CAMH) 2004.

Appendix B-1.2: Interview Guide for Substance Use

1. **Cannabis**: number of joints per day, week
2. **Cocaine**: any use in the past year
3. **Over the counter drugs**: especially sedating antihistamines
4. **Opioids**:
   - In past year, use of opioids from any source: e.g., OTC (Tylenol® No. 1), prescriptions from other physicians, borrowed from friends/family, buying from the street
   - How much, how often
   - Crushing or injecting oral tablets
   - Opioid withdrawal symptoms: myalgias, GI symptoms, insomnia, dysphoria
   - Previous opioid problem
   - Attendance at treatment program for opioid addiction (e.g., methadone)
5. **Benzodiazepines**: Amount, frequency, source

Appendix B-1.3: CAGE Questionnaire

"CAGE" is an acronym formed from the italicized words in the questionnaire (cut-annoyed-guilty-eye).

The CAGE is a simple screening questionnaire to id potential problems with alcohol.
Two "yes" responses is considered positive for males; one "yes" is considered positive for females.

CAGE Questionnaire

Please note: This test will only be scored correctly if you answer each one of the questions. Please check the one response to each item that best describes how you have felt and behaved over your whole life.

1. Have you ever felt you should *cut* down on your drinking?
__Yes
__No
2. Have people *annoyed* you by criticising your drinking?
__Yes
__No
3. Have you ever felt bad or *guilty* about your drinking?
__Yes
__No
4. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (*eye*-opener)?
__Yes
__No

For more detail:
Go to: http://lib.adai.washington.edu/instruments/ and enter CAGE in the search box. Under Description, click "more"

Appendix B-2: Opioid Risk Tool

Opioid Risk Tool

Item	Mark each box that applies	Item score if female	Item score if male
1. Family History of Substance Abuse:			
Alcohol	[ ]	1	3
Illegal Drugs	[ ]	2	3
Prescription Drugs	[ ]	4	4
2. Personal History of Substance Abuse:			
Alcohol	[ ]	3	3
Illegal Drugs	[ ]	4	4
Prescription Drugs	[ ]	5	5
3. Age (mark box if 16-45)	[ ]	1	1
4. History of Preadolescent Sexual Abuse	[ ]	3	0
5. Psychological Disease			
Attention Deficit Disorder, Obsessive-Compulsive Disorder, or Bipolar, Schizophrenia	[ ]	2	2
Depression	[ ]	1	1
Total		____	____
Total Score Risk Category: Low Risk: 0 to 3 Moderate Risk: 4 to 7 High Risk: 8 and above			

Attribution:
By Lynn R. Webster, MD; Medical Director of Lifetree Medical, Inc.
Salt Lake City, UT 84106

Appendix B-3: Urine Drug Screening (UDS)

Table B Appendix 3.1 Immunoassay versus Chromatography for Detection of Opioid Use

Immunoassay	Chromatography
• Does not differentiate between various opioids	Differentiates: codeine, morphine, oxycodone, hydrocodone, hydromorphone, heroin (monoacetylmorphine).
• Will show false positives: Poppy seeds, quinolone antibiotics.	Does not react to poppy seeds.
•Often misses semi-synthetic and synthetic opioids, e.g., oxycodone, methadone, fentanyl.	More accurate for semi-synthetic and synthetic opioids.

Table B Appendix 3.2 Detection Times for Immunoassay and Chromatography

	Number of days drug is detectable	
Drug	Immunoassay	Chromatography
Benzodiazepines (regular use)	• 20+ days for regular diazepam use. • Immunoassay does not distinguish different benzodiazepines. • Intermediate-acting benzodiazepines such as clonazepam are often undetected.	Not usually used for benzodiazepines.
Cannabis	20+	Not used for cannabis.
Cocaine + metabolite	3–7	1–2
Codeine	2–5	1–2 (Codeine metabolized to morphine.)
Hydrocodone	2–5	1–2
Hydromorphone	2–5	1–2
Meperidine	1 (often missed)	1
Morphine	2–5	1–2: Morphine can be metabolized to hydromorphone
Oxycodone	Often missed	1–2

Source: Adapted from Brands 1998.

Appendix B-4: Opioid Information for Patients

NOTE: These messages could be used to create patient education materials.

Messages for Patients Taking Opioids

Opioids are a group of similar medications that are used to help with pain — there is more than one type of opioid and they have different names for example, Percocet®, OxyContin®, Tylenol® No. 2, Tramacet®.

1. Opioids are used to improve your ability to be active and reduce pain.

- You and your doctor will set goals and ensure the medication is effective in achieving the goals, e.g. improving your ability to do the things you did before pain prevented you.
- If you seem to benefit from the pain medication, your doctor will see you for follow-up visits to assess pain relief, any adverse effects, and your ability to meet your set activity goals.

2. There are side effects from opioids, but they can be mostly controlled with increasing your dose slowly.

- Common side effects include: nausea (28% of patients report it), constipation (26%), drowsiness (24%), dizziness (18%), dry-skin/itching (15%), and vomiting (15%).
- Side effects can be minimized by slowly increasing the dose of the drug and by using anti-nausea drugs and bowel stimulants.

3. Your doctor will ask you questions and discuss any concerns with you about your possibility of developing addiction.

- Addiction means that a person uses the drug to "get high," and cannot control the urge to take the drug.
- Most patients do not "get high" from taking opioids, and addiction is unlikely if your risk for addiction is low: those at greatest risk have a history of addiction with alcohol or other drugs.

4. Opioids can help but they do have risks — these can be managed by working cooperatively with your doctor.

- Take the medication as your doctor prescribed it.
- Don't drive while your dose is being gradually increased or if the medication is making you sleepy or feel confused.
- Only one doctor should be prescribing opioid medication for you — don't obtain this medication from another doctor unless both are aware that you have two prescriptions for opioids.
- Don't take opioids from someone else or share your medication with others.
- You may be asked for a urine sample — this will help to show all the drugs you are taking and ensure a combination is not placing you at risk.
- Your doctor will give you a prescription for the amount of medication that will last until your next appointment — keep your prescription safe and use the medications as instructed — if you run out too soon or lose your prescription your doctor will not likely provide another
- If you cannot follow these precautions it may not be safe for your doctor to prescribe opioid medication for you.

...continued page 2

...*Page 2 of 2*

5. If you stop taking your medication abruptly, you will experience a withdrawal reaction.

- Withdrawal symptoms do not mean you are addicted — just that you stopped the drug too quickly — your doctor will direct you on how to slowly stop this medication so you won't have this experience.
- Opioid withdrawal symptoms are flu-like, e.g., nausea, diarrhea, and chills.
- Withdrawal is not dangerous but it can be very uncomfortable.
- If you interrupt your medication schedule for three days or more for any reason, do not resume taking it without consulting a doctor.

6. Overdose from opioids is uncommon, but you and your family should be aware of the signs.

- Opioids are safe over the long term, BUT can be dangerous when starting or increasing a dose.
- Overdose means thinking and breathing slows down — this could result in brain damage, trauma, and death.
- Mixing opioids with alcohol or sedating drugs such as pills to help anxiety or sleeping, greatly increases the risk of overdose.
- You and your family should be aware of signs of overdose — contact a doctor if you notice: slurred or drawling speech, becoming upset or crying easily, poor balance or, "nodding off" during conversation or activity.

7. The medication the doctor prescribes for you can be very dangerous to others.

- Your body will get used to the dose your doctor sets for you but this same dose can be very dangerous to others.
- You have reached your proper dose slowly, but someone who is not used to the medication could have a serious reaction, including death — don't give your medication to anyone else – it is illegal and could harm them.
- Keep you medication securely stored at home — the bathroom medicine cabinet is *not* a safe place; research has shown that others, particularly teenagers might help themselves to these drugs from friends or relatives.

Appendix B-5: Sample Opioid Medication Treatment Agreement

I understand that I am receiving opioid medication from Dr. _____ to treat my pain condition. I agree to the following:

1. I will not seek opioid medications from another physician. Only Dr. _____ will prescribe opioids for me.
2. I will not take opioid medications in larger amounts or more frequently than is prescribed by Dr. _____.
3. I will not give or sell my medication to anyone else, including family members; nor will I accept any opioid medication from anyone else.
4. I will not use over-the-counter opioid medications such as 222's and Tylenol® No. 1.
5. I understand that if my prescription runs out early for any reason (for example, if I lose the medication, or take more than prescribed), Dr. _____ will not prescribe extra medications for me; I will have to wait until the next prescription is due.
6. I will fill my prescriptions at one pharmacy of my choice; pharmacy name: _____
7. I will store my medication in a secured location.

I understand that if I break these conditions, Dr. _____ may choose to cease writing opioid prescriptions for me.

Source: Modified from Kahan 2006.

Appendix B-6: Benzodiazepine Tapering

1. Benefits of Benzodiazepine Tapering

- Lower the risk of future adverse drug-related risks such as falls.
- Increased alertness and energy.

2. Approach to Tapering

- Taper slowly: slow tapers are more likely to be successful than fast tapers.
- Use scheduled rather than p.r.n. doses.
- Halt or reverse taper if severe anxiety or depression occurs.
- Schedule follow-up visits q. 1–4 weeks depending on the patient's response to taper.
- At each visit, ask patient about the benefits of tapering (e.g., increased energy, increased alertness).

3. Protocol for Outpatient Benzodiazepine Tapering

3.1 Initiation

- May taper with a longer-acting agent such as diazepam or clonazepam, or taper with the agent that the patient is taking. (Diazepam can cause prolonged sedation in the elderly and those with liver impairment.)
- There is insufficient evidence to strongly support the use of one particular benzodiazepine for tapering.
- Convert to equivalent dose in divided doses (see equivalence table below, Table B Appendix 6.1).
- Adjust initial dose according to symptoms (equivalence table is approximate).

3.2 Decreasing the Dose

- Taper by no more than 5 mg diazepam equivalent per week.
- Adjust rate of taper according to symptoms.
- Slow the pace of the taper once dose is below 20 mg of diazepam equivalent (e.g., 1–2 mg/week).
- Instruct the pharmacist to dispense daily, twice weekly, or weekly depending on dose and patient reliability.

3.3 Another Approach

Taper according to the proportional dose remaining: Taper by 10% of the dose every 1–2 weeks until the dose is at 20% of the original dose; then taper by 5% every 2–4 weeks.

Source: Adapted from Kahan 2002.

4. Benzodiazepine Equivalent Table

Table B Appendix 6.1 Benzodiazepine Equivalent Table

Benzodiazepine	Equivalent to 5 mg diazepam (mg) *
Alprazolam (Xanax®)**	0.5
Bromazepam (Lectopam®)	3–6
Chlordiazepoxide (Librium®)	10–25
Clonazepam (Rivotril®)	0.5–1
Clorazepate (Tranxene®)	7.5
Flurazepam (Dalmane®)	15
Lorazepam (Ativan®)	0.5–1
Nitrazepam (Mogadon®)	5–10
Oxazepam (Serax®)	15
Temazepam (Restoril®)	10–15
Triazolam (Halcion®)**	0.25

* Equivalences are approximate. Careful monitoring is required to avoid oversedation, particularly in older adults and those with impaired hepatic metabolism.

**Equivalency uncertain.

Source: Adapted from Kalvik 1995, Canadian Pharmacists Association 1999.

Appendix B-7: Example of Documenting Opioid Therapy

Opioid Therapy Record Example

Date:	Jan 13 2008	Mar 23 2008	May 23 2008	
Opioid type	Oxycodone	Oxycodone		
Opioid dose	20 tid	30 tid		
MEQ dose	90 mg	135		
Pain worst	8 →	6		
Pain least	3	3		
Pain average	6	5		
Pain right now	6 →	4		
BPI functional improvement	Sleep improved	Back to work		
Adverse effects	Nausea	Nausea continues		
Medical complications	nil	nil		
Compliance	UDS clear	No concerns		
Action	Increase to 30 tid	Keep this dose		
Other Comments				

Appendix B-8: Opioid Conversion and Brand Availability in Canada

Appendix B-8.1 Oral Opioid Analgesic Conversion Table

- The table is based on oral dosing for chronic non-cancer pain.
- The figures are based on the Compendium of Pharmaceutical & Specialties (Canadian Pharmacists Association 2008) and a systematic review by Pereira (2001). Wide ranges have been reported in the literature.
- These equivalences refer to analgesic strength of oral opioids, and not psychoactive effects or effectiveness in relieving withdrawal symptoms.

1. Equivalence to oral morphine 30 mg:

Table B Appendix 8.1 Oral Opioid Analgesic Conversion Table

	Equivalence to oral morphine 30 mg:	To convert to oral morphine equivalent multiply by:	To convert from oral morphine multiply by:
Morphine	30 mg	1	1
Codeine	200 mg	0.15	6.67
Oxycodone	20 mg	1.5	0.667
Hydromorphone	6 mg	5	0.2
Meperidine	300 mg	0.1	10
Methadone and tramadol	Morphine dose equivalence not reliably established.		

2. Equivalence between oral morphine and transdermal fentanyl:

Transdermal fentanyl*	60–134 mg morphine = 25mcg/h 135–179 mg = 37 mcg/h 180–224 mg = 50 mcg/h 225–269 mg = 62 mcg/h 270–314 mg = 75 mcg/h 315–359 mg = 87 mcg/h 360–404 mg = 100 mcg/h

*Formulations include 12, 25, 50, 75 and 100 ucg/hour patches, but the 12 ucg/hour patch is generally used for dose adjustment rather than initiation of fentanyl treatment.

Appendix B-8.2 Opioids: Generic and Brand Names Available in Canada

(Canadian Pharmacists Association 2008)

Drug (generic name)	Brand names
STRONG OPIOIDS	
Fentanyl (transdermal)	Duragesic®
Hydromorphone HCL	Dilaudid®, Hydromorph Contin®, Hydromorphone HCL, Hydromorphone HP® (10, 20, 50, Forte), Jurnista®, PMS-Hydromorphone®
Methadone HCL	Metadol®
Morphine sulfate	Statex®, Kadian®, M-Eslon®, M.O.S.-Sulfate®, Morphine HP, Morphine sulphate, MS Contin®, MS-IR®, PMS-Morphine®, Morphine Sulfate SR®, ratio-Morphine SR®
Oxycodone HCL	OxyContin®, Oxy-IR®, Supeudol®
Oxycodone HCL with acetaminophen	Endocet®, Percocet®, Percocet-Demi®, ratio-Oxycocet®, PMS- Oxycodone- Acetaminophen®
Oxycodone HCL/ ASA	Endodan®, Percodan®, Percodan-Demi®, ratio-Oxycodan®
WEAK OPIOIDS	
Codeine monohydrate/ sulphate trihydrate	Codeine, Codeine Contin®
Codeine phosphate/ acetaminophen/ caffeine	Tylenol® (No. 1, 2, 3); Atasol® (No. 8, 15, 30); Lenoltec®
Codeine phosphate/ Acetaminophen without caffeine	Empracet®
Propoxyphene Napsylate	Darvon-N®
Pentazocine HCL	*Talwin®
Pethidine HCL (meperidine)	Demerol®
**Tramadol	Ralivia™, Zytram XL®, Tridural™
**Tramadol/ Acetaminophen	Tramacet®
CANNABINOIDS	
Nabilone	Cesamet®
Dronabinol	Marinol®
	***Sativex®

* Opioid agonist/antagonist
** Tramadol is a weak opioid and serotonin/norepinephrine reuptake inhibitor
*** Orobuccal spray containing extracts of natural cannabis

Note: Reference throughout this document to specific pharmaceutical products as examples does not imply endorsement of any of these products.

Appendix B-9: Brief Pain Inventory©

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form) - Experimental

Date: ____/____/____ Time: _____

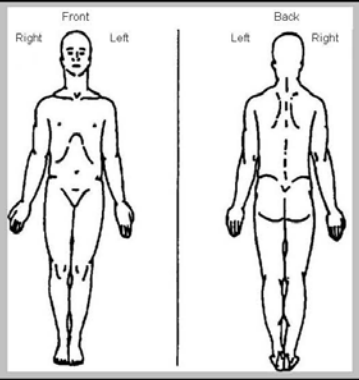
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

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Brief Pain Inventory©: Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, editors. Issues in Pain Measurement. New York: Raven Press; pp. 391-403, 1989. Advances in Pain Research and Therapy; Vol. 12.

For further information and to obtain copies for clinical use: www.mdanderson.org/BPI

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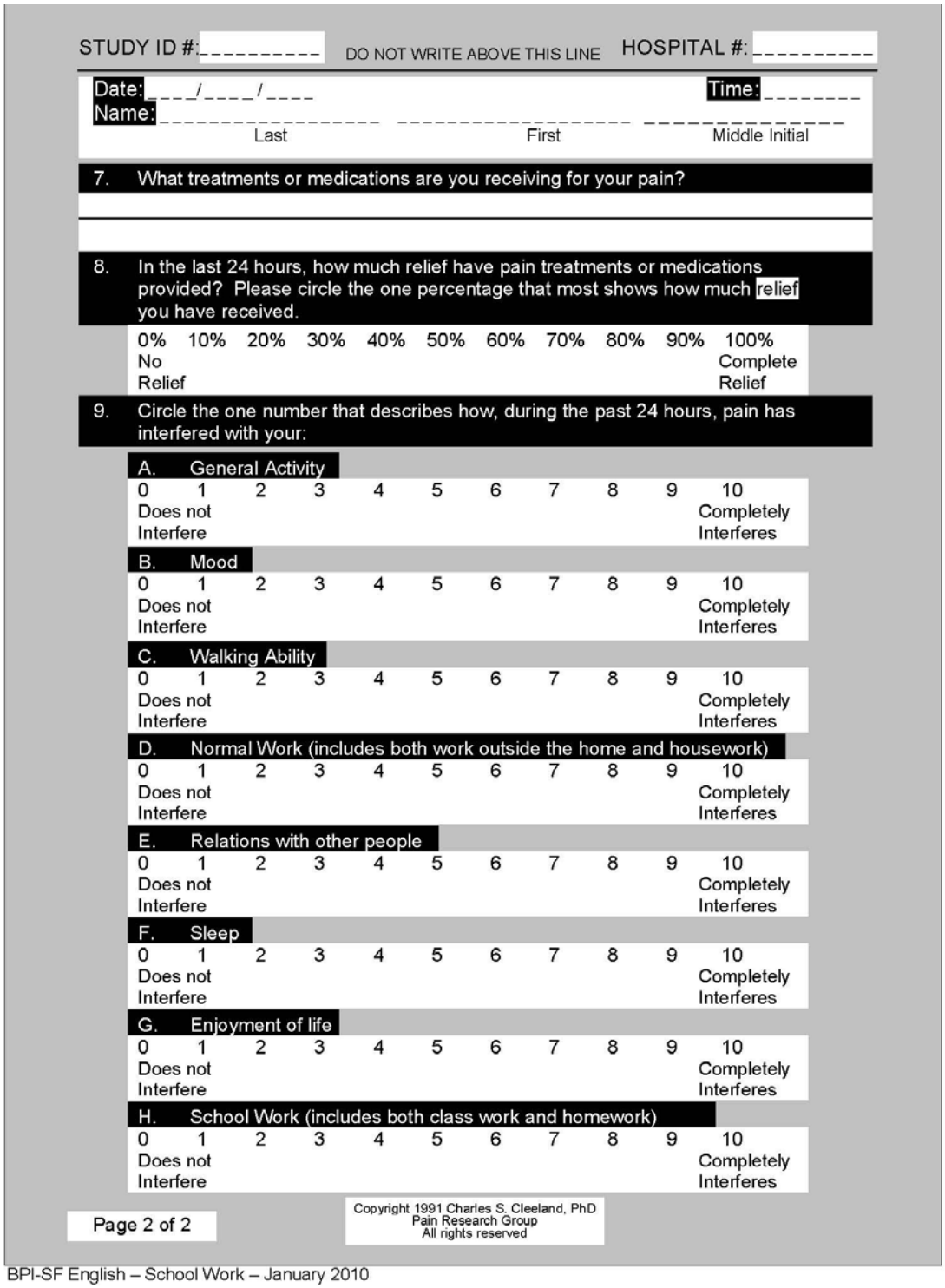
Brief Pain Inventory©, page 2 of 2



STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date:___/___/____ Time:_____

Name:_____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

H. School Work (includes both class work and homework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

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Appendix B-10: Aberrant Drug-Related Behaviours Resources

Table B Appendix 10.1 Aberrant Drug-Related Behaviours Indicative of Opioid Misuse
(Modified from Passik 2004)

Note: * = behaviours more indicative of addiction than the others

Indicator	Examples
*Altering the route of delivery	• Injecting, biting or crushing oral formulations
*Accessing opioids from other sources	• Taking the drug from friends or relatives • Purchasing the drug from the "street" • Double-doctoring
Unsanctioned use	• Multiple unauthorized dose escalations • Binge rather than scheduled use
Drug seeking	• Recurrent prescription losses • Aggressive complaining about the need for higher doses • Harassing staff for faxed scripts or fit-in appointments • Nothing else "works"
Repeated withdrawal symptoms	• Marked dysphoria, myalgias, GI symptoms, craving
Accompanying conditions	• Currently addicted to alcohol, cocaine, cannabis or other drugs • Underlying mood or anxiety disorders not responsive to treatment
Social features	• Deteriorating or poor social function • Concern expressed by family members
Views on the opioid medication	• Sometimes acknowledges being addicted • Strong resistance to tapering or switching opioids • May admit to mood-leveling effect • May acknowledge distressing withdrawal symptoms

Supporting Information:

1. **Aberrant drug-related behaviours are common in patients with chronic pain.**
   A systematic review (Fishbain 2008) estimated that the prevalence of aberrant drug-related behaviours among chronic pain patients was 11.5% (range 0–44%). Urine drug screening with illicit drugs present was 14.5%, while a non-prescribed opioid or no opioid present was 20.4%.

2. **There is evidence that some aberrant drug-related behaviours are more predictive of opioid addiction than others.**
   One study compared a sample of HIV patients with a history of substance abuse, to cancer patients without a history of substance abuse (Passik 2006a). Both groups were on opioids for chronic pain. Aberrant behaviours were significantly more common in the group with a history of substance abuse, and pain control was worse. Behaviours strongly predictive of opioid **addiction** (illegal activity, altering the route of delivery) were much more common in the group with a history of substance abuse than the group with no history of substance abuse. Aberrant behaviours in the group with a history of substance abuse were seen as frequently in patients who reported good pain control as in patients who reported poor pain control, suggesting that aberrant behaviours usually indicate something other than inadequately treated pain.

... continued

Appendix B-10: Aberrant Drug-Related Behaviours Resources... continued

Tools used to assist in identifying aberrant drug-related behaviours.

- *Addiction Behaviors Checklist* (ABC): In 2006, Wu, Compton et al. also developed and tested the ABC, a 20-item instrument designed to identify problematic drug-use in chronic pain patients treated with opioids (Wu 2006).
- *Current Opioid Misuse Measure* (COMM®): In 2007, Butler et al. developed and demonstrated the potential for a brief and easy-to-administer 17-item questionnaire, the COMM®, to identify aberrant drug-related behaviours (Butler 2007).
- *Patient Assessment and Documentation Tool* (PADT): developed by Passik et al. 2004, Clin Ther. This instrument focuses on key outcomes and provides a consistent way to document progress in pain management therapy over time. Items assess four domains: pain relief, patient functioning, adverse events, and drug-related behaviors.
- *Prescription Drug Use Questionnaire* (PDUQ): In 1998, Compton et al. developed and piloted the *PDUQ* for screening for addiction in chronic pain patients receiving opioids (Compton 1998). This is a 42-item interview to assess abuse/misuse for pain patients.
- *Prescription Opioid Therapy Questionnaire* (POTQ): In 2004, Michna et al. developed and tested the POTQ, an 11-item scale where the provider answers "yes" or "no" to questions indicative of misuse of opioids (Michna 2004).
- *Screener and Opioid Assessment for Patients with Pain* (SOAPP®-R). In 2004, Butler et al. developed the SOAPP® instrument (Butler 2004). In 2008 they published the revised SOAPP®-R, a 24-item self-report questionnaire that may also be useful for identifying risk of aberrant behaviours (Butler 2008).

Appendix B-11: SOAPP®-R and COMM®

1. SOAPP®-R

Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP®-R)

The following are some questions given to patients who are on or being considered for medication for their pain. Please answer each question as honestly as possible. There are no right or wrong answers.

	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
1. How often do you have mood swings?	○	○	○	○	○
2. How often have you felt a need for higher doses of medication to treat your pain?	○	○	○	○	○
3. How often have you felt impatient with your doctors?	○	○	○	○	○
4. How often have you felt that things are just too overwhelming that you can't handle them?	○	○	○	○	○
5. How often is there tension in the home?	○	○	○	○	○
6. How often have you counted pain pills to see how many are remaining?	○	○	○	○	○
7. How often have you been concerned that people will judge you for taking pain medication?	○	○	○	○	○
8. How often do you feel bored?	○	○	○	○	○
9. How often have you taken more pain medication than you were supposed to?	○	○	○	○	○
10. How often have you worried about being left alone?	○	○	○	○	○
11. How often have you felt a craving for medication?	○	○	○	○	○
12. How often have others expressed concern over your use of medication?	○	○	○	○	○

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SOAPP®-R, page 2

	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
13. How often have any of your close friends had a problem with alcohol or drugs?	○	○	○	○	○
14. How often have others told you that you had a bad temper?	○	○	○	○	○
15. How often have you felt consumed by the need to get pain medication?	○	○	○	○	○
16. How often have you run out of pain medication early?	○	○	○	○	○
17. How often have others kept you from getting what you deserve?	○	○	○	○	○
18. How often, in your lifetime, have you had legal problems or been arrested?	○	○	○	○	○
19. How often have you attended an AA or NA meeting?	○	○	○	○	○
20. How often have you been in an argument that was so out of control that someone got hurt?	○	○	○	○	○
21. How often have you been sexually abused?	○	○	○	○	○
22. How often have others suggested that you have a drug or alcohol problem?	○	○	○	○	○
23. How often have you had to borrow pain medications from your family or friends?	○	○	○	○	○
24. How often have you been treated for an alcohol or drug problem?	○	○	○	○	○

Please include any additional information you wish about the above answers.
Thank you.

Appendix B-11…continued

2. COMM®

Current Opioid Misuse Measure (COMM)®

Please answer each question as honestly as possible. Keep in mind that we are only asking about the **past 30 days**. There are no right or wrong answers. If you are unsure about how to answer the question, please give the best answer you can.

Please answer the questions using the following scale:	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
1. In the past 30 days, how often have you had trouble with thinking clearly or had memory problems?	O	O	O	O	O
2. In the past 30 days, how often do people complain that you are not completing necessary tasks? (i.e., doing things that need to be done, such as going to class, work or appointments)	O	O	O	O	O
3. In the past 30 days, how often have you had to go to someone other than your prescribing physician to get sufficient pain relief from medications? (i.e., another doctor, the Emergency Room, friends, street sources)	O	O	O	O	O
4. In the past 30 days, how often have you taken your medications differently from how they are prescribed?	O	O	O	O	O
5. In the past 30 days, how often have you seriously thought about hurting yourself?	O	O	O	O	O
6. In the past 30 days, how much of your time was spent thinking about opioid medications (having enough, taking them, dosing schedule, etc.)?	O	O	O	O	O

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Appendix B-11…continued

2. COMM®… page 2

Please answer the questions using the following scale:	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
7. In the past 30 days, how often have you been in an argument?	O	O	O	O	O
8. In the past 30 days, how often have you had trouble controlling your anger (e.g., road rage, screaming, etc.)?	O	O	O	O	O
9. In the past 30 days, how often have you needed to take pain medications belonging to someone else?	O	O	O	O	O
10. In the past 30 days, how often have you been worried about how you're handling your medications?	O	O	O	O	O
11. In the past 30 days, how often have others been worried about how you're handling your medications?	O	O	O	O	O
12. In the past 30 days, how often have you had to make an emergency phone call or show up at the clinic without an appointment?	O	O	O	O	O
13. In the past 30 days, how often have you gotten angry with people?	O	O	O	O	O
14. In the past 30 days, how often have you had to take more of your medication than prescribed?	O	O	O	O	O
15. In the past 30 days, how often have you borrowed pain medication from someone else?	O	O	O	O	O
16. In the past 30 days, how often have you used your pain medicine for symptoms other than for pain (e.g., to help you sleep, improve your mood, or relieve stress)?	O	O	O	O	O
17. In the past 30 days, how often have you had to visit the Emergency Room?	O	O	O	O	O

Appendix B-12: Opioid Tapering

1. Precautions for Outpatient Opioid Tapering

1) **Pregnancy**: Severe, acute opioid withdrawal has been associated with premature labour and spontaneous abortion.
2) **Unstable medical and psychiatric conditions that can be worsened by anxiety**: While opioid withdrawal does not have serious medical consequences, it can cause significant anxiety and insomnia.
3) **Addiction to opioids obtained from multiple doctors or "the street:"** Outpatient tapering is unlikely to be successful if the patient regularly accesses opioids from other sources; such patients are usually best managed in an opioid agonist treatment program (methadone or buprenorphine).
4) **Concurrent medications**: Avoid sedative-hypnotic drugs, especially benzodiazepines, during the taper.

2. Opioid Tapering Protocol

2.1 Before Initiation

1) Emphasize that the goal of tapering is to make the patient feel better: to reduce pain intensity and to improve, mood and function.
2) Have a detailed treatment agreement.
3) Be prepared to provide frequent follow-up visits and supportive counselling.

2.2 Type of Opioid, Schedule, Dispensing Interval

1) Use controlled-release morphine if feasible (see 2.3 below).
2) Prescribe scheduled doses (not p.r.n.).
3) Prescribe at frequent dispensing intervals (daily, alternate days, weekly, depending on patient's degree of control over opioid use). Do not refill if patient runs out.
4) Keep daily schedule the same for as long as possible (e.g., t.i.d.).

2.3. Rate of the Taper

1) The rate of the taper can vary from 10% of the total daily dose every day, to 10% of the total daily dose every 1–2 weeks.
2) Slower tapers are recommended for patients who are anxious about tapering, may be psychologically dependent on opioids, have co-morbid cardio-respiratory conditions, or express a preference for a slow taper.
3) Once one-third of the original dose is reached, slow the taper to one-half or less of the previous rate.
4) Hold the dose when appropriate: The dose should be held or increased if the patient experiences severe withdrawal symptoms, a significant worsening of pain or mood, or reduced function during the taper.

2.4 Switching to Morphine

1) Consider switching patients to morphine if the patient might be dependent on oxycodone or hydromorphone.
2) Calculate equivalent dose of morphine (see Appendix B-8: Oral Opioid Analgesic Conversion Table).
3) Start patient on one-half this dose (tolerance to one opioid is not fully transferred to another opioid).
4) Adjust dose up or down as necessary to relieve withdrawal symptoms without inducing sedation.

…Appendix B-12 continued next page

Appendix B-12: "Opioid Tapering"…continued

2.5 Monitoring during the Taper

1) Schedule frequent visits during the taper (e.g. weekly).
2) At each visit, ask about pain status, withdrawal symptoms and possible benefits of the taper: reduced pain and improved mood, energy level and alertness.
3) Use urine drug screening to assess compliance.

2.6 Completing the Taper

1) Tapers can usually be completed between 2–3 weeks and 3–4 months.
2) Patients who are unable to complete the taper may be maintained at a lower dose if their mood and functioning improve and they follow the treatment agreement.

Appendix B-13: Meta-analysis Evidence Table

Characteristics of the 62 randomized controlled trials included in this updated systematic review.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
1. Placebo-controlled (Neuropathic pain)				
Harati 1998 **USA** **Parallel** Quality: 4	Diabetic neuropathy 131 (49)	Tramadol 50 – 400 mg/d for 6 wk	**Primary:** Pain intensity* (5-point Likert scale). **Secondary:** Pain relief, quality of life (Medical Outcomes Study): physical functioning*, social functioning, current health perception, psychological distress, overall role functioning, and the two overall sleep problem indexes and sleep subscales.	Tramadol, at an average dose of 210 mg/d was significantly more effective than placebo. Patients on tramadol scored significantly better in physical and social functioning.
Sindrup 1999 **Germany** **Crossover** Quality:4	Polyneuropathy 45 (11)	Tramadol 200 – 400 mg/d for 4 wk	**Primary:** Pain ratings* (0-10 NRS), paraesthesia and touch-evoked pain. **Secondary:** Dynamic allodynia, rescue medication, patient's preference.	Pain, paraesthesia, touch-evoked pain and allodynia were lower on tramadol than on placebo. NNT to obtain one patient with ≥50% pain relief was 4.3 (95% CI 2.4 to 20).
Boureau 2003 **France** **Parallel** Quality:5	Postherpetic neuralgia 127 (19)	Tramadol 100 – 400 mg/d for 6 wk	**Primary:** Pain intensity (100-mm VAS* and 5-point NRS). **Secondary:** Global improvement, quality of life (Nottingham scale) and rescue medication (paracetamol).	Mean pain intensity was significantly lower with tramadol in both per protocol and intention-to-treat population. No significant difference was found between groups in pain intensity on a 5-point verbal scale or in quality of life measurement.
Norrbrink 2009 **Sweden** **Parallel** Quality:3	Spinal Cord Injury with neuropathic pain at or below level > 6 months. 35 (13)	Tramadol 50 mg TID – 400 mg/day. For 4 weeks.	**Primary:** present, general and worst pain. MPI subscale pain severity. Patient Global Impression of Change. **Secondary:** anxiety, global life satisfaction, and sleep quality.	Significant differences in present pain, general pain, and worst pain as well as MPI favouring tramadol. Seven patients on active drug (30%) rated an improvement, but only 4 (17%) rated their pain to be much improved. One patient in the placebo group reported minimal improvement (8%). No patients in either group reported their pain to be very much improved.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Watson and Babul 1998 Canada Crossover Quality:3	Postherpetic neuralgia 50 (12)	CR Oxycodone 20 – 60 (mean 45) mg/d for 4 wk	**Primary:** Pain intensity (100-mm VAS* and 5-point categorical scale). **Secondary:** Pain relief, steady pain, brief pain, skin pain, disability* (using a categorical scale: 0= no disability, 3= severe disability), BDI, POMS.	Oxycodone was significantly better in pain relief, reductions in steady pain, allodynia, paroxysmal spontaneous pain, global effectiveness, disability and masked preference.
Watson 2003 Canada Crossover Quality:4	Diabetic neuropathy 45 (3)	CR Oxycodone 20 – 80 (mean 40) mg/d for 4 wk	**Primary:** Pain intensity (100-mm VAS* and 5-point categorical scale). **Secondary:** Pain relief, steady pain, brief pain, skin pain, PDI*, SF-36 health survey, pain and sleep questionnaires.	Oxycodone was significantly better on daily pain, steady pain, brief pain, skin pain,total pain and disability. NNT to obtain one patient with at least 50% pain relief was 2.6
Gimbel 2003 USA Parallel Quality:5	Diabetic neuropathy 159 (44)	CR Oxycodone 20 – 120 (mean 37) mg/d for 6 wk	**Primary:** Pain intensity* (0-10 numeric scale). **Secondary:** Current and worse pain, satisfaction, BPI* (physical function score), SF-36 health survey.	Oxycodone provided more analgesia than placebo in the intent-to-treat cohort.
Huse 2001 Germany Crossover Quality:1	Phantom limb pain 12 (3)	SR morphine 70 – 300 (mean 120) mg/d for 4 wk	**Primary:** Pain intensity* (2-cm VAS) **Secondary:** PES, SDS, PRSS, WHYMPI, BSS.	Based on pain diary data, 42% of patients on morphine showed a pain reduction of more than 50% compared to only one patient in the placebo group.
Harke 2001 Germany Parallel Quality:4	Peripheral neuropathy 38 (3)	SR morphine 90 mg/d for 1 wk	Pain intensity* (0-10 numeric analogue scale), and reactivation of their spinal cord stimulator.	The differences between morphine and placebo were not significant.
Wu 2008 USA Crossover Quality:4	Postamputation pain 60 (25)	SR Morphine 15 - 180 mg day x 6 weeks.	**Primary:** Average change in overall pain intensity from the baseline to the last week of maintenance therapy using 0-10. **Secondary:** Pain relief (0-100%) and the interference and general activity subscales from the MPI. Side effects.	Morphine provided lower pain scores compared with placebo. The mean percent pain relief during treatment with placebo and morphine was 19 53%, respectively. NNT to obtain 50% and 33% decreases in pain intensity with morphine were 5.6 and 4.5, respectively.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Raja 2002(a) **USA** **Crossover** Quality:4	Postherpetic neuralgia 76 (32)	CR morphine 15-240 (mean 91) mg/d for 6 wk or methadone 15mg/d.	**Primary:** Pain intensity* (0-10 NRS). **Secondary:** Pain relief, cognitive function, MPI* (physical functioning subscale), sleep, mood, global preference.	Morphine reduced pain (1.9) more than placebo (0.2). Pain relief was greater with morphine (38%) compared with placebo (11%).
Gilron 2005 **Canada** **Crossover** Quality:4	35 diabetic neuropathy and 22 postherpetic neuralgia. 57 (16)	A) SR morphine maximum tolerated for 5 wk. B) SR morphine maximum tolerated combined with gabapentin for 5 wk C) Gabapentin maximum tolerated for 5 wk	**Primary:** Pain intensity* (0-10 NRS) **Secondary:** SF-MPQ, Maximal tolerated doses, Mood (BDI), SF-36 (physical function*), Mental Status (Mini-Mental), and global pain relief.	Mean pain intensity at the maximal tolerated dose was 4.49 with placebo, 4.15 with gabapentin, 3.7 with morphine and 3.06 with gabapentin-morphine combination. Total scores in SF-36 were lower with gabapentin-morphine combination than placebo or each drug alone.
Khoromi 2007 **USA** **Crossover** Quality:1	Chronic lumbar radiculopathy (sciatica) 55 (27)	A) SR morphine 15-90 mg/d B) Nortriptyline 25-100 mg/d C) Combination Each phase: 5 + 2 + 2 wk	**Primary:** Average leg pain during the two weeks*. **Secondary:** Global pain relief, ODI*, BDI and SF-36.	None of the treatments produced significant reductions in average leg pain or other leg or back pain scores.
Simpson 2007 **USA** **Crossover (Enrichment)** Quality:4	Acute on chronic pain 79 (4)	Fentanyl buccal tablet 100-800 mcg. (This formulation is not available in Canada) Duration: 9 episodes or 21 days	**Primary:** Sum of pain intensity differences (0-10 NRS) in the first 60 minutes (SPID-60). **Secondary:** Proportion of breakthrough episodes with 33% and 50% improvement; time to significant pain relief, pain intensity differences, proportion of episodes with meaningful pain relief, and proportion of episodes that required supplemental medication.	SPID-60 was significantly greater for breakthrough pain episodes treated with fentanyl buccal tablets compared with those in which placebo was administered.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
2. Placebo-controlled (Nociceptive pain)				
Roth 1998 **USA** **Parallel (Enrichment)** Quality:3	Osteoarthritis (not specified) 42 (8)	Tramadol 200 – 400 mg/d for 2 wk	**Primary:** Time to exit from the study due to therapeutic failure. **Secondary:** Severity of pain*(0-3 numeric scale), Ability to perform activities.	Time to exit from the study because of insufficient pain relief was longer in the tramadol group. Pain at rest and severity of pain on motion were less in the tramadol group. No differences were noted in general severity of current pain and on disability to perform ADLs.
Silverfield 2002 **USA** **Parallel** Quality:5	Osteoarthritis (not specified) 308 (68)	Tramadol 37.5 – 70 mg/d + acetaminophen 325 – 650 mg/d for 1.5 wk	**Primary:** Pain intensity*(0-3 numeric scale), Pain relief. **Secondary:** SPID, WOMAC* (physical function subscale).	The addition of tramadol/acetaminophen to NSAID or COX-2 selective inhibitor therapy was effective in the treatment of OA flare pain.
Emkey 2004 **USA** **Parallel** Quality:3	Osteoarthritis (not specified) 307 (80)	Tramadol 37.5 – 300 mg/d + acetaminophen 325 – 2600 mg/d for 13 wk	**Primary:** Pain intensity* (100-mm VAS) **Secondary:** Pain relief, WOMAC* (physical function subscale), SF-36 survey.	Mean final VAS scores, mean final pain relief rating scores, WOMAC physical function and SF-36 role-physical measures were all significantly better with tramadol/acetaminophen than with placebo.
Fleischmann 2001, USA **Parallel** Quality:4	Osteoarthritis knee 129 (93)	Tramadol 50-400 mg/d for 12 wk	**Primary:** Pain intensity* (0-4 Likert scale). **Secondary:** Pain relief, WOMAC* (overall), global assessment, time to failure	Mean final pain intensity score, and all secondary outcomes were significantly better in the tramadol group than in the placebo group.
Babul 2004 **USA** **Parallel** Quality:4	Osteoarthritis knee 246 (122)	CR Tramadol 100 – 400 mg/d for 11 wk	**Primary:** Pain intensity* (100-mm VAS). **Secondary:** WOMAC* (physical function subscale), CSPI.	Tramadol resulted in significant improvements in pain, stiffness, physical function, global status and sleep.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Ruoff 1999 **USA** **Parallel** Quality:5	Chronic joint pain 465 (113)	A) Tramadol starting at 200mg/d B) Tramadol starting at 50mg/d and reaching 200 mg/d on day 4 C) Tramadol starting at 50mg/d and reaching 200 mg/d on day 10 Duration of treatment: 2 wk	**Primary:** Discontinuation due to adverse effect or ineffectiveness.	40 patients (30.8% of group taking 200 mg/d from day 1) reached the primary end point; 31 patients (24.0% from day 4); 20 patients (15.2% from day 10); and 3 (4.4% of placebo group).
Schnitzer 1999 **USA** **Parallel (Enrichment)** Quality:3	Osteoarthritis knee 240 (4)	Tramadol 200 mg/d + Naproxen 750 mg/d reduced by 250 mg/d every 2 wk. Duration total: 8 wk	**Primary:** Minimum effective naproxen dose.	The addition of tramadol allowed a significant reduction in the dosage of naproxen without compromising pain relief.
Schnitzer 2000 **USA** **Parallel (Enrichment)** Quality:5	Low-back pain 254 (22)	Tramadol 200 – 400 (mean 242) mg/d for 4 wk	**Primary:** Time to exit the double-blind trial. **Secondary:** Pain intensity* (10-cm VAS), Pain relief, SF-MPQ, RDQ*	Discontinuation rate due to therapeutic failure was 20.7% in the tramadol group and 51.3% in the placebo group. Pain scores, MPQ and RDQ were significantly better in the tramadol group.
Ruoff 2003 **USA** **Parallel** Quality:3	Low-back pain. 322 (157)	Tramadol 37.5 – 300 (mean 157.5) mg/d + acetaminophen 325 – 2600 mg/d for 13 wk	**Primary:** Pain intensity* (100-mm VAS) **Secondary:** PRRS, SF-MPQ, RDQ*, SF-36.	Pain intensity, final PRRS scores, RDQ scores and many subscales of SF-MPQ and SF-36 were significantly better with tramadol than with placebo.
Peloso 2004 **Canada** **Parallel** Quality:3	Low-back pain 338 (191)	Tramadol 37.5 – 300 (mean 158) mg/d + acetaminophen 325 – 2600 mg/d for 91 days	**Primary:** Pain intensity* (100-mm VAS) **Secondary:** PRRS, SF-MPQ, SF-36, RDQ*, overall medication assessment.	VAS, pain relief scores, RDQ, physical-related subcategories of MPQ and Sf-36 were significantly better for tramadol/acetaminophen than for placebo. More patients rated tramadol/acetaminophen as “very good” or “good” than placebo.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Vorsanger 2008 USA and CANADA Parallel (Enrichment) Quality:4	Chronic Low Back Pain 386 (145)	A) CR Tramadol 300 mg/d* for 12 wk B) CR Tramadol 200 mg/d for 12 wk	**Primary:** pain intensity VAS since the previous visit. **Secondary:** current pain intensity VAS*, global assessment of study medication, Roland Disability Index*, and overall quality of sleep.	The placebo group had greater mean deterioration for pain intensity since the previous visit (+12.2 mm) compared with patients who continued to receive tramadol 300 mg (+5.2 mm) and patients whose dose was reduced to Tramadol 200 mg (+7.8). There were better response in the tramadol groups versus placebo for the secondary variables.
Burch 2007 Canada Parallel (Enrichment) Quality:5	Osteoarthritis knee 646 (155)	Tramadol (200-300 mg/d) for 12 wk	**Primary**: Pain intensity (11-point NRS)* **Secondary:** Patient and physician global impression of change.	The absolute mean reduction in pain intensity in the tramadol group was 3.0 ± 2.1. There was a statistically significant difference from placebo.
Kosinski 2007 Gana 2006 Schein 2008 USA Parallel Quality:2	Osteoarthritis (knee or hip), ACR Functional Class I-III 1020 (462)	A) Tramadol ER 100 mg/d for 12 wk B) Tramadol ER 200 mg/d for 12 wk C) Tramadol ER 300 mg/d for 12 wk D) Tramadol ER 400 mg/d for 12 wk	**Primary:** Pain intensity (100-mm VAS)* **Secondary:** Chronic pain sleep inventory.	Mean pain reduction at 12 weeks was -0.4 mm and -21.5 mm for tramadol ER and placebo, respectively (P < 0.001).
Lee 2006 Korea Parallel Quality:3	Rheumatoid arthritis pain inadequately controlled by NSAIDs and DMARD 277 (10)	Tramadol 37.5 mg/d plus acetaminophen 325 mg/d for 1 wk	**Primary:** mean daily pain relief score on a 6-point scale. **Secondary:** mean daily pain intensity (100-mm VAS)*, pain intensity at day 7, subjects and investigators mean overall assessment, physical function* (Health Assessment Questionnaire).	Pain relief scores and Pain intensity scores were significantly better in the tramadol/acetaminophen group compared with the placebo group Physical function did not differ significantly between tramadol/acetaminophen and placebo.
Thorne 2008 Canada Crossover Quality:3	OA knee or hip 100 (25)	CR Tramadol: 150 – 300 mg x 8 weeks	**Primary:** daily diary pain intensity score* **Secondary:** WOMAC pain and physical function*	Tramadol resulted in significantly lower pain intensity (37.4±23.9) compared with placebo (45.1±24.3). WOMAC index subscale score for pain and physical function were significantly better with tramadol than placebo.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Boureau 1991 **France** **Parallel** Quality:3	Rheumatoid Arthritis 40 (2)	Codeine 90 mg/d + acetaminophen 1500 mg/d for 1 week	**Primary:** Pain intensity (100-mm VAS* and 5-point Likert scale). **Secondary:** Pain relief, activity, sleep, overall efficacy.	Analgesic efficacy was significantly better with codeine/acetaminophen than with placebo for all criteria except the number of awakenings.
Arkinstall 1995 **Canada** **Crossover** Quality:3	Mixed nociceptive 46 (16)	CR Codeine 200 – 400 mg/d for 1 week	**Primary:** Pain intensity (100-mm VAS* and 5-point categorical scale). **Secondary:** Rescue acetaminophen + codeine consumption, PDI*, and patients' and investigators' treatment preferences.	The codeine group was significantly better on overall pain intensity (35±18) than placebo (49±16), on categorical pain intensity and on pain scores by day and time of day. Daily rescue analgesic consumption was lower in the codeine group. Disability was lower in the codeine group compared with placebo.
Peloso 2000 **Canada** **Parallel** Quality:3	Osteoarthritis hip or knee 103 (37)	CR Codeine 100 – 400 mg/d for 4 wk	**Primary:** WOMAC – Pain intensity* (0-500 VAS). **Secondary:** WOMAC* (stiffness and physical function), sleep, global assessment.	All variables in the efficacy analysis indicated superiority of codeine over placebo. The WOMAC improved 44.8% over baseline in the codeine group compared with 12.3% in the placebo group.
Roth 2000 **USA** **Parallel** Quality:3	Osteoarthritis 133 (70)	A) CR Oxycodone 20mg/d for 2 wk(*) B) CR Oxycodone 40mg/d for 2 wk	**Primary:** Pain intensity* (4-point numeric scale). **Secondary:** Quality of sleep, BPI, Interference of pain on key functional activities.	Oxycodone was superior to placebo in reducing pain intensity and the interference of pain with mood, sleep and enjoyment of life.
Caldwell 1999 **USA** **Parallel (Enrichment)** Quality:3	Osteoarthritis 107 (36)	A) IR Oxycodone 20 mg/d + acetaminophen 1300 mg/d for 4 wk(*) B) CR Oxycodone 20 mg/d for 4 wk	**Primary:** Pain intensity* (4-point numerical scale). **Secondary:** Global measure of sleep.	Pain intensity and quality of sleep were significantly improved in both active groups compared with the placebo group.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Webster 2006 **USA** **Parallel** Quality:3	Low-back pain 719 (391)	A) Oxycodone 10-80 mg/d once daily* B) Oxycodone 10-80 mg/d + ultra-low dose naltrexone once daily C) Oxycodone 10-80 mg/d + ultra-low dose naltrexone twice daily Duration: 12 wk	**Primary:** 11-point numerical diary pain intensity scale* **Secondary:** SF-12, ODI*, Quality of analgesia, global assessment of study drug.	All active treatment groups were significantly better than placebo on measures of pain reduction, physical component score of the SF-12 and ODI.
Markenson 2005 **USA** **Parallel** Quality:4	Osteoarthritis 109 (73)	Oxycodone CR 10-120 (mean 57) mg/d for 12 wk	**Primary:** BPI average pain intensity*, WOMAC scores at days 30 and 60, the number of patients who discontinued the study due to inadequate pain control. **Secondary:** BPI (pain interference and function), WOMAC, PGI, time to stable dosing, percentage of patients achieving stable dosing within 30 days, average daily dose at completion of initial titration, patient satisfaction, average and current pain intensity from pain diaries.	Oxycodone was significantly superior to placebo in decreasing average pain intensity and in reducing pain induced interference with general activity, walking ability (except at day 30), and normal work, as well as mood, sleep, relations with people (at days 60 and 90), and enjoyment in life. Daily functioning, as measured by WOMAC was also significantly improved in the oxycodone group. In the placebo group, a significantly greater percentage of patients discontinued due to inadequate pain control.
Chindalore 2005 **USA** **Parallel** Quality:3	Osteoarthritis hip and knee 362 (121)	A) Oxycodone 10 mg qid* B) Oxycodone 10 mg plus ultra-low dose naltrexone 0.001 mg qid C) Oxycodone 20 mg plus ultra-low dose naltrexone 0.001 mg bid Duration: 3 wk	**Primary:** Pain intensity measured by 11-point NRS* **Secondary:** quality of analgesia, pain control, global assessment of study drug, SF-12, WOMAC.	Although oxycodone was significantly better than placebo at wk 1, this treatment was not different from placebo at later time points. Oxycodone was significantly better than placebo on the pain subscale, the physical function scale, and the WOMAC total score, but at week 1 only.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Ma 2008 China Parallel Quality:4	Chronic neck pain with acute flare ups 116 (0 on day 7)	A) CR Oxycodone 5 to 10 mg bid for 4 wk	**Primary and secondary:** Frequency of pain episodes, pain intensity* (VAS), quality of life (QOL)*, quality of sleep (QOS), side effects, withdrawal symptoms, SF-36, performance status, patient satisfaction.	Results were extracted for the 7-day measurement. The frequency of pain episodes and VAS were decreased significantly with Oxycodone. Improvements in QOL and QOS were significant on day 3 after treatment with Oxycodone. Most domains of SF-36 were improved in the treated patients at the end of study.
Caldwell 2002 USA Parallel Quality:3	Osteoarthritis hip and/or knee 295 (111)	A) ER Morphine 30 mg/d (morning) for 4 wk* B) ER morphine 30 mg/d (evening) for 4 wk C) CR morphine 15 mg twice a day for 4 wk	**Primary:** WOMAC OA index pain (0-500) and overall arthritis pain intensity* (0-100). **Secondary:** WOMAC stiffness and physical function* (0-1700).	Morphine once daily and morphine twice daily both reduced pain and improved several sleep measures when compared with placebo. Analgesic efficacy was comparable between once daily and twice daily formulations.
Moran 1991 UK Crossover Quality:2	Rheumatoid Arthritis 20 (16)	CR Morphine 20 – 120 mg/d for 2 wk	**Primary:** Pain intensity* (100-mm VAS) **Secondary:** FIHAQ*, RS, GSS.	Although only 4 patients completed the study, results showed a significant improvement in pain in those taking morphine.
Moulin 1996 Canada Crossover Quality:4	Musculoskeletal pain 61 (18)	SR Morphine 30 – 120 (mean 83.5) mg/d for 6 wk	**Primary:** Pain intensity* (10-cm VAS) **Secondary:** Pain relief, MPQ, Drug liking, rescue medication, SCL-90, POMS, SIP, PDI*, HSCS, patient's preferences.	On VAS of pain, the morphine group showed a reduction in pain intensity relative to placebo in period I and this group also fared better in a crossover analysis of the sum of pain intensity differences from baseline. No other significant differences were detected.
Hale 2007 USA Parallel (Enrichment) Quality:2	Low-back pain 143 (76)	Oxymorphone ER 20-260 (mean 87.2, median 60 mg/d)o for 12 wk	**Primary:** change in average pain intensity (VAS) from baseline to final study visit* **Secondary:** 24-h pain intensity, use of medication, patients and physicians overall satisfaction.	Pain intensity increased significantly more for patients randomized to placebo than for patients who continued their stabilized dose of oxymorphone. The increase from baseline to final visit was 31.6 mm for placebo and 8.7 mm with oxymorphone.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Matsumoto 2005 **USA** **Parallel** Quality:4	Osteoarthritis 491 (222)	A) Oxymorphone ER 40 mg bid* B) Oxymorphone ER 20 mg bid C) Oxycodone CR 20 mg bid Duration: 4 wk	**Primary:** Pain intensity (VAS) at week 3 **Secondary:** Pain intensity from pain diary at wk 4*, WOMAC, patient and physician global assessments, drop outs due to lack of analgesia, sleep assessment, quality of life physical* and mental components (SF-36.	The primary end point showed a significant difference in favour of oxymorphone over placebo. Compared to placebo, both Oxymorphone 20 and 40 mg produced greater reductions in the WOMAC subscales at weeks 3 and 4.
Kivitz 2006 **USA** **Parallel** Quality:4	OA hip or knee 370 (172)	A) Oxymorphone ER 10 mg bid for 2 wk B) Oxymorphone ER 20 mg bid for 1 week, then 40 mg bid for 1 wk C) Oxymorphone ER 20 mg bid for 1 wk, then 50 mg bid for 1 wk.*	**Primary:** Arthritis pain intensity from VAS at week 1 and 2*. **Secondary:** WOMAC*, SF-36, chronic pain sleep inventory (CPSI), vital signs, clinical laboratory parameters, and adverse events.	Oxymorphone ER administered twice daily for 2 weeks produced dose-related reductions in arthritis pain intensity and improvements in physical function.
Zautra 2005 **USA** **Parallel** Quality:3	Moderate to severe pain due to OA 107 (71)	A) CR Oxycodone 10 mg bid for 2 wk They reported the results at 2-weeks, but the study lasted for 3 months.	**Primary:** Average 24 hour pain rating* (average of twelve daily reports was used for the 2-weeks posttest score on pain). **Secondary:** Positive and negative Watson's scale for affect. Vanderbilt multidimensional pain coping inventory. Coping efficacy and arthritis helplessness.	Oxycodone administered twice daily for 2 weeks demonstrated a significant reduction not only in 24 hour pain intensity but also in the other variables (coping and affect) favouring the active group. A significant drop out rate was observed (75% and 59% in the placebo and active group respectively)

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Portenoy 2007 **USA** **Parallel (Enrichment)** Quality:5	Acute on chronic low-back pain, 77 (3)	Fentanyl buccal tablets, maximum dose 800 mcg per episode. Duration 3 wk	**Primary:** electronic pain diary, 0 to 120 minutes after pain crisis. SPID-60 was the sum of pain intensity differences for the first 60 min. **Secondary:** proportion of breakthrough pain episodes with improvement >33% and 50%, pain relief at each posttreatment time point, proportion of episodes in which meaningful pain relief was obtained, time to meaningful pain relief, and proportion of episodes that required the use of supplemental medication.	SPID-60 was significantly better in the fentanyl group. All secondary measures also favoured fentanyl.
Langford 2006 **Multicenter in Europe** **Parallel** Quality:4	Osteoarthritis of hip and knee. Moderate to severe pain. 416 (217)	Transdermal fentanyl (25-100 mcg) for 6 wk	**Primary:** pain relief* (average area under the curve of the VAS scores over time). **Secondary:** WOMAC* score and its components.	Transdermal fentanyl provided significantly better pain relief than placebo, as demonstrated by the primary area under the curve for VAS scores -20 in the TDF group versus -14.6 in the placebo group. TDF was also associated with significantly better overall WOMAC scores and pain scores.
Landau 2007 **UK and USA** **Parallel (Enrichment)** Quality:4	Non-cancer pain (49% low back) 267 (12)	Buprenorphine transdermal (5-20 mg) for 2 wk	**Primary:** proportion of subjects with ineffective treatment* **Secondary:** time to ineffective treatment, proportion of subjects who reached ineffective treatment or discontinued for any reason, amount of escape medication used.	The proportion with ineffective treatment was lower in the buprenorphine group than in the placebo group (51.2% vs 65%). The odds of ineffective treatment were 1.79 times greater for placebo than buprenorphine.
3. Placebo-controlled (Fibromyalgia pain)				
Russell 2000 **USA** **Parallel (Enrichment)** Quality:5	Fibromyalgia 69 (1)	Tramadol 50 – 400 mg/d for 6 wk	**Primary:** Nº of patients exiting due to inadequate pain relief. **Secondary:** Pain intensity* (10-cm VAS), pain relief, tender-point count, myalgic score, FMIQ* (0-100).	Twenty (57.1%) patients in the tramadol group successfully completed the double-blind phase compared with nine (27%) in the placebo group.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Bennett 2003 **USA** **Parallel** Quality:4	Fibromyalgia 315 (177)	Tramadol 37.5 – 300 mg/d + acetaminophen 325 – 2600 mg/d for 11.5 wk	**Primary:** Cumulative time of discontinuation due to lack of efficacy. **Secondary:** Pain Intensity* (100-mm VAS), pain relief, tender-point count, myalgic score, FMIQ*, SF-36,12-SQ.	Discontinuation was less common in the tramadol group (48%) compared with the placebo group (62%). Tramadol treated patients also had significantly less pain at the end of the study, better pain relief and better FMIQ scores.
4. Placebo-controlled (Mixed pain)				
Maier 2002 **Germany** **Crossover** Quality:5	Neuropathic (67%) Nociceptive (32%) 49 (13)	SR Morphine 10 – 180 mg/d for 1 week (mean 114 mg/d)	**Primary:** Pain intensity* (0-10 NRS). **Secondary:** Tolerability of pain, sleep quality, physical fitness, mental state and mood, PDI*, symptom complain.	At the first wk, 44% under morphine and 0% under placebo had full responsiveness. After 2 wk 40% under morphine and 2% under placebo had full responsivenss.
5.Opioids versus other analgesics				
Gobel 1995 **Germany** **Parallel** Quality:1	Postherpetic neuralgia 35 (14)	Tramadol 200 – 600 mg/d for 6 wk Control: Clomipramine 50 – 100 mg/d with or without Levomepromazine 25–50 mg/d	**Primary:** Pain intensity*(5-point verbal rating scale). **Secondary:** Psychological and physical condition.	In both groups the pain intensity decreased over the 6-wk treatment period. (Reviewers' comments: no significant difference between groups). There were no essential differences in the current psychic/physical conditions during tramadol treatment.
Pavelka 1998 **Czech Republic** **Crossover** Quality:5	Osteoarthritis hip and knee 60 (6)	Tramadol 150 - 300 mg/d for 4 wk Control: Diclofenac 75 - 150 mg/d	**Primary:** WOMAC OA index (pain*, stiffness and physical disability*). **Secondary:** Drug preference.	Both treatments modestly improved median pain intensity, paralleled by an improvement in functional parameters, and there were no statistically significant differences between the groups.
Beaulieu 2008 **Canada** **Parallel** Quality:5	OA knee or hip 129 (32)	CR Tramadol 200 - 400/d for 6 wk Control: SR diclofenac 75mg/d for 6 wk	**Primary:** daily pain intensity by VAS* and WOMAC* pain subscale.	Mean change for WOMAC pain subscale was 73.2 ± 99.9 for tramadol and 80,2 ± 108 for diclofenac. Mean change for overall VAS pain score was 17.3 ± 22.6 for tramadol and 16.4 ± 24.4 for diclofenac.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Parr 1989 **USA** **Parallel** Quality:3	Pain in ≤2 joints. 846 (213)	D&A:dextropropoxyphene 1080 mg/d + acetaminophen 1950 mg/d for 4 wk Control: SR Diclofenac 100 mg/d	**Primary:** Pain intensity* (100-mm VAS) **Secondary:** Nottingham Health Profile. (NHP)*, energy, sleep, social isolation and emotional reactions.	Pain as measured by VAS showed 8% greater pain reduction with diclofenac as compared with D&A. Physical mobility as measured by the NHP improved by 13% more with diclofenac as compared with D&A.
Salzman and Brobyn 1983 (A) **USA** **Parallel** Quality:4	Osteoarthritis 57 (11 at 1 wk) in Salzman's group and 57 (7 at 1 wk) in Brobyn's	Propoxyphene 250 mg/d for 24 wk Control: Suprofen 800 mg/d	**Primary:** Pain intensity* (5-point numerical scale). **Secondary:** Pain relief, global improvement.	Both suprofen and propoxyphene produced a considerable reduction in pain intensity from baseline after only 1 wk treatment. This beneficial effect did not diminish with continued therapy. Further improvement occurred in both groups by 24 wk.
Glowinski 1999 **France** **Parallel** Quality:3	Rheumatoid Arthritis 60 (2)	Codeine 90 mg/d + acetaminophen 1500 mg/d for 1 week. Control: Diclofenac 100 mg/d + placebo.	**Primary:** Global efficacy (5-point verbal scale). **Secondary:** Pain intensity* (100-mm VAS), Impairment of activity (4-point scale), duration of morning stiffness, number of awakenings.	Analgesic efficacy was not significantly different between the two groups on all criteria.
Kjaersgaard-Andersen 1990 **Denmark** **Parallel** Quality:3	Osteoarthritis hip 161 (64)	Codeine 180 mg/d + acetaminophen 3 g/day for 4 wk Control: Acetaminophen 3 g/day. Rescue Medication: Ibuprofen tablets 400 mg	**Primary:** Daily intake of rescue medication. **Secondary:** Daily and weekly hip pain.	At 7 days, the addition of codeine was better than acetaminophen alone. After this, there was no difference.
Jamison 1998 **USA** **Parallel** Quality:2	Back pain 36 (3)	A) Oxycodone + SR Morphine 90 mg/d for 16 wk(*) B) SR Oxycodone 40 mg/d for 16 wk Control: Naproxen 1000 mg/d.	**Primary:** Pain intensity* (0-100 scale). **Secondary:** Mood. Level of activity, Number of hours and amount of study medication.	Both opioid groups had significantly less pain and emotional distress than the naproxen-only group. No differences in activity level or hours of sleep were found.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Vlok 1987 South Africa Crossover Quality:4	Osteoarthritis 31 (3)	Codeine 20 mg/d + Ibuprofen 400 mg/d + acetaminophen 500 mg/d for 4 wk Control: Ibuprofen 1200 mg/d	**Primary:** Pain intensity (VAS) **Secondary:** PAD, drug choice.	Combination of codeine with ibuprofen with acetaminophen was better than ibuprofen alone.
Raja 2002(b) USA Crossover Quality:4	Postherpetic neuralgia 76 (32)	CR morphine up to 240 mg/d for 6 wk. Methadone was an alternative opioid. Control: Nortriptyline up to 160 mg/d. Desipramine was an alternative antidepressant	**Primary:** Pain intensity* (0-10 NRS). **Secondary:** Pain relief, cognitive function, MPI* (physical functioning subscale), sleep, mood, global preference.	The trend favouring opioids over tricyclic antidepressants fell short of significance and reduction in pain with opioids did not correlate with that following tricyclics.
Gilron 2005 Canada Crossover Quality:4	35 diabetic neuropathy and 22 postherpetic neuralgia. 57 (16)	A) SR morphine maximum tolerated for 5 wk. B) SR morphine maximum tolerated combined with gabapentin for 5 wk C) Gabapentin maximum tolerated for 5 wk	**Primary:** Pain intensity (0-10 NRS). **Secondary:** SF-MPQ, Maximal tolerated doses, Mood (BDI), SF-36, Mental Status (Mini-Mental), and global pain relief.	Mean pain intensity at the maximal tolerated dose was 4.49 with placebo, 4.15 with gabapentin, 3.7 with morphine and 3.06 with gabapentin-morphine combination. Total scores in SF-36 were lower with gabapentin-morphine combination than placebo or each drug alone.
Wu 2008 USA Crossover Quality:4	Postamputation pain 60 (25)	A) SR Morphine 15 - 180 mg day for 6 wk B) Mexiletine: 75 – 1200 mg day for 6 wk	**Primary:** Average change in overall pain intensity from the baseline to the last week of maintenance therapy using 0-10. **Secondary:** Pain relief (0-100%) and the interference and general activity subscales from the MPI.	Morphine treatment provided lower pain scores compared with placebo and mexiletine. The mean percent pain relief during treatment with mexiletine, and morphine was 30 and 53%, respectively.

Study Country Design Quality	Population Number randomized (drop-outs)	Interventions and comparison groups	Outcomes: Primary and Secondary	Results (as reported in the studies)
Khoromi 2007 **USA** **Crossover** Quality:1	Chronic lumbar radiculopathy (sciatica) 55 (27)	A) SR morphine 15-90 mg/d B) Nortriptyline 25-100 mg/d C) Combination Duration: 9 wk	**Primary:** Average leg pain during the two weeks. **Secondary:** Global pain relief, ODI, BDI and SF-36.	In the 28 out of 61 patients who completed the study, none of the treatments produced significant reductions in average leg pain or other leg or back pain scores. Within the limitations of the modest sample size and high dropout rate, these results suggest that nortriptyline, morphine and their combination may have limited effectiveness in the treatment of chronic sciatica.
Frank 2008 **UK** **Crossover** Quality:3	Neuropathic pain 96 (32)	A) Dihydrocodeine maximum 240 mg/d for 14 wk B) Nabilone maximum 2 mg/d for 14 wk	**Primary:** difference in pain (VAS) computed over the last 2 weeks of each treatment period. **Secondary:** change in mood, quality of life, sleep and psychometric function.	The mean score was 6.0 mm longer for nabilone than for dihydrocodeine in the available case analysis and 5.6 mm in the per protocol analysis. Dihydrocodeine provided better pain relief than the synthetic cannabinoid nabilone. Nabilone was significantly superior to dihydrocodeine on the SF-36 (role-physical).
6. N of 1 randomized trial				
Sheather-Reid 1998 **Australia** Quality:3	Regional cervicobrachial pain 8 (3)	A) Codeine 120 mg/d for 4 wk B) Ibuprofen 800 mg/d for 4 wk C) Placebo for 4 wk	**Primary:** Pain intensity (VAS). **Secondary:** Change in pain, uptime, and hours of sleep.	In none of the 5 subjects who completed the 12-week trial was analgesic efficacy of either drug shown.

* Data used for meta-analysis; ADL: Activity of Daily Living, BDI = Beck Depression Inventory, BPI = Brief Pain Inventory©, BSS = Brief Stress Scale, CR = controlled-release, DMARD= Disease-Modifying Anti Rheumatic Drug, MPI = Multidimensional Pain Inventory, NNT: number needed to treat, NRS = numeric rating scale, ODI = Oswestry Disability Index, PES = Pain Experience Scale, POMS = Profile of Mood State, PDI = Pain Disability Index, PRSS = Pain-Related Self statement Scale, SDS = Self-Rating Depression Scale, SF-36 = Short Form 36 Health Survey, SR = sustained release, VAS = visual analog scale, WHYMPI = West Haven–Yale Multidimensional Pain Inventory,

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GLOSSARY

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Terms

Aberrant drug-related behaviours	Behaviours that may cause suspicion about addiction in opioid-treated pain patients. (Passik 2006b)
Abuse, drug	Any use of an illegal drug, or the intentional self-administration of a medication for a non-medical purpose such as altering one's state of consciousness, e.g., "getting high." (APS/ACPM 2009)
Addiction	A primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. (Utah Department of Health 2009)
Dependence, Physical	A state of adaptation manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. (APS/ACPM 2009) (Utah Department of Health 2009)
Diversion	The intentional transfer of a controlled substance from legitimate distribution and dispensing channels. (APS/ACPM 2009)
Dose, optimal	The optimal dose is reached with a BALANCE of three factors: 1) **effectiveness**: improved function or at least 30% reduction in pain intensity 2) **plateauing**: effectiveness plateaus—increasing the dose yields negligible benefit, and 3) **adverse effects/complications**: adverse effects or complications are manageable.
Dose, stable	A "pharmacologically stable dose" is one that produces a fairly steady plasma level; it is established when the *total daily dose* is fixed for at least two weeks *and*: 1) frequency is scheduled and spread throughout the day AND/OR 2) at least 70% of the prescribed opioid is controlled release.
Dose, watchful	Watchful dose = morphine or equivalent dose exceeding 200 mg/day.
Double-doctoring	… receiving a prescription for a narcotic, and then seeking and receiving another prescription or narcotic from a different practitioner without disclosing to that practitioner particulars of every prescription or narcotic obtained within the previous 30 days. (Minister of Justice)

Glossary, continued…

Hyperalgesia	An increased response to a stimulus which is normally painful. (APS/ACPM 2009)
Misuse, opioid	Use of an opioid in ways other than those intended by the prescribing physician (sometimes also called problematic opioid use). (Ballantyne 2007).
Narcotic	Narcotic: any drug included in the "Schedule" under the *Controlled Drugs and Substances Act: Narcotic Control Regulations.* (Minister of Justice)
Opioid, controlled release (CR)	CR (Sustained Release) preparations consist of an opioid embedded in a wax matrix, micro-granules or other milieu that slowly releases the opioid into the GI tract or subcutaneous tissues. CR preparations of morphine, codeine, oxycodone and hydromorphone induce analagesia for up to 12 hours (e.g., MS-Contin®, Codeine-Contin®, OxyContin®, Hydromorph-Contin®). These CR preparations can be easily converted to immediate-release by biting or crushing the tablet. The duration of action of Kadian® (*slow-release morphine*) is 24 hours and for the *transdermal fentanyl patch* (e.g., Duragesic®), 72 hours. Tramadol is also available in a CR preparation (e.g., Zytram®, Tridural™, and Ralivia™).
Opioid, immediate release (IR)	IR formulations release the full dose of the opioid into the GI tract as the tablet dissolves. IR tablets generally contain a much smaller opioid dose than CR preparations. Some of the IR formulations also contain acetaminophen and caffeine. Examples of IR formulations include Tylenol® No. 1, 2, 3 and 4 (acetaminophen plus codeine), Percocet® and Oxycocet® (acetaminophen and oxycodone), Dilaudid® (hydromorphone), Statex® (morphine), Supeudol® (oxycodone), Codeine (codeine), and Tramacet® (tramadol 37.5 mg and acetaminophen 325 mg).
Opioids	A family of drugs that act by attaching to endogenous mu, kappa and delta receptors in the brain and share a common set of clinical effects, including analgesia, sedation, constipation, and respiratory depression. **Note**: Reference throughout this document to specific pharmaceutical products as examples does not imply endorsement of any of these products.
Pain, breakthrough	Transient or episodic exacerbation of pain that occurs in patients with pain that is otherwise considered stable but persistent. (APS/ACPM 2009)
Pain, chronic	Pain that persists for more than six months. (College of Physicians and Surgeons of Ontario 2000)
Pain, chronic non-cancer	(CNCP) Chronic pain that is not associated with cancer.
Pain, chronic non-malignant	Not used in this document; see chronic non-cancer pain.
Pain, neuropathic	Pain initiated or caused by a primary lesion or dysfunction in the nervous system. Peripheral neuropathic pain occurs when the lesion or dysfunction affects the peripheral nervous system. Central pain may be retained as the term when the lesion or dysfunction affects the central nervous system. (IASP)
Substance	Any drug with pleasant psychoactive effects and addiction potential, including alcohol, illegal drugs, and prescription drugs.
Substance dependence	See addiction.

Glossary, continued…

Tapering	A gradual decrease in a dose of a drug; could result in a lower daily dose or cessation of the drug.
Therapy, structured opioid	Use of opioids to treat CNCP with specific controls in place, including: patient education, written treatment agreement, agreed-on dispensing intervals, and frequent monitoring**.**
Therapy, chronic opioid	Not used in this document; see therapy, long-term opioid.
Therapy, long-term opioid	(LTOT). Use of opioids to treat chronic non-cancer pain for prolonged duration.
Titration	A technique of adjusting a dose until a stable/optimal dose is reached; usually means gradually increasing the dose to allow the body to develop tolerance and minimize adverse effects.
Tolerance	A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more opioid effects over time. (APS/ACPM) (Utah Department of Health)
Withdrawal	Characteristic syndrome produced by abrupt cessation of a drug.