Opioids in Chronic Non-Malignant Pain
Troubleshooting Drug Therapy Issues

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Objective Comparisons for Optimal Drug Therapy

The RxFiles Academic Detailing Program
Saskatoon City Hospital
701 Queen Street, Saskatoon, SK S7K 0M7
www.RxFiles.ca

Key Highlights
- Pain, the 5th vital sign [APS], is often under-treated.
- Optimize use of both drug and non-drug interventions.
- Pain reduction and **improved function**, and **not pain elimination** are the goals of drug therapy. Those with CNMP must be helped to refocus on positive, incremental gains. Multiple visits are often required.
- Opioids have a role in select patients; carefully assess and use a **treatment agreement** to guard against abuse.
- Initiation of opioids doesn't always mean a lifelong Rx.
- Consider long-acting formulations at regular intervals.
- Avoid meperidine (Demerol) use in general!
- Combination opioid/non-opioid drugs such as Tylenol #1 & Tylenol #3 are easily overused in chronic pain.

Introduction
Chronic non-malignant pain (**CNMP)** is complex involving physical, psychological, emotional, social, financial and spiritual factors. Non-drug modalities are critical in long-term optimal management. Non-pharmacological approaches include interdisciplinary programs, physiotherapy, cognitive / behavioral strategies, nutritional / exercise programs, etc. Regulations regarding the prescription of opioids attempt to encourage optimal opioid use when indicated while minimizing potential for misuse, abuse and diversion.
{Chronic: ≥6months. Pain: includes nociceptive &/or neuropathic; idiopathic.}

Recommended Reviews and Guidelines:
- Use of Opioid…Noncancer Pain…Canadian Pain Society, 2002 [1]
- Evidence-Based Recommendations…CNMP-Ontario, 2000 [2]
- General Principles…Pain Management with Opioids, SK [3]
- Opioid Therapy for Chronic Pain, NEJM 2003 [4]
- Drug Class Review–Long-Acting Opioid(s)… Oregon. Apr 2005 [5]
- Issues in Opioid Management…Chronic Pain, Mar 2005 [6]
- Opioids …Chronic Pain. CSAM, Oct 2000 [7]
- Position Statement Opioid…Chronic Pain. APS, AAPM 1996 [8]
- Universal Precautions in Pain Medicine, Pain Medicine 2005 [9]
- Principles of Opioid Use in Chronic Noncancer Pain, CMAJ 2005 [10]

How strong is the evidence for opioids in CNMP?
- There is limited evidence supporting a role for opioids in CNMP. Most randomized control trials (RCT) have involved small numbers and short durations (<32 wks). Much of the literature consists of surveys, uncontrolled case series and open label follow up to RCTs.
- Systematic reviews suggest that opioids provide a short-term benefit with low risk of addiction and tolerable side effects when used appropriately in select patients.[2,4,6,11] Whether opioids are beneficial in the long-term remains to be assessed. Trials exclude persons with history of past or current substance abuse. **The NNT estimate is 3**.[1] In other words, for every 3 CNMP patients treated with an opioid, 1 will have **at least a 50% reduction in pain**.
- Drop out rates were around 30% in one analysis.[6] Minor adverse events were common (63%); serious adverse events were rare. Long-term data is not available.
- Although there is no ceiling dose for strong opioids, lack of progressive pain relief with escalating doses in a opioid naïve patient may signal pain that is non-responsive to opioids. Most CNMP studies have used doses of morphine ≤ 200mg/day.

When should opioids be considered in CNMP?
- "In the absence of good evidence for a specific curative treatment for a given pain problem, a trial of long-term opioid therapy is a legitimate medical practice when a reasonable trial of other treatment modalities fails to improve comfort or function of the patient. There are very few types of pain that would absolutely preclude a trial of opioid therapy."[1 CPS- 2002]

Table 1: Definitions
Addiction: LOSS of control over substance use WITH compulsive continued use despite harm.
Pseudoaddiction: drug seeking behavior mimicking addiction resulting from under-treatment of pain.
Dependence, physical: a state of adaptation resulting in drug class-specific withdrawal symptoms upon abrupt dose reduction, decreasing drug levels or antagonist administration. (not to be confused with addiction).
Tolerance: decreasing effect of a drug over time.

Tolerance, Dependence and Addiction
- **Tolerance and physical dependence should not be confused with addiction.** Addiction is characterized by compulsive use of a substance or preoccupation with obtaining it despite evidence that continued use causes harm (physical, emotional, social or economic).[1] See Table 1.

Table 2: CAGE Questionnaire – Addiction Screening
C – have you ever felt the need to **C**ut down or **C**hange your drinking/drug use?
A – do you get **A**nnoyed when others criticize your drinking/drug use?
G – have you ever felt **G**uilty about your drinking/drug use for any reason?
E – **E**ye-opener: Have you ever felt the need for a drink early in the morning to decrease hangover or withdrawal?

One positive suggests caution; 2 or more suggests strong caution/need for vigilance.

- **Assessment for risk of addiction is important.** ASK: "Have you or anyone in your family had problems with either alcohol or drugs?" Inquire into the quantity and frequency of alcohol or drug use to ensure it is within low risk parameters for the former, and as prescribed for the latter. The **CAGE Questionnaire** (see Table 2) is also useful. *History of* or *risk factors for* addiction is a complicating factor in pain management warranting co-management with an addiction medicine specialist.

Table 3: Universal Precautions in Pain Medicine [8]

1. Make a Diagnosis with Appropriate Differential
2. Psychological Assessment Including Risk of Addictive Disorders (include discussion of urine drug testing)
3. Informed Consent
4. Treatment Agreement
5. Pre/Post-Intervention Assessment of Pain & Function
6. Appropriate Trial of Opioid Therapy +/- Adjunct Agents
7. Reassessment of Pain Score and Level of Function
8. Regularly Assess the "six A's" of Pain Medicine: Analgesia, Activity, Adverse effects, Affect, Aberrant behavior & Accurate medical records.
9. Periodically Review Pain Diagnosis and Comorbid Conditions, Including Addictive Disorders
10. Document Assessment, Discussions and Progress

- "**Universal Precautions in Pain Medicine**" is an approach to the assessment and management of chronic pain patients based on the assumption that one can not always determine who will become a problem user. Thus, it suggests a minimum level of care in assessing and managing risk. (See Table 3)

Preventing Abuse, Misuse and Diversion

- **In pain patients without a history of substance abuse, prevalence of opioid addiction is thought to be low.** This issue is not well studied in CNMP. {Reported opioid addiction rates in CNMP range from 3-19%[12]}
- **History of substance abuse** complicates but does not contradict use of opioids in CNMP; however consultation with a specialist in pain & addiction is recommended.
- In Saskatchewan, the Triplicate and/or the new **PIP** Rx programs are useful in identifying previous opioid usage.
- **Consider faxing prescriptions**; avoids alteration.
- **Dated Prescriptions**; notes expected duration of supply.
- ***Treatment Agreements*** provide a framework for abuse, misuse, diversion and addiction concerns by providing patient education, conveying treatment goals, encouraging patient adherence and proactively outlining how non-adherence will be handled. Patients at greater abuse risk, or with significant psychological component will require more structure / stricter boundaries in the agreement. See Appendix A or www.RxFiles.ca for sample / customizable form.

How can one handle a CNMP patient who tests the boundaries of a treatment agreement?

This issue will inevitably arise when prescribing opioids in CNMP. For example, a patient may request just a few extra tablets, run out of drug early, or lose a prescription. If an agreement has previously been outlined and discussed, then the prescriber can note the issue, and respond accordingly. Options may include:

- make an exception but consider tightening boundaries
- document and warn the patient that a 2nd break in the agreement will result in:
  - urine drug testing
  - referral to addiction medicine
  - discontinuation of opioid therapy
- discontinue opioid

Table 4: Red Flags – Aberrant Opioid Use [4,13]

Consider Discontinuation of Opioids / Specialist Referral

1. Prescriptions from multiple physicians
2. Frequent visits to emergency room requesting opioids
3. Requests from patients from outside of local area
4. Stolen or modification of prescriptions
5. Extensive polypharmacy with CNS depressants and/or non-prescribed habituating substances
6. Forgery, selling, stealing, or using other persons medications; tampering with prescriptions.
7. Injecting oral or chewing LA formulations

Reassess Regimen and/or Treatment Agreement

1. Rapid escalation of dose in CNMP
2. Frequent excuses for running out of medication
3. Frequent loss of prescriptions and/or medications
4. Frequent changes of the opioid prescribed
5. Aversion to concurrent recommended treatments
6. Request for Brand-name versus generic product
7. Lack of request for adjunct analgesic refills
8. Unsanctioned noncompliance with the regimen
9. Missed follow-up visits

Prescribing Considerations for Opioids in CNMP

- Pain reduction, **improved function**, & **not pain elimination** are the goals of drug therapy. {A pain score ≤ 4/10 may = success}
- Thorough, ongoing assessments & pain scoring are useful!
- Start at low-dose and titrate up gradually; "dose to effect"
- Be cautious in the elderly; *start low, go slow, but go*
- Remember neuropathic pain often requires higher doses
- Use the oral route when available
- *Round-the-clock dosing for round-the-clock pain.* Generally use long-acting and minimize use of short-acting opioids
  "PRN dosing may not be appropriate for every patient. In some cases it promotes patient autonomy while allowing the lowest dose of opioids. In others, such as patients with poor impulse control or "at risk" substance abuse patients, it may lead to inappropriate dose escalation and undermine attempts to stabilize the medication regimen"[14]
- Be aware of and prevent constipation (Table 6)
- Assess risk for nausea; provide antinauseant as needed
- Consider using a treatment agreement (patient contract)
- Document (assessment, drug trials, discussions, treatment plan, informed consent and/or treatment agreement)
- Ensure non-opioid therapies used when indicated for specific types of pain (see RxFiles Q&A Supplement: Pain – CNMP – Pharmacological Considerations – Table 1)
- Ensure psychosocial, behavioral and physical exercise aspects of pain are dealt with concomitantly as opioid therapy alone may reinforce abnormal pain behavior
- Adjust drug regimens to find the optimal balance between pain relief, function and side effects. {↓ sedative/alcohol use}
- Be aware that CNMP patients require higher doses of post-operative opioids, and experience fewer adverse effects [15]
- Some patients will improve when taken off opioids

Long-acting opioids vs Short-acting opioids

- Long-acting regular opioids offer several advantages:
  - encourages patient compliance
  - allows tolerance to side effects (e.g. cognitive)
  - discourages the psychological dependence on opioids, often seen with short-acting PRN based regimens
- Short-acting opioids are useful for initial dose titration and in select patients prior to activities likely to worsen pain. Breakthrough "PRN" opioids may be suitable during the titration phase and in patients with flare-ups; however since some patients never obtain total relief, over-reliance on short-acting PRN opioids is common; minimize use. {Chronic use of short-acting agents ≥2x/day, convert to long-acting.}
- Be aware of the injection drug users' preferences in your community and avoid those frequently diverted to the street (e.g. MS Contin, Dilaudid, OxyContin) in those at high risk or whose safety and security is in question. {Kadian may be more difficult to abuse; generic hydromorphone often has a lower street value}

Options for Apparent Tolerance to an Opioid

- If opioid is otherwise well tolerated, one may increase the dosage and monitor for increased effect
- If side effects develop, **opioid rotation strategies** may be effective although evidence is lacking.[16] Switching to ½ - ¾ of the usual equivalent dose of another opioid is recommended to allow for incomplete cross-tolerance.
- Adding or modifying adjunct agents may also be effective, depending on the pain condition treated.

What Role does Methadone have in CNMP?

- Methadone may be useful in opioid rotation strategies.[17] Its potential but unproven NMDA antagonist effect may have benefits in neuropathic pain.[18] It may be particularly useful in patients who have concomitant pain and addiction conditions.[19,20] Due to **risks** associated with its **long half-life** a special authorization to prescribe is required in SK (List available from the College of Physicians and Surgeons of SK; SK drug plan covers for palliative pain use only.)

Why Avoid Meperidine (DEMEROL) in CNMP? ISMP [21]

- Its very short duration results in early recurrence of pain, need for frequent dosing, and increased abuse potential
- Normeperidine, a toxic metabolite may accumulate with chronic use causing delirium, seizures and myoclonic jerks.
- The oral formulation has very poor absorption.
- Evidence does not support any advantage in pancreatitis [22]
- RQHR Regina recently removed oral form from formulary
- {Anileridine (LERITINE) has similar disadvantages}

Problems with Combination Drugs (e.g. Tylenol #3)

Due to the nature of chronic pain, it is not uncommon to see overuse of combination products. Their short duration of action and low potency makes them poor long-term choices. Risk of acetaminophen toxicity increases with excessive single doses or chronic use of usual high doses. In addition, psychological dependence is reinforced by the frequent use.

- Minimize reliance on opioid/acetaminophen (e.g. Tylenol #3, Tramacet) combination products in the long-term treatment plan.
- Ensure daily dose of acetaminophen does not exceed 4g (some literature suggests limiting chronic use to 2.4-3.2g/d)
- Assess for overuse of OTC combinations (e.g. Tylenol #1)

Dose Dumping - Long-acting Formulations & Alcohol

- The potential for "dose dumping" with long-acting opioids, especially once-daily formulations, should be considered and patients cautioned to take only with water.
  {PALLADONE, a once-daily long acting formulation of hydromorphone, was recently removed from the US market because it was found to have peak concentrations up to 6X greater when given with alcohol compared to water.[23]}

Transdermal Fentanyl (DURAGESIC) – Cautions

- Although potency can vary widely, 25mcg/hr fentanyl patch is roughly equivalent to 90mg/day oral morphine. This high potency has caused serious life-threatening toxicity, especially in opioid naïve patients, and kids <18yrs.[24,25] {Patients with poor response to codeine e.g. Tylenol #3 or tramadol may be non-metabolizers and considered opioid naïve.}
- Any adverse events or overdose effect is prolonged due to the long-acting reservoir of drug in the skin. Corticosteroid sprays, may be useful to reduce skin irritation. e.g. Flovent topically
- Rate of absorption is much more rapid with heat (e.g. hot tubs, heat blankets, exercise, fever). This can increase risk of toxicity and/or shorten duration of patch effectiveness.
- Delayed effect of any dosage changes limit the usefulness of this agent in individuals with frequent variations in their pain intensity. Due to the time required for plasma concentrations to stabilize, dosage adjustments should not be made any more frequently than q3-6days.
- Patients who abuse DURAGESIC may do so by leaving on extra patches, chewing them or making teas. This can be "contained" by having the patient exchange patches at the pharmacy every 3 days.

Opioid Withdrawal [6]

- Gradual withdrawal of opioids will minimize the sympathetic rebound that otherwise occurs (see Table 5); wean the daily dose by up to 10-20% per day or taper opioids over several weeks to minimize withdrawal.
- Clonidine may be used in abrupt discontinuation:
  - 5-15mcg/kg/day in divided doses **x 7-14** days, then taper {e.g. 0.1mg TID & 0.2mg HS x2wks, then taper over 2wks}
  - monitor for withdrawal and orthostatic hypotension
  - taper clonidine to avoid rebound hypertension
- Patients with strong addiction history or risk require special consideration and management by a specialist.

Table 5: Opioid Toxicity vs Withdrawal

Opioid Toxicity	Opioid Withdrawal {flu-like}
◆Confusion, agitation, visual defects, vivid dreams or nightmares, hallucinations, myclonic jerk ◆Severe, acute: respiratory depression; sudden severe sedation (reversed by naloxone)	◆opioid craving, anxiety, restlessness, yawning, perspiration, lacrimation, rhinorrhea, insomnia, mydriasis, piloerection, tremors, hot / cold flashes, hypertension, tachycadia, fever, tachypnea, vomiting, diarrhea, muscle aches ◆unpleasant but not life-threatening

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L. Regier BSP, BA, *B. Jensen* BSP

A Few Thoughts on Adjunct Agents

- A variety of adjunct agents should be considered in specific pain conditions. See RxFiles Supplement Chart - *Pain Conditions – Specific Drug Therapy Options* –Table 1. For neuropathic pain, TCAs have been the most effective agents [NNT=2-3], followed by anticonvulsants [NNT=3-5] or venlafaxine. SSRIs have sometimes been effective [NNT=7]. [26]
- **TCAs: Nortriptyline** is often preferred or a good alternative when amitriptyline is not tolerated. Encourage patients to be patient and allow for an adequate trial. Dose may be titrated up to effective dose gradually to reduce side effects.
- **Gabapentin** has good evidence for diabetic neuropathy, and post-herpetic neuralgia but remember that the dose required is usually in the 900-1800mg/day range. Adding to morphine produced a small benefit of questionable clinical significance in neuropathic pain patients.[27] One may consider weighting the dose towards nighttime (e.g. 300mg BID & 600mg HS).

Table 6: Opioid Adverse Effects

- nausea vomiting
- constipation
- dizziness/somnolence/confusion
- opioid induced neurotoxicity syndrome: CNS excitation (myoclonus, agitation, delirium); treatment may include rehydration, checking renal fx, taper/switch opioid; benzodiazepines
- Other long-term opioids concerns: development of tolerance/ hyperalgesia; hormonal changes: ↓plasma cortisol levels, ↑prolactin, ↓LH, FSH & testosterone [4]; suppression of immune fx (animal studies) [4]

Managing Opioid Side Effects

Nausea & Vomiting (N&V)	◆Reassure that tolerance usually develops in <1-2 wks ◆Titrate opioid dose slowly & consider short-term prochlorperazine 5-10mg q6h PRN, haloperidol 0.5-1mg BID PRN, metoclopramide 5-10mg q6h PRN, domperidone 5-10mg TID AC (transdermal scopolomine for dizziness & secretions) ◆prophylactic use if patient gives history of N&V ◆May consider other routes of administration (e.g. patch)
Histamine - urticaria, pruritis	◆Reassure that tolerance usually develops (true allergy rare) ◆Utilize adjuvant therapy that may allow ↓ dose ◆Premedicate with antihistamine e.g. diphenhydramine 25-50mg (ranitidine 150mg HS or q12h may also be useful adjunct) ◆Switch opioids; {if class effect, naltrexone solution has been used}
Sweating	◆↓ sweating: glycopyrrolate, scopolamine or clonidine
Drowsy, Mental confusion	◆Reassure that tolerance usually develops in a few days ◆↓ dose/use of any non-essential CNS depressants ◆↓ opioid dose; hold opioid for 1-2 doses as necessary ◆Consider giving lower dose more frequently; or switch to alternate opioid (at ~25% lower dose-equivalent)
Dry Mouth	◆Regular sips of water, sugarless gum etc. ◆Consider saliva substitute (e.g. ORAL BALANCE GEL)

Options for Opioid Induced Constipation ✞

Diet	◆encourage fibre (bran 1 cup All Bran®), flax 1 tablespoon seeds, prunes/prune juice 1 cup, water 4-6 cups, & a balanced diet
Exercise	◆regular activity as tolerated
Step 1 Oral Laxatives	◆Senna 1-2tablets at HS⇨2 BID (max ~8 tabs/day) or Bisacodyl 1-2tablets at HS (max ~8 tabs/day) {Docusate 1 BID -stool softener only; minimal effect!} ◆MOM 30-60ml OD (CI if renal failure); Sorbitol 70% 30ml OD-QID; Lactulose 15ml BID, max 30ml TID
Step 2 Laxatives	◆May combine step 1 agents; if no bowel movement: Mg Citrate, Fleet enema, PegLyte or GoLytely 250ml OD-BID PRN
Step 3	Consult physician if several days (96+hrs), pain, severe bloating. {temporarily ↓ opioids}

✞Fentanyl may cause less constipation / histamine release (poor quality evidence)[5] CI=contraindication

A Pain & Medication Diary is useful to track patterns of pain occurrence and the time, dosages, and side effects of analgesics used, assisting in therapy adjustments.

Opioid Prescribing / CNMP Tools

1) Treatment Agreement:
http://www.paincare.ca/Documents/En/Patient_Treatment_Agreement.pdf
2) Mental Status Assessment (Folstein Mini Mental):
http://www.paincare.ca/Documents/En/Mental_Status_Examination.pdf
3) Letter to Pharmacist:
http://www.paincare.ca/Documents/En/Pharmacist_Letter.pdf
4) Patient Resources: a) http://www.chronicpaincanada.org ; b) http://familydoctor.org/x5412.xml ;c) http://www.theacpa.org
5) Pain Assessment Tools:
http://www.partnersagainstpain.com/index-mp.aspx?sid=3&aid=7824

Long-Acting Opioids – Findings from a Systematic Review [5]

- Fentanyl vs morphine LA [4wks; n=256; heterogenous CNMP]: equivocal results:
  - ◆fentanyl good pain control (40% vs 19%) & marginally better physical functioning score (28.6 vs 27.4, p=0.004) & mental health score (44.4 vs 43.1, p=0.03)
  - ◆morphine – lower withdrawal rate (9% vs 16%)
  - ◆post-hoc analysis -benefit in fentanyl group in subset who had "bad" or "very bad" score when on previous morphine; no difference in score for those who were opioid naïve
- Morphine - OD_{am} vs OD_{pm} vs BID vs placebo [4wks; n=295; OA]
  - ◆no difference between morphine regimens
  - ◆morphine greater efficacy than placebo
- LA opioids vs placebo [18 trials; n=1181; heterogenousCNMP; ≤ 16wks]
  - ◆superior efficacy for LA opioids over placebo; no difference between opioids.
  - ◆data regarding whether LA preparations have fewer adverse events was equivocal
- No data to support that any LA opioid is superior to any other in any CNMP subpopulation (efficacy or adverse effects)

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