Opioids in Chronic Non-cancer Pain (CNCP)

New Guidelines, Tools & Evidence Review

March, 2011

Weighing the Trend Towards Increasing Opioid Use For Better Pain Control with Concerns of Increased Harm, Misuse and Diversion

Two noble purposes exist side by side:

- the better treatment of pain
- the reduction of individual and societal harms associated with opioids (e.g. misuse & diversion)

Increasing opioid use in treating CNCP

- Over the past 15-20 years, there has been an emphasis on encouraging physicians to treat pain more effectively. Prior to this time, prescribed opioids were predominantly used in treating acute and cancer pain. There was a wide reluctance to use opioids for non-acute & non-cancer pain due to concerns that: a) the opioid might eventually lose its effectiveness and b) addiction and diversion issues would increase.
- The issue of opioid misuse, while not disregarded completely, was minimized in the effort to take advantage of the pain relief benefit that opioids offered. The benefit of opioids in CNCP has very limited evidence, but their role has grown in acceptance by clinicians. The emergence of new opioids and opioid long-acting formulations has brought new therapeutic options and marketing associated with the new drugs has resulted in a dramatic increase in prescribing.

The increase in prescription opioid use has brought along it's own array of related harms and concerns.[1] Opioid related deaths have risen and availability of diverted prescription opioids has also increased.[2,3,4,5]

{In Ontario, opioid-related mortality doubled, from 13.7 per million in 1991 to 27.2 per million in 2004; a 41% increase was seen from 1999-2004.[2]}

Rising to the challenge of optimal treatment of CNCP while addressing opioid concerns

- The Canadian Pain Society notes "opioids can be a very safe and effective treatment for pain when used for the right reason by the right person".[6]
- The desire to encourage the appropriate use of opioids when suitable for CNCP while minimizing opioid related harm, misuse and diversion is at the heart of the recent Canadian Opioid Guidelines.
- While patient scenarios often present difficult and complex challenges, a number of tools and recommendations have been developed to assist physicians in better navigating this area. A few of these will be highlighted in our academic detailing sessions (see Table 1). The reader is also encouraged to check out the Opioid Guideline - Part B [7,8] and it's related tools and resources.

See also:

1)	Opioid Evidence Summary	Page 2,3
2)	Opioid Manager Tool [9]	Page 4,5
3)	RxFiles related charts references online	
	a. Chronic Non-cancer Pain pg 66,67	Page 6,7
	b. Opioids pg 70	Page 8
4)	References	Supplement i
5)	Opioids in the Elderly Q&A [10]	Supplement ii
6)	& recent study in OA & RA [11]	Supplement iii
7)	Urine Drug Screening Q&A [12]	Supplement iv
8)	Opioid Treatment Agreements [15]	Supplement vi
9)	Canadian Opioid Guidelines-Part B [8]	
10)	Opioid in CNCP Newsletter 2005 [13]	

Accompanying documents/ links

Table 1: Opioid for CNCP: Select Highlights from the Canadian Guidelines [8]

A) Before Initiating Opioid Therapy	1) Consider the ***evidence*** for opioids in CNCP (effectiveness pain/function vs harms) 2) Decide on both ***pain and functional goals*** with patient and ***document*** *progress* 3) Use a tool such as the ***Opioid Risk Tool*** (ORT) to screen for addiction risk [14] 4) Obtain ***informed consent*** and consider the value of a ***treatment agreement*** [15,16,17]
B) Conducting an Opioid Trial	1) Start low-dose, increase gradually; monitor and document progress 2) **>200mg/day** of morphine equivalent is a ***"watchful dose"*** for CNCP. Carefully reassess before titrating to higher doses. (diagnosis, compliance, etc.) 3) The ***Opioid Manager Tool*** (OMT) [9] may be used for reference & documentation 4) Know and outline your ***exit strategy*** for those who fail an opioid trial
C) Managing Misuse	1) Take advantage of ***prescription monitoring programs*** (e.g. PIP[18] in SK) 2) Consider using ***Urine Drug Screening*** (UDS) for optimal patient care[12] 3) Strategies to reduce prescription ***fraud*** should be part of routine practice (e.g. faxed or electronic Rx, writing of quantities in both numerical & written form, draw line through empty portion of Rx.)[13]

CNCP= chronic non-cancer pain PIP=prescription information program RCT=randomized controlled trial vs= versus

Opioids and Chronic Non-cancer Pain (CNCP)

A) EVIDENCE REVIEW: SUMMARY STATEMENTS

(Adapted from Dalhousie Academic Detailing Service[19])

Question 1: What are the benefits and harms of opioids in treating CNCP?

- Evidence for long-term use of opioids is limited because the longest duration of most comparisons is 13 weeks and most comparisons were against placebo.
  - For pain reduction, opioids
    - Have a **medium** average effect compared to **placebo.**
    - Have **not** been shown to be superior to **other drugs**.
      - However weak evidence suggests that the **strong** opioids morphine and oxycodone may provide a **small** effect compared to other drugs.
  - For improving function, opioids
    - Have a **small** average effect compared to **placebo**.
    - Have **not** been shown to be superior to **other drugs**.
- Many people cannot tolerate opioids and stop taking them with a NNH of approximately 8 over 1 to 13 weeks.
- Weak evidence suggests that patients who are able to continue taking opioids long-term experience clinically significant pain relief.
  - Whether quality of life or functioning improves is inconclusive.
- Addiction is probably rare, but aberrant behaviour occurs in an average of 11.5% of patients and in studies ranged from 0% to 44%. RCTs generally have not been long enough or specifically designed to measure rates of addiction and aberrant behaviour. Also, patients at high risk of addiction or aberrant behaviour are usually excluded from such studies.

Question 2: Are some weak opioids more efficacious or associated with fewer adverse events than others?

- There is **insufficient evidence** to conclude that any one weak opioid is more efficacious or associated with fewer adverse events than other weak opioids.
- There are more RCTs of tramadol vs placebo or other agents than there are of codeine or buprenorphine vs placebo or other agents.
- Tramadol may be sought by abusers even though it is thought to have a lower addiction risk.

{One of the manufacturers of tramadol, in cooperation with the United States Food and Drug Administration has notified healthcare professionals that the drug may be sought by drug abusers and people with addiction disorders. Misuse or abuse poses a significant risk that could result in overdose or death.}

Question 3: Are some strong opioids more efficacious or associated with fewer adverse events than others?

- There is **insufficient evidence** to conclude that any one strong opioid is more efficacious or associated with fewer adverse events than other strong opioids. [RxFiles note: the WHO stepped approach to analgesia lists oxycodone as a step 2 agent along with combination codeine products; however as a potent analgesic it should be considered along with the step 3 potent opioids, morphine and hydromorphone.]

Question 4: Are long-acting opioid preparations more efficacious or associated with fewer adverse events than short-acting preparations?

- There is **insufficient evidence** to conclude that long-acting opioid preparations are more efficacious or associated with fewer adverse events than short-acting preparations. [RxFiles note: it is widely held that although evidence is lacking, long-acting preparations are less problematic in treating CNCP. Specifically, it is felt that less frequent dosing and/or more stable drug levels lessens the potential psychological dependence.]

Weak opioids	**Mixed Agonist/Antagonist**	**Strong opioids**		
Codeine	*Buprenorphine*	*Morphine*	*Oxycodone*	*Methadone*
Tramadol		*Hydromorphone*	*Fentanyl*	

B) Opioids & CNCP: Evidence from Cochrane/Systematic Reviews of RCTs[a]

Condition	Drug(s)	Pain [b]	Function	Harm / Adverse Events (AE)
Osteo-arthritis (OA)	Opioids, non-tramadol vs Pl[20]	◆small to moderate effect SMD 0.36 95% CI: 0.26-0.47 vs Pl ◆10 studies, n=2268, 1-12wks	◆small to moderate effect [c] SMD 0.33 (95% CI: 0.12-0.45) vs Pl ◆7 studies, n=1894, 2-12wks	◆Any AE: opioids vs Pl: 87% vs 54%; NNH=3 95% CI: 2-4 [c] over 4-13 wks (4 studies, n=1080) ◆AE leading to DC: opioid vs Pl: 33% vs 8%; NNH=4 95% CI: 3 to 5 ~ 1-12 wks (10 studies, n=2403)
	Tramadol vs Pl[21]	◆small to moderate effect ◆≥50% ↓ pain: NNT=6 95% CI: 4-9 over ~12wks; 4 studies, n=793	[Pain: 3 other studies n=749 found a ↓ of 8.5 points (12%) on 100 point scale; of questionable clinical significance]	◆AE leading to DC : tramadol vs Pl: 22% vs 8%; NNH=8 95% CI:7-12 over 1-13 wks (7 studies, n=1336)
Neuropathic Pain	Opioids, non-tramadol[22] vs Pl	◆medium effect Furlan Unpublished SMD 0.56 95% CI: 38-0.73 vs Pl [23] ◆13 studies; over 3-8wks	◆small effect (7 trials Furlan) SMD 0.24 95% CI: 0.09-0.39 vs Pl [5] ◆no consistent reduction in disability per Cochrane	◆AE leading to DC: opioid vs Pl: 11% vs 5%; NNH=17 95% CI 9-100 over 3-6wks
	Tramadol vs Pl [24]	◆medium effect ◆≥50% ↓ pain: NNT=4 95% CI :3-6 ◆3 studies, n=302, 4-6wks	Not available	◆AE leading to DC: tramadol vs Pl: 17% vs 4%; NNH=8 95% CI 5-20 over 4-6wks (2 studies, n=195)
Low Back Pain (LBP)	Opioids, non-tramadol vs Nsaid [25]	◆no observed difference but study too small to draw conclusions	◆no observed difference	Not available
	Tramadol vs Pl [25]	◆medium effect ? statistical signif. SMD 0.71 95% CI: 0.39-1.02 vs PL ◆3 studies, n=908, 4-13wks	◆small effect SMD 0.17 95% CI: 0.04-0.3 vs Pl ◆3 studies, n=878, 4-13wks	Not available

AE=adverse events CI=confidence interval DC=discontinuation NNT/NNH=number needed to treat for one extra benefit/harm Pl=placebo SMD=standardized mean difference [b]

[a] Remember that most studies compare to placebo, rather than common alternatives and studies are relatively short term.

[b] Measurement of treatment effect: standardized mean difference (SMD) used to assess continuous outcomes in meta-analysis. {SMDs correlate with effect sizes as follows: <0.5 = *Small*: mean difference <10% of the scale (e.g. <10mm on a 100mm visual analog scale); 0.5 to <0.8 = *Medium*: mean difference 10-20% of the scale; ≥ 0.8 = *Large*: mean difference >20% of the scale} If outcomes are not dichotomous, it is not possible to calculate some statistics such as risk ratios (RR) and NNTs.

[c] Authors concluded that small-moderate benefits are outweighed by substantial risks and should not be routinely used for OA; however AEs generally reversible with discontinuation and need not preclude a trial of opioids since some may benefit.

C) Opioids & CNCP: Evidence from Longer Term Studies

- A 2010 Cochrane review[26] looked at long term (≥6months) studies for opioids in CNCP. Many were unblinded continuation of RCTs. The findings, based on relatively low quality data suggest:
  - Patients discontinue opioids due to adverse effects:
    - Weak opioids: 11% 95% CI: 7-18%
    - Strong opioids: 34% 95% CI: 29-39% (except Transdermal fentanyl was lower at 12%)
  - Patients discontinuing oral opioids due to insufficient pain relief: 10% 95% CI: 8-14%
  - Transdermal fentanyl had a lower discontinuation rate of 6% 95% CI: 4-8%
  - Patients who are able to continue opioids long term for ≥6 months experience clinically significant pain relief. Data on quality of life and function is inconclusive.
  - The most frequent adverse effects were gastrointestinal (constipation, nausea, dyspepsia), headache, fatigue/lethargy/somnolence and urinary (retention, hesitancy).

A note on *Hyperalgesia*

(Adapted from Dalhousie Academic Detailing Service) 19

- Opioid-induced hyperalgesia should be distinguished from opioid tolerance and/or disease progression.
- It is characterized by **increased pain sensitivity** (hyperalgesia and allodynia) that extends beyond the area of initial complaint despite increased doses of opioids.
- A recent systematic review points out that evidence for opioid-induced hyperalgesia is limited and comes mostly from acute infusions of opioids in healthy people.[27] However, some content experts consider this a real entity that may respond to slowly decreasing the dose of opioids.

Weak opioids	Mixed Agonist/Antagonist	Strong opioids		
Codeine	*Buprenorphine*	*Morphine*	*Oxycodone*	*Methadone*
Tramadol		*Hydromorphone*	*Fentanyl*	

Opioids in CNCP - Supplement
⇨ Q&As, Extras & References

www.RxFiles.ca - March 2011

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Costs of Selected Opioids (in oral formulation unless otherwise noted)

Weak Opioid	Brand	Dose *	$/month Approx.
ACC 30	Tylenol #3	2 tabs q6h	40
Tramadol 37.5mg + acetamin. 325mg	Tramacet Generic (Apo)	2 tabs q6h	190 ✗ ⊗ 170 ✗ ⊗
Codeine IR	Generic	2 tabs q4h	40
Codeine ER	Codeine Contin	150mg q12h	70 ☎✆
Tramadol IR	Ultram	50-100mg q6h	96-185 ✗ ⊗
Tramadol CR (once daily)	Tridural Ralivia Zytram XL	300mg daily	$108 ✗ ⊗
Tapentadol	Nucynta CR	200mg q12h	$180 ✗ ⊗
Buprenorphine Patch (Partial agonist)	Butrans Patch	10mcg/hr 20mcg/hr	$105✗ ⊗ $187 ✗ ⊗

ACC=acetaminophen/caffeine/codeine CR=controlled release ER-extended release
*dose represents moderate-high therapeutic dose; lower doses used for initiation of tx
YELLOW color represents possible value choice.

Strong Opioid	Brand	Dose Comparative	$/month Approx.
Morphine IR	Generic	20mg q4h	76
Morphine SR (q12h)	MS Contin Generic MOS-SR M-Eslon	60mg q12h (120mg / day)	131 73 64 71
Morphine SR (q24h)	Kadian	100mg q24h	96
Hydromorphone IR	Dilaudid, Generic	4mg q4h	51
Hydromorphone CR	Hydromorph Contin	12mg q12h	128 ✆
Hydromorphone CR	Jurnista (q24h)	24mg q24h	200✗ ⊗
Oxycodone IR	Generic	10-20mg q6h	61-116
Oxycodone CR	Oxycontin	30-40mg q12h	132-165 ✆
Oxycodone 5mg + Acetaminophen 325mg	Percocet Generic	2 tablets q6h	207 58
Oxycodone/Naloxone	Targin	30-40mg q12h	$215-230✗ ⊗
Fentanyl Patch	Duragesic Patch Generic Patch	25mcg/hr q72h	130 ☎✆ 72 ☎✆

References for RxFiles Opioids in Chronic Non-cancer Pain – Newsletter – March, 2011 [28]

Note: additional references are available online for pages 4-8:

- Opioid Manager: page 4-5: http://nationalpaincentre.mcmaster.ca/opioidmanager/
- RxFiles Charts
  Pain, Chronic Non-Malignant (CNMP or CNCP) page 6-7:
  http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Pain-Chronic-NonCa.pdf
  Opioids pg 8: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Opioid.pdf

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[7] National opioid guideline website hosted at: http://nationalpaincentre.mcmaster.ca/opioid/

[8] Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain — Part B: Recommendations for Practice, Version 5.5 April 30, 2010. [NOUGG] Accessed at: http://nationalpaincentre.mcmaster.ca/documents/opioid_guideline_part_b_v5_6.pdf

[9] Opioid Manager Tool, from Canadian Opioid Guidelines 2011. Accessed at: http://nationalpaincentre.mcmaster.ca/opioidmanager/

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[13] RxFiles Opioids in Chronic Non-malignant Pain: Troubleshooting drug therapy issues. Oct 2005. Accessed online at: http://www.rxfiles.ca/rxfiles/uploads/documents/Pain-Chronic-NonCa-NEWSLETTER-Header.pdf

[14] Opioid Risk Tool. Accessed at: http://nationalpaincentre.mcmaster.ca/opioid/cgop_b_app_b02.html

[15] Treatment Agreements:
Canadian Guideline at http://nationalpaincentre.mcmaster.ca/opioid/cgop_b_app_b05.html
RxFiles 1 page version at http://www.rxfiles.ca/rxfiles/uploads/documents/Pain-CNMP-Opioid-TreatmentAGREEMENT.pdf
RxFiles 2 page version at: ♦customizable MS Word: http://www.rxfiles.ca/rxfiles/uploads/documents/Opiod-Informed-Consent-And-Agreement.docx ♦pdf: http://www.rxfiles.ca/rxfiles/uploads/documents/Opiod-Informed-Consent-And-Agreement.pdf

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[28] Link to RxFiles Newsletter "Opioids in Chronic Non-cancer Pain" March 2011: http://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-2011-Newsletter.pdf

Link: Opioid / Substance Abuse Clinic Policy and Rx Flow Sheet – sample forms:
http://www.rxfiles.ca/rxfiles/uploads/documents/members/Opioid-Controlled-Substance-Rx-Clinic-POLICY.pdf