Pain Management & Opioids

Addressing Important Challenges and Introducing a Chronic Pain & Opioids Mini-Book

FALL 2017

TWO WORTHY GOALS

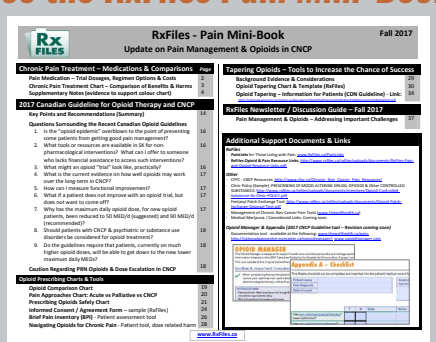
RETHINKING OUR APPROACH...

Opioid Stewardship

Let's ensure opioids, are necessary, safe and effective.

The Risk of Over-Reaction

See the RxFiles Pain Mini-Book


RxFiles - Pain Mini-Book
Update on Pain Management & Opioids in CNCP
Fall 2017

Pain management is often a challenge and even more so in the context of the current concerns around opioids. Two decades ago, the prevailing priority was around pain management. Today, the pendulum for many has swung towards patient safety. Both are worthy goals! Sometimes these goals seem to compete and be at odds. Our goal is to pursue a balanced approach.

Much of the current "opioid crisis" is driven by organized crime and illicit manufacturing. However, it is also important to consider fully the potential safety issues around prescription opioids. There is a lot to be learned from recent evidence and our collective clinical experience. Chronic pain is complex, as is a potential role for opioids. Opioids offer a net benefit for some, but harm for others. Coordinated strategies and prescribing safeguards will hopefully help protect both patient and society.

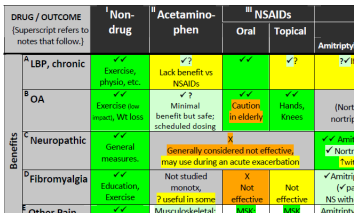
It sometimes seems that for every crisis, we create an equal and opposite crisis to deal with it. In the case of the "opioid crisis" there is the risk that an opioid may not be prescribed adequately when it is indicated, such as during initial management of acute injury. Sometimes this is the result of media and societal pressure. Sometimes it is the result of perceived pressure from policy makers and regulating bodies. Sometimes, it is just the result of frustration with the extra hassle. In addition, if patients on high doses are forced to discontinue or taper too rapidly, they may seek illicit opioids to deal with the withdrawal, putting themselves at even greater risk.

The recent 2017 Opioid Prescribing Guideline for Chronic Non-cancer Pain (CNCP), provides 10 recommendations for opioids in CNCP.[1] There are challenges with any attempt to summarize and seek simplicity. Thus attention to the detail, the strength of the recommendation and the qualifying remarks will be essential in getting the whole picture.

To address some of these challenges, our upcoming academic detailing sessions and supporting materials, such as the RxFiles Pain Mini-Book, will try to explore the evidence, clarify a few misunderstandings and discuss potential "best practice" approaches around opioids and pain.

The illicit manufacturing and distribution of opioids, although a major part of the larger "opioid crisis", is largely beyond the scope of this discussion.

PAIN MANAGEMENT AND OPIOID PRESCRIBING
OVERVIEW OF PRACTICAL TIPS FOR SAFE AND EFFECTIVE PRACTICE



DRUG / OUTCOME (Superscript refers to notes that follow.)	[I] Non-drug	[II] Acetamino-phen	[III] NSAIDs		
			Oral	Topical	Amitripty
Benefits: [A] LBP, chronic	✓✓ Exercise, physio, etc.	✓? Lack benefit vs NSAIDs	✓✓	✓?	✓?
[B] OA	✓✓ Exercise (low impact), Wt loss	✓? Minimal benefit but safe; scheduled dosing	✓✓ Caution in elderly	✓✓ Hands, Knees	(Nort nortri
[C] Neuropathic	✓✓ General measures.	X Generally considered not effective, may use during an acute exacerbation			✓✓ Amit ✓ Nortr Twi
[D] Fibromyalgia	✓✓ Education, Exercise	Not studied monoth, ? useful in some	X Not effective	Not effective	✓Amitrip ✓pa NS with
[E] Other Pain	✓✓	Musculoskeletal:			Amitripty

1) Individualize & optimize non-opioid therapy

➡ See the *RxFiles CNCP Treatment Colour Chart* & supplementary notes. This chart is intended to provide ideas for treatment with considerations of relevant evidence, experience & guidelines.[2]

➡ Non-pharmacological interventions are essential to long-term success in CNCP. Individualization of a plan is important due to availability, motivation and practicality limitations. Financial coverage will be a barrier for some people. We have provided suggestions and links to support tools/services where available (national, provincial & local). See PainLinks document - Pain Mini-Book, Pg 29.

➡ Wherever possible, involve multidisciplinary team-members to assist in dealing with the complexities & multifaceted nature of CNCP.[3]

2) In those unresponsive to non-opioid therapy, one may consider an opioid trial

➡ Opioids have a potential role in patients with inadequate pain relief who have trialed non-drug and drug therapy.[1] Discuss with the patient, the potential for benefit (i.e. pain and function), versus harm (e.g. addiction, overdose, fatal overdose, potential side effects) and other practical issues.
See the *RxFiles CNCP Treatment Colour Chart* & supplementary notes.

➡ Given 1000 patients with chronic pain treated over ≤ 6 months with <u>opioid therapy compared to continuing previous care</u>:[1]

- Pain: 112 more patients would have a pain reduction of 1/10 on a visual analog scale (over 3-6 mos)
- Function: 102 more patients would have a small but important improvement in function (over 1-6 mos)

➡ The 2017 Canadian CNCP Opioid Guidelines recommend against an opioid trial in patients with an active[*strong recommendation] or a history[**weak recommendation] of substance use disorder or an active psychiatric disorder[**weak recommendation].

- These patient populations were excluded from opioid trials showing benefits in CNCP, and observational data suggests a higher risk of harm (e.g. addiction, overdose) compared to those without these disorders.

3) Saying "NO" when your instincts send you in that direction.

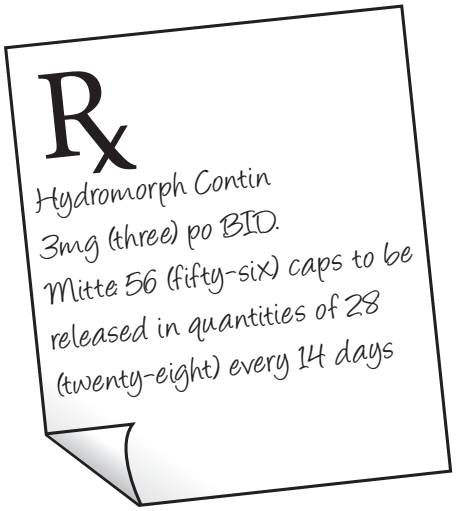
➡ **One physician advisor's perspective:** Sarah Liskowich, MD, CCFP

"Through my experience working with patients with chronic pain, I have learned to stop and listen to my instincts. Although opioid risk tools, guidelines and a plethora of other resources can be useful, they do not replace the expertise gained through your experiences and pattern recognition skills. We regularly use these skills across the domains of medicine to diagnose and treat patients appropriately.
If you feel starting a prescription for an opioid might not be a good idea for your patient at any point in a consultation, you have an opportunity to stop and communicate to the patient your concern and reasons around not initiating opioids. Although it may be uncomfortable at first to say no, in the long run you are doing your patient a great service and practicing compassionate medicine."

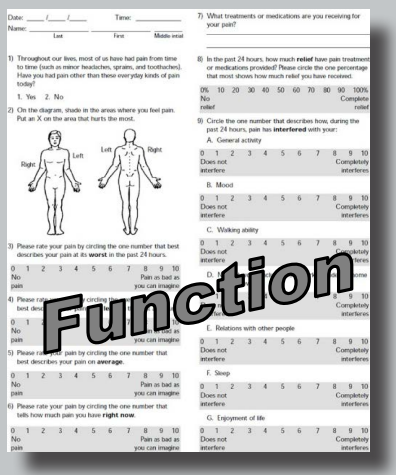
4) When prescribing opioids, include safeguards from the get-go

- ➞ Confirm **patient identity** as necessary (e.g. check driver's license)
- ➞ Check **medication profile** (e.g. PIP Profile in SK)
  - Assess previous use of opioids, benzodiazepines
- ➞ Introduce as an "**opioid trial**" & discuss **exit strategy** up-front
- ➞ Discuss and document **functional goals** (baseline & follow-up)
  - tools such as the *Brief Pain Inventory* (BPI) & the *Opioid Manager* may be useful in assessing & tracking goals
  - small, incremental gains in function are key
  - beware of increasing doses without resulting improvement in function, however small the functional gains may be
- ➞ Obtain **informed consent / agreement**
  - be able to discuss potential benefits and harms of opioid use
  - set boundaries around prescribing in advance
  - deal with unrealistic expectations around opioid benefits.

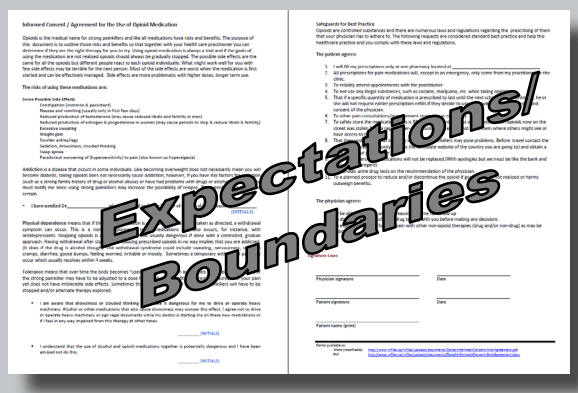
  For some, pain scores may only reduce 1-2 points on a 10 point scale; thus for those with scores of 8-9, achieving <6 may be unrealistic. For others, pain scores may not be reduced at all.
- ➞ Develop a **prescription writing routine** that helps minimize the chance of forgery/diversion
- ➞ Why not include a routine **urinary drug screen** component as part of standard practice?
  - consider baseline and random at least once yearly thereafter



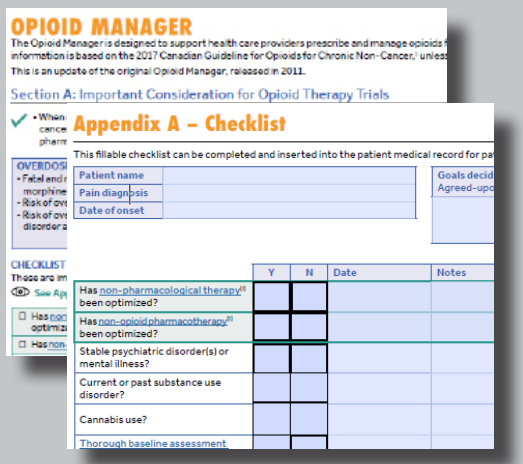
- ➞ Why not avoid **PRNs**? While there will be exceptions to this approach, it is common for CNCP patient to use up all PRNs. For many, structured opioid therapy with minimal or no PRN option lessens the risk of overuse, chemical coping, and dose escalation. See discussion - RxFiles Pain Mini-Book, Pg 18.
- ➞ Take advantage of the various **forms/tools** that are available to provide structure and facilitate process. See the *Prescribing Opioids Safely* chart in the RxFiles Pain Mini-Book, or online http://www.rxfiles.ca/rxfiles/uploads/documents/members/Prescribing%20Opioids%20Safely.pdf



Brief Pain Inventory



Informed Consent / Agreement



Opioid Manager

Documentation is key to successful chronic pain management.

The *Opioid Manager* is one form/tool intended to help facilitate. It is also integrated into some EMRs.

5) Contextualize recommended/suggested maximum opioid dosage recommendations from the 2017 Canadian CNCP Opioid Guidelines.[1] Note: MED = Morphine Equivalent Dose.

➡ The 2017 guideline committee considered available evidence, clinical experience, and patient values and preferences. Dosage thresholds require careful understanding in terms of how they will be useful in guiding any particular patient's therapy.

Let opioid dose guidelines... serve the patient, not the other way around.

1) The dose *restrictions* of **50** MED and **90** MED are for new, NOT existing patients already on higher doses.

Drug	50 MED/day	90 MED/day
Morphine	50 mg/day	90 mg/day
Hydromorphone	10 mg/day	18 mg/day
Oxycodone	33 mg/day	60 mg/day

Note: Transdermal Fentanyl 25mcg/h Patch = ~ 60–134 MED (Uncertain)

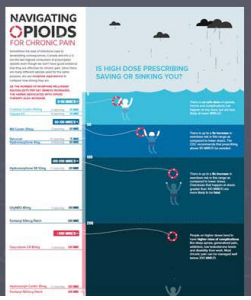
2) The 50 MED/day and 90 MED/day *restrictions* are NOT absolutes.

- STRONG Recommendation*:
  - "...recommend restricting..." to <90 MED/d
- WEAK Recommendation**:
  - "...suggest restricting..." to <50 MED/d

3) Caveat: Some may benefit from higher dose...

- REMARK notes "some patients may gain important benefit..." at a dose > 90 MED/d
  - Referral to a colleague for 2nd opinion...may therefore be warranted in some individuals.

4) Dose *restrictions* related primarily to evidence for harm, not benefit!



	FATAL Overdose Rate	Non-fatal Overdose Rate
<20 MED/d	0.1%	0.2%
20-49 MED/d	0.14%	na
50-99 MED/d	0.18%	0.7%
>100 MED/d	0.23%	1.8%

Navigating Opioids Infographic available at ISMP Canada: Opioid Stewardship; accessible online at https://www.ismp-canada.org/opioid_stewardship/ or https://www.ismp-canada.org/download/OpioidStewardship/navigating-opioids-11x17-canada.pdf

5) Other relevant points...

- **No overall dose response** was found for benefits on pain or function at the population level!
- The **majority of opioid benefit in CNCP RCTs** have been seen with relatively lower doses (< 100 MED/day).
- **Reassess current opioid patients.** Some will find benefit from a dose reduction as well as ↓ harm.

***STRONG recommendations** indicate that all or almost all fully informed patients would choose the recommended course of action, and indicate to clinicians that the recommendation is appropriate for all or almost all individuals. Strong recommendations represent candidates for quality of care criteria or performance indicators.

****WEAK recommendations** indicate that the majority of informed patients would choose the suggested course of action, but an appreciable minority would not. With weak recommendations, clinicians should recognize that different choices will be appropriate for individual patients, and should assist patients to arrive at a decision consistent with their values and preferences. Weak recommendations should not be used as a basis for Standards of Practice (other than to mandate shared decision-making).

1) Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, et al. Guideline for opioid therapy and chronic noncancer pain. CMAJ. 2017 May 8;189(18):E659-E666. Online at: http://nationalpaincentre.mcmaster.ca/guidelines.html
2) RxFiles Pain Treatment Colour Outcomes Chart. Accessed online at http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Pain-Tx-Outcomes-Colour.pdf
3) CADTH Rapid Response: Multidisciplinary Treatment Programs for Patients with Chronic Non-Malignant Pain: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. June 2017. Accessed online at https://cadth.ca/multidisciplinary-treatment-programs-patients-chronic-non-malignant-pain-review-clinical

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RxFiles - Pain Mini-Book

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Additional Support Documents & Links

RxFiles

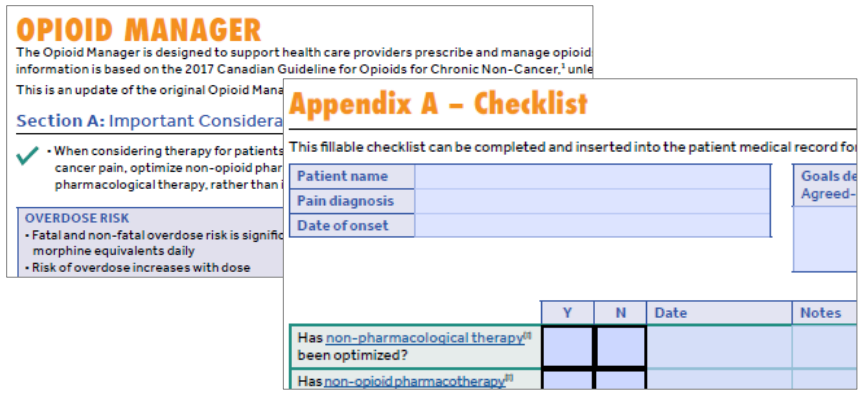
- **Urine Drug Screening (UDS)– Frequently Asked Questions**: http://www.rxfiles.ca/rxfiles/uploads/documents/members/Urine-Drug-Screening-UDS-QandA.pdf
- **RxFiles Opioid & Pain Resource Links**: http://www.rxfiles.ca/rxfiles/uploads/documents/RxFiles-Pain-and-Opioid-Resource-Links.pdf

Other

- CFPC - CNCP Resources: http://www.cfpc.ca/Chronic_Non_Cancer_Pain_Resources/
- Clinic Policy (Sample): PRESCRIBING Of MOOD-ALTERING DRUGS, OPIOIDS & Other CONTROLLED SUBSTANCES: http://www.rxfiles.ca/rxfiles/uploads/documents/members/Opioid-Controlled-Substance-Rx-Clinic-POLICY.pdf
- Fentanyl Patch Exchange Tool: http://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-Patch-Exchange-Disposal-Tool.pdf
- Management of Chronic Non-Cancer Pain Tools: www.thewellhealth.ca
- Medical Marijauna / Cannabinoid Links: Coming soon.

Opioid Manager & Appendix (2017 CNCP Guideline tool)

- Documentation tool - available at the following: www.thewellhealth.ca/pain; http://nationalpaincentre.mcmaster.ca/opioidmanager/; www.opioidmanager.com



Chronic Pain Treatment Colour Chart - Comparison of Benefits & Harms

M LeBras, L Regier, A Crawley, L Kosar – Jan 2018 - www.RxFiles.ca

	DRUG / OUTCOME {Superscript refers to notes that follow}	I Non-drug	II Acetamino-phen	III NSAIDs		IV Antidepressants				V Gabapentinoids		VI Opioids[1,2]			VII Canna-binoids	VIII Other
				Oral	Topical	TCA		SNRI		Gabapentin	Pregabalin	Atypical / Weak*	Strong (MED/d)			
						Amitriptyline	Nortriptyline	Venlafaxine	Duloxetine				≤50-90	>90		
Benefits	A Low Back Pain (LBP)	✓✓ Exercise, Physio	? useful in some	✓✓	✓?	✓?If neuropathic			✓ 60mg/d	✓? If neuropathic, radicular Otherwise little-no benefit but ↑AEs (X Pregabalin leg pain 2° sciatica)		✓?Tramadol 150-300mg/d; ?Buprenorphine	✓? Benefit		?	Muscle relaxants e.g. cyclobenzaprine (short - term only ≤2wk; ↑ harms)
	B Osteo-arthritis (OA)	✓✓ Exercise (low impact), Wt loss	✓ ? Minimal benefit but ~safe; 3-4g/d scheduled dosing	✓✓ Caution in elderly	✓✓ Elbows, Hands, Knees, Toes	? (NortIKA study with nortriptyline ongoing)		?	✓Knee 60-120mg/d	?		✓?Tramadol 150-250mg/d	✓Average dose ~60 MED/d	Most data @ lower doses! No dose response	?	?Intra-articular injections Topical capsaicin, other; Synvisc?, glucosamine?, Combinations
	C Neuropathic	✓✓ General measures	X Generally considered not effective, may use during an acute exacerbation			✓✓ Amitriptyline 25-100mg/d ✓ Nortriptyline 25-100mg/d		✓ Less well studied vs duloxetine	✓✓ PDN: 60mg/d	✓✓ Pregabalin 300-600mg/d ✓✓ Gabapentin 900-2400-3600mg/d		✓?Tramadol 300-400mg/d	✓Average dose 45-91 MED/d	Most data @ lower doses!	✓? SATIVEX for MS pain	TN: Carbamazepine Combinations Topical: Lidocaine, Capsaicin
	D Fibromyalgia central sensitized pain syndrome	✓✓ Education, Exercise	Not studied monotherapy, ? useful in some	X Not effective	Not effective	✓Amitriptyline 25-50mg/d (✓pain; ✓? other sx) NS discontinuation 2° AE		✓ Duloxetine 60-120mg/d (✓pain; ✓? other sx)		✓Pregabalin 300-600mg/d (✓pain; ✓? other sx)		✓?Tramadol 200-300mg/d ✓pain	XX ↑ harms & ? worse pain control vs non-opioid treatment		?	Cyclobenzaprine ≤1-3mos Combinations
	E Other Pain, Chronic	✓✓	Musculoskeletal; Pain in dementia	MSK; Bone pain	MSK	?Amitriptyline in post-stroke pain & IBS related pain		Duloxetine in pain associated with MMD				✓?Tramadol ✓?SUBOXONE	✓?	End of life/ palliative	✓? Nabilone ✓MS:SATIVEX	Bisphosphonate: bone pain Lamotrigine: post-stroke
	F Sleep	✓✓	✓?	✓?	✓?	✓	✓	X?		✓?	✓?	✓?	✓?	X	✓ / X	See F-IV for other e.g. Mirtazapine 7.5-15mg
Harms / Adverse Events	G Overdose	✓✓	If >4g/day &/or with ↑ alcohol			Unintentional overdose uncommon but can be fatal		X?		X?		X Often unintentional. Rx Naloxone Kit!	X	XX	X? XX Toddlers	High doses & med combos ↑ risk, e.g. opioids-benzos
	H Mortality	✓✓	X Rare										X?	XX?	X?	? Impairment/accidents
	I Addiction /SUD risk	✓✓	✓✓	✓✓	✓✓	✓		✓		X		X? Role for SUBOXONE or methadone in SUD	X	XX	X	Take good Hx; EtOH, UDS; family Hx, early trauma; assess risk; manage/refer
	J GI risk	✓✓	✓✓	X GI ulcer	✓	✓ Some GI AEs		✓ Some GI AEs		✓		X (bowel obstruction)			X?	Role: PPI; bowel regimen
	K Hepatic caution	✓✓	See overdose	✓ / X	✓✓	✓ Caution impairment		✓	✓ ?↑LFT	✓✓		✓ Caution impairment				Monitor LFTs if risk
	L Renal caution	✓✓	✓	XX	X?	✓ Caution impairment		10-70mL/min	<30mL/mL	<60mL/min		<30mL/min	Caution with morphine			Hydration, K^+, DIs
	M CV Risk	✓✓	✓	X		↓BP, ↑HR; widen QRS		↑BP				Tramadol:↑QT	Methadone:↑QT		↑HR; X	Consider activity, pacing
	N HF Risk	✓✓	✓	XX		✓?		✓?		? Peripheral edema		✓?	✓?	✓?		Avoid NSAIDs in HF
	O Seizure risk	✓✓	✓✓	✓ / X	✓	X Toxic doses		X Toxic doses		✓✓ (However taper to stop)		XX Tramadol			✓/ ?	Baclofen; ?Cyclobenzaprine Watch DIs
	P Falls / # risk	✓✓	✓	✓	✓	XX	X	X		X		?	X	XX	?	Advise re: impairment
	Q CNS eg drowsy/dizzy	✓✓	✓✓	✓	✓✓	XX	X	X?		X– XX At high doses or in combo		X	X	XX	XX	CNS Combos of 3+: ↑↑↑
	R ACh eg dry mouth	✓✓	✓✓	✓✓	✓✓	XX	X									Muscle relaxants
	S DIs	✓✓	few		✓	esp CNS, ACh; 5HT		5HT,3A4,2D6	5HT,1A2,2D6	Few; opioids: respiratory depression		T: 2D6,5HT	3A4; benzodiazepines		3A4,2C9	Topicals have few DIs
	T Weight Gain	✓✓	✓✓	✓	✓	XX	X	✓	✓	Dose related	Dose related	✓	✓	?	X?	Ensure exercise; diet
	U Tolerable AE	✓✓	✓✓		✓✓	X? ↑ D/C 2° AE	✓? - X?	X? ↑ D/C 2° AE (120mg/d)		X? ↑ D/C 2° AE esp at ↑ doses		X?	X?	XX	✓/ X?	Start low, go slow, assess
	V Psychosis	✓✓	✓	✓	✓	✓Comorbidities (e.g. depression, anxiety). May interact with other psychiatric drug therapy.				✓		X Stabilize psychiatric illness before considering opioid. Caution if depression.			X (& may uncover)	SSRIs & SNRIs may be useful for PTSD
	W Peri-Pregnancy	✓✓	✓✓	P_1, P_2, P_3 L	✓ ?P_3					✓ Lactation		XX Codeine / ✓Some can be used safely			XX	Use lowest effective dose
	X Cost typical/month	✓✓ - XX	$5 - 20	$20+	$26-92 ✗⊗	$20+		$20+	$40+	$40+	$48 - $73	$40 - 167 ✗⊗	$30+	$50+	$20-100 ?	Nabilone: ☎ ✆ SATIVEX: ✗ ⊗
	Y Other	Essential for success!!!	DIs: Ingredient in many OTCs	Add PPI if high GI risk	++Form-ulations	✓ Option if concomitant headache, insomnia		✓ Option if concomitant depression, anxiety, PTSD		?✓ Combining with an antidepressant or an opioid		AEs: hypogonadism; hyperalgesia, sleep apnea; DI: Benzos ↑ overdose risk			Complexities: legal/psycho/social	

Overall:
- ♦ **Potential benefits and harms** of each treatment option can **vary considerably** depending on the patient (including their mindset), the condition, and the dose/intensity of the intervention. Ensure an adequate trial of the medication. **Individualization of therapy is key!**
- ♦ An **adequate trial** will generally require a titration period (days-weeks) and an evaluation period; assess both benefit and harms.
- ♦ It is important to emphasize the value of a **long-term, holistic approach, focusing on incremental gains in function**, no matter how small.

"Is the patient moving in the right direction?" "Is life and overall functioning slowly getting better?" "Is the patient able to live meaningfully beyond their pain experience?"

* Analgesic effect of codeine & tramadol is variable & dependant on patient's 2D6 metabolizer status; **#**=fracture **2°** =secondary **5HT**=serotonin activity **AE**=adverse event **ACh**=anticholinergic **CBD**=cannabidiol **CV**=cardiovascular **CNS**=central nervous system **D/C**=discontinue(d) **DI**=drug interaction **EtOH**=alcohol **Fx**=function **HF**=heart failure **Hx**=history **LBP**=low back pain **MED**=morphine equivalent dose **MMD**=major mood disorder **MS**=multiple sclerosis **MSK**=musculoskeletal **OA**=osteoarthritis **PDN**=painful diabetic neuropathy **PHN**=post-herpetic neuralgia **PPI**=proton-pump inhibitor **PTSD**=post traumatic stress disorder **SNRI**=serotonin norepinephrine reuptake inhibitor **SUD**=substance use disorder **sx**=symptoms **TCA**=tricyclic antidepressant(s) **TN**=trigeminal neuralgia **UDS**=urinary drug screen **Wt**= weight

An Advantage ✓✓	✓	Neutral	X	A Disadvantage XX	Unknown/Ongoing ?

For each column number & row letter, see detailed notes that follow, or online at http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Pain-Tx-Outcomes-Colour.pdf .

Pain Medication – Trial Dosages, Regimen Options & Costs Includes off-label use

Nov 2017 - www.RxFiles.ca

Drug	Dose Titration / Taper Options*	$/mos
Acetaminophen	Analgesic effect: within hours. Trial: initiate at 2.6-4g/d, may allow up to 4wks in CNCP to assess benefit/tolerability.	
Acetaminophen ✗ ▼OTC CR has biphasic release	650mg po q6h low-dose, adequate for some	$5
	1g po q6h 4g/day=max dose; 3.2g/day elderly?	$7
	CR: 1.3 g po Q8-12H longer acting form	$8-12
NSAIDS, Oral	Analgesic effect: within hours. Trial: full anti-inflammatory effect may require higher dose for ≥7d. {If high-GI risk, add gastroprotection (e.g. pantoprozole 40mg /d)}	
Celecoxib ☎ ▼	100-200mg po daily	17-22
	100-200mg po BID	22-33
Diclofenac SR	75mg po daily	20
	100mg po daily	24
Ibuprofen OTC: all caps/tabs ≤ 600mg ER: Advil 12hr	400mg po TID max OTC dose	15
	600mg po TID anti-inflammatory dose	24
	800mg po TID	18
	800mg po QID	21
Naproxen 220mg OTC	375mg po BID low-dose, adequate for some	20
	500mg po BID anti-inflammatory dose	25
NSAIDS, Topical	Analgesic effect: within hours. Trial: full effect may take 2 weeks.	
Diclofenac Diethylamine ✗ ⊗	1.16%-2.32% gel (VOLTAREN EMULGEL); 2-4g (4-8cm) TID-QID	26
Diclofenac Sodium ✗ ✆	1.5% solution (PENNSAID); 40 drops (16mg) QID or 50 drops TID	92
Antidepressants TCA {more evidence but less well tolerated than nortriptyline}	Trial: start low / titrate; allow ~ 1wk at each dose level to assess tolerability; allow ≥2wks at an effective dose to assess benefit. {If dry mouth, consider adding saliva substitute product e.g. Xylimelts, OralBalance gel.} [~ 4wks = adequate trial]	
Amitriptyline	10mg po HS low starting dose	13
	25mg po HS	15
	50mg po HS	18
	75mg po HS	23
	100mg po HS	26
	Effective dose in trials for neuropathic pain: ~ 25-100mg/day.	
Nortriptyline	10mg po HS low starting dose	19
	25mg po HS	28
	50mg po HS	44
	75-100mg po HS	60-77
SNRI	Trial: start low / titrate; allow ~1wk at each dose level to assess tolerability; allow ≥2wks effective dose to assess benefit. [~ 4wks = adequate trial]	
Venlafaxine XR EFFEXOR XR	37.5mg po daily low starting dose x4-7 days	16
	75mg po daily	21
	150-225mg po daily effective dose	22-32
Duloxetine CYMBALTA	30mg po daily low starting dose x1-2wks	27
	60mg po daily usual effective dose	42
	120mg po daily high effective dose, & ↑AEs	74

*** INDIVIDUALIZE & ADJUST doses for patient factors** (e.g. elderly/frail: start low, go slow; renal Fx; multiple drugs with potential interactions & additive CNS adverse effects (AEs); medication Hx; weight; patient concerns re. medications

Gabapentinoids	Trial: start low / titrate;↑ every 3-7 days, as tolerated, until at an effective dose. Allow 1-2 weeks to assess benefit & tolerability; may ↑ further if tolerated. [~ 3-4wks = adequate trial]	
Gabapentin NEURONTIN	100-300mg po HS lowest starting doses	13-17
	100mg po TID low starting dose	18
	300-600mg po TID low, usual effective doses	28-42
	600mg po BID + 900mg po HS	50
	600mg po QID upper, usual effective dose	53
	900mg po QID usual maximum dose	78
Pregabalin LYRICA ✆	25-50mg po BID low starting dose	24-31
	75mg po BID common starting dose	38
	150mg po BID low, usual effective dose	48
	225mg po BID sweet spot for efficacy/tolerability	76
	300mg po BID maximum dose	48
Topicals, other	(Compounded combos & options also available)	
Capsaicin ✗ ▼OTC	0.025% (for OA) Apply TID 0.075% (for PHN, PDN)	20
Lidocaine 5%	Topical oint (alt Emla Cream) ✗ ⊗	15-30
Maxilene 4, 5%	Liposomal crm; better penetration	12-50
Opioids, Atypical or Weak		
Codeine – reg – CR ☎✆	60mg po q4h (**334mg/d=50 MED/d**)	71
	100-150mg po q12h	55-78
Acetaminophen + Codeine +/- Caffeine e.g. TYLENOL #__	1 2x [A. 300mg+C. 8mg +Cf.15mg tab] q4-6h	42
	2 2x [A. 300mg+C. 15mg +Cf.15mg tab] q4-6h	32
	3 2x [A. 300mg+C. 30mg +Cf.15mg tab] q4-6h	33
	4 2x [A. 300mg + C. 60mg tab] q4-6h	52
Buprenorphine Patch 5, 10,15,20	*BuTrans* 5 mcg/hr, Apply q7days ✗ ⊗	69
	BuTrans 20 mcg/hr, Apply q7days (≤ 50MED/d*)	206
SUBOXONE, g ☎✆ buprenorphine/naloxone	2mg/0.5mg SL tab daily May dose BID-TID if for pain.	32
	8mg/2mg SL tab daily (**16mg/d SL=90 MED/d ???***)	65
Tramadol ✗ ⊗	Trial: start low/ titrate [~4wks = adequate trial] (**300mg/d=50 MED/d ???***)	
ULTRAM (IR)	50-100mg po Q4-6h (Max 400mg/day)	100-188
ZYTRAM XL ✗ ⊗	75-100mg po q24h lowest starting dose	41-48
	150mg po q24h usual starting dose	66
	200-300-400mg po q24h	93-167
TRIDURAL, g ✗ ⊗	100mg po q24h usual starting dose	40
	200-300mg po q24h *300mg/day max dose, monograph	64-88
RALIVIA ✗ ⊗	100mg po q24h usual starting dose	55
	200-300mg po q24h *300mg/day max dose, monograph	92-130
Acetaminophen +Tramadol ✗ ⊗	1 tab [A. 325mg + T. 37.5mg] Q6H	98
	2 tabs [A. 650mg + T. 75mg] Q6H TRAMACET	185
Tapentadol IR NUCYNTA IR ✗ ⊗	50mg po q4-6h	143
	75-100mg po q4-6h usual max 600mg/day	176-210
Tapentadol ER NUCYNTA ER ✗ ⊗ (~ tamper resistant)	50mg po q12h usual starting dose	78
	100mg po q12h lowest dose in msk trials	112
	150mg po q12h (**300mg/d=90 MED/d ???***)	146
	200-250mg po q12h highest dose in msk trials	186-254

Pain/Opioid Links: http://www.rxfiles.ca/rxfiles/uploads/documents/RxFiles-Pain-and-Opioid-Resource-Links.pdf

▼=on NIHB ☎ =EDS Sask ✆=prior NIHB ✗ =Non Formulary SK ⊗ = not covered by NIHB
AE=adverse event **CR**=controlled release **DI**=drug interactions **IR**=immediate release **mo(s)**=month(s) **MED**=Morphine Equivalent Dose **msk**=musculoskeletal **SUD**=substance use disorder **OTC**=over-the-counter **wks**=weeks
*suggested MED amounts may be unreliable.

Opioids, Strong	Trial: start low / titrate; ↑ gradually (minimum 2 days, but **preferred ≥2 weeks** at a given dose), assess benefit (function & pain) & tolerability; follow up every 2-4 weeks. [adequate trial=3-6 months] {Titration ends if optimal dose reached, insufficient benefit after 2-3 dose increments, unacceptable AEs or misuse/diversion.}[3]	
Morphine IR STATEX, g M-ESLON ✗ ⊗	2.5mg po q4-6h	17-20
	5mg po q4-6h	24-31
	10mg po q4-6h	31-43
	20mg po q4-6h	55-77
Morphine SR		
MS Contin, g	15mg po q12h	26
	30mg po q12h	33
	45mg po q12h (**90mg/d = 90 MED/d**)	48
M-ESLON ER	10mg po q12h	31
	15mg po q12h	34
	20mg po q12h	52
	30mg po q12h	58
	45mg po q12h	82
KADIAN ✆	10-20mg po q24h	23-37
	50mg po q24h (**50mg/d = 50 MED/d**)	59
	100mg po q24h	96
HYDROmorphone IR DILAUDID	0.5mg po q4-6h (½ tablet or liquid)	17-20
	1mg po q4-6h low starting dose - healthy adult	23-29
	2mg po q4-6h	29-38
	4mg po q4-6h	40-54
HYDROmorphone CR ✆ HYDROMORPH-CONTIN	3mg po q12h	57
	6mg po q12h (**10mg/d = 50 MED/d**)	81
	9mg po q12h (**18mg/d = 90 MED/d**)	97
OXYcodone IR	5-10mg po q4-6h	27-35
OXYcodone CR OxyNEO ☎ ⊗ (~ tamper resistant)	10-15mg po q12h (**33mg/d=50 MED/d**)	70-83
	20mg po q12h	100
	30mg po q12h (**60mg/d=90 MED/d**)	129
Opioids, Strong	The long & variable duration of action requires added caution in dose titration, follow-up!	
Fentanyl Patch ☎✆	12mcg/hr, apply for 3 days Not for opioid naïve!	35
	25mcg/hr, apply for 3 days	50
	37mcg/hr, apply for 3 days	104
	{**Fentanyl MED uncertain**; however 25mcg/hr Patch = ~ 60–134 MED}*	
Methadone ☎✆ {MED uncertain}	1mg po q8h	26
	2.5mg po q8h Daily dosing for SUD; TID for pain. {Special license to prescribe}	39
	5mg po q8h	67
Muscle Relaxants	*Very sedating*; watch for CNS DIs. Use: lowest effective dose & short term (≤2wks).	
Baclofen	5-10mg po TID	18-27
Cyclobenzoprine ☎▼	5mg po HS low starting dose	16
	5-10mg po TID	28-47
Tizanidine ☎✆	2mg✗⊗-4mg po TID - QID	44-100
Misc. Other		
Nabilone ☎✆	0.5mg po HS - 2mg po BID CESAMET	18-215
SATIVEX Buccal Spray THC/CBD ✗ ⊗	1 spray q4h; often use ~4-5 sprays/day	252/vial
Trazodone	25-50-100 mg po HS used for sleep	11-15
Mirtazapine	7.5-15 (max30mg) po HS for depression/sleep	12-21
Carbamazepine	100-400mg po BID start low, ↑ in 2-3 days	12-20

Supplementary Notes for Colour Chart - By Row Letter & Column Number[1 CDN CNCP & Opioid '17, 2 CDC'16]

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Rows A-F: *Generally, trials were **compared to placebo** (± background treatment); however, there were some small head-to-head trials. Most trials were **≤ 12 weeks duration** (exceptions noted below). Typically, we reported the following outcomes: ≥ 30-50% reduction in pain, change in pain (based on a pain scale e.g. NRS, VAS), global improvement, or change in function.*

A — Low Back Pain (LBP)[4 ACP'17,5 NICE'16,6,7]

A I Non-drug tx: may include: exercise (NNT=4-8[8]), physio, multidisciplinary rehab, tai chi, yoga, stress reduction, mindfulness, CBT, acupuncture, massage; in acute LBP also consider heat.

II Acetaminophen: *does not appear effective and is not recommended by guidelines [ACP'17, NICE'16]; however, may be trialed as relatively safe compared to alternatives.*

Acute: 1 RCT (n=550), 4g/day had similar effects vs placebo for pain & disability.[9] No difference between acetaminophen and NSAIDs (4 RCTs, n=309).[10]

Chronic: not adequately studied vs placebo e.g. 1 RCT (n=133) studied 2 days of therapy; however, 1 small RCT (n=30) showed no significant difference between acetaminophen 4g/day vs an NSAID. Not studied in subacute LBP.[11,12]

III Oral NSAIDs: *appear effective for acute & chronic low back pain.[ACP'17, NICE'16] COXIB and non-selective NSAIDs appear to have similar benefit, but limited head-to-head studies.*

Acute: meta-analysis (N=4, n=745), NSAIDs x ≤1 week ↓ mean pain score (~8 on 0-100 VAS) and ↑ global improvement (RR. 1.2) vs placebo; but also increased AE (RR 1.25). Head to head studies: similar effect between NSAIDs vs acetaminophen (N=4, n=309); limited RCT data vs muscle relaxants or weak opioids (i.e. codeine) but appear similar. The majority of RCTs report no difference between types of NSAIDs.[10]

Chronic: meta-analysis (N=6, n=1354) NSAID ↓ mean pain score (~7 on 0-100 VAS) and improved disability vs placebo; however, when limited to high quality studies differences were NS. Head to head studies: in 1 RCT (n=30), NSAID vs acetaminophen 4g/day demonstrated similar effects. In 2 RCTs (n=1598) celecoxib 400mg/day ↓ pain (NNT~10) and & ↓ AE vs tramadol 200mg/day. In 3 RCTs (n=530) similar effect among NSAIDs.[12]

Topical NSAIDs: *limited data; however, may consider if localized pain.*

IV Duloxetine: *may be effective in chronic low back pain (including non-neuropathic low back pain).[ACP'17] May consider TCAs if neuropathic component to low back pain.*

Chronic: in RCTs (largest study, n=404), duloxetine 60-120mg/d generally ↓ mean pain score, but inconsistent results for ≥30% reduction in pain; ↑ withdrawal due to AE NNH~6-12 & ↑ AE (especially nausea, dry mouth, and somnolence).[13,14,15] ✓Health CND indication- LBP chronic

Venlafaxine: no RCTS in LBP available.

V Gabapentinoids: *may consider if neuropathic component to LBP. Otherwise, limited data and not generally recommended.[ACP'17, NICE'16]*

There was no difference between gabapentin 300-3600mg/d vs placebo in a meta-analysis (N=3, n=185); pregabalin ≤600mg/d was inferior to active treatment (amitriptyline ~50mg/d, celecoxib~200-400mg/d, **TRAMACET** 2 tabs/d) for pain reduction in a meta-analysis (N=3, n=332). Also, increased risk of harms, especially dizziness NNH 7-11.[16] In addition, 1 RCT (n=209) showed similar leg pain associated with sciatica results in those receiving pregabalin or placebo but ↑ AE with pregabalin (especially dizziness).[17] These agents may be of potential benefit if neuropathic component to LBP or if radicular pain (i.e. pain radiating from the spine to a limb).[16]

VI Opioids: not *generally recommended.[ACP'17, NICE'16] May consider use during an acute exacerbation or when other therapies are ineffective.*

Tramadol: in chronic LBP, tramadol 150-300mg/day ± acetaminophen ↓ pain and disability vs placebo in a systematic review (N=5 RCTs, n=1378).[18] However, in 2 RCTs (n=1598) there was ↓ pain (NNT~10) and & ↓ AE with celecoxib 400mg/day vs tramadol 200mg/day.[19]

Buprenorphine: in chronic LBP, transdermal buprenorphine ~20mcg/h ↓ pain but not disability (meta-analysis N=2, n=653).[18]

Strong opioids: role is unclear. In chronic LBP, strong opioids (overall mean dose studied ~110MED/d; range 40-243 MED/d) ↓ pain and disability (meta-analysis N=6, 1887); however, other reviews suggest no clinically important pain relief or improvement in disability with opioids. Also, increased risk of AEs NNH~9-17 (e.g. somnolence, nausea, constipation).[18,20,21]

VII Cannabinoids: *no RCTs in LBP available.*

VIII Muscle relaxants (non-benzodiazepine): *may consider as a potential short term option (≤2 weeks) in acute LBP.* ↓ pain/muscle spasm; however, ↑ AE NNH=12 (esp CNS NNH=9) and no significant difference >2 weeks. Most data with cyclobenzaprine, tizanidine, or baclofen.[22]

Interventional procedures: *may have value especially in difficult to treat patients* (e.g. facet joint injections, medial branch blocks & neurotomy, sacroiliac joint injections & neurotomy, interlaminar & transforaminal epidural steroid injections, intradiscal glucocorticoid injection).

B — Osteoarthritis (OA)

B I Non-drug treatment: surgery (hip, knee), if severe. Tailored exercise therapy improved knee OA at 3 mos in those with comorbidities.[23] Consider: weight loss; physiotherapy. Braces, splints, orthotics, & assistive devices often helpful. {? heat; ? cold}

II Acetaminophen: *appears to offer little clinically meaningful benefit, but trial often recommended for older adults as relatively safe compared to alternatives.*

For OA knee/hip: meta-analysis (N=10, n=2541), acetaminophen ~3-4g/day vs placebo reached a statistically but not clinically significant ↓ pain and function; studies were typically 6-12 weeks in duration with the exception of 1 study which was 6 months.[24,25]

For OA knee/hip: meta-analysis (N=15, n=2991), acetaminophen 2.6-4g/day vs NSAIDs (e.g. ibuprofen 1200-2400mg/d, diclofenac 150mg/d, celecoxib 200mg/d, naproxen 440-750mg/d) resulted in a small ↓ pain in favour of NSAIDs (Mean Difference= -0.29, 95% CI -0.35 to -0.22); study duration range was 1-104 wks (median duration not reported).[26]

III Topical NSAIDs: *appear effective for single joint osteoarthritis; limited data vs oral NSAIDs.*

Meta-analysis (N=39, n=10,631), in OA (typically knee) topical NSAID ↓ pain NNT=7-10 vs topical placebo; study duration was ~6-12 weeks; most studies assessed **VOLTAREN EMULGEL** (1-3%) or topical ketoprofen. Limited data; however, topical and oral NSAIDs appeared similar.[27]

Oral NSAIDs: *appear effective; potentially greater pain reduction than acetaminophen but similar effects as opioids. COXIB and non-selective NSAIDs appear to have similar benefit, but limited head-to-head studies.* For OA knee/hip: meta-analysis (N=15, n=2991), acetaminophen 2.6-4g/day vs NSAIDs (e.g. ibuprofen 1200-2400mg/day, diclofenac 150mg/day, celecoxib 200mg/day, naproxen 440-750mg/day) resulted in a small pain reduction in favour of NSAIDs (Mean Difference= -0.29, 95% CI -0.35 to -0.22); study duration range 1-104 weeks (median duration not reported).[26] No agent clearly superior (indirect comparisons).[28,29,30]

IV Duloxetine: *may be effective for knee OA.* Meta-analysis (N=3, n=1011), 60-120mg/d vs placebo ↓ knee pain NNT~6; however, ↑risk of D/C RR 1.43 & AEs (esp nausea, constipation, diarrhea, dizziness, somnolence, and insomnia).[225] ✓(Health CND indication- OA of the knee)

V Gabapentinoids: *limited data; not generally recommended.*

One RCT (n=89) in knee OA demonstrated similar results for pain and function among those treated with pregabalin 25mg HS or meloxicam 10mg/d; however combination therapy (pregabalin + meloxicam) was statistically more effective than monotherapy.[31] Another study in hand OA (n=65) showed ↓ pain vs placebo.[Sofat'17]

VI Opioids: *appear to have some benefit; consider use during an acute exacerbation or when other therapies are ineffective.*

Tramadol: meta-analysis, tramadol 150-250mg/d vs placebo ↓ pain score (~9 on 0-100 scale) and resulted in global improvement NNT=6; however, ↑ major AE (NNH=8). Variable results vs active comparators.[32,33] Tapentadol: small benefit vs placebo, NNT=16 @12 wks; NNH=10.[34]

Strong opioids: meta-analysis, opioids vs placebo resulted in a ↓ pain NNT=10 and ↑ in function NNT=12, but ↑ withdrawal due to AE NNH=21 & ↑ any AE NNH=14; median dose 59 MED/d (range 13-160 MED/d) and no association between daily equivalent dose & improvement in pain or function; median treatment duration 4 wks (range 3d to 6 mons).[35]

VII Cannabinoids: *no RCTs in osteoarthritis available.*[36]

VIII Other: Intraarticular glucocorticoid injections for knee OA may result in short-term pain relief, data for longer-term outcomes are less favourable.[37,38] (Intra-articular triamcinolone

vs saline, to symptomatic knee every 12 weeks, resulted in greater cartilage volume loss and no difference in pain over 2 years.)[39] Sodium hyaluronate (viscosupplementation): some evidence supports a role in knee OA, however, overall evidence is conflicting. May consider after failure of other treatment.[40] Combo pharmacotherapy: limited data; some combinations studied include acetaminophen, NSAID, tramadol.[41,33]
Glucosamine: likely not effective for pain or function.[42,43,44]
Topicals, counter-irritants (e.g. capsaicin 0.025%): [45,46,47] may provide some benefit.
(Emerging: stem cell injections for OA; preliminarily +'ve but bias & low level of evidence.)[48]
Bisphosphonates in ♀ knee OA ↓ knee replacement surgery in a retrospective study (n=4012) compared to no bisphosphonate therapy.[AnnRheumDis2017]

C Neuropathic [49 CPS'16, 50 NICE'13(updated'17),51] PDN=painful diabetic neuropathy PHN=post-herpetic neuralgia

C I Non-drug treatment: physiotherapy, exercise, psychological treatment are essential.[CPS'14]

II, III Acetaminophen & NSAIDS: *generally not recommended; however may use during an acute exacerbation.* [Expert Opinion] No RCTs in neuropathic pain available.[51]

IV TCAs & SNRIs: *appear effective;* [CPS'14(1st line)] *amitriptyline (potentially nortriptyline) & duloxetine may be preferred.* [NICE'13(updated'17; 1st line, Strong Recommendation)]
TCAs: [CPS'14(1st line)] meta analysis (N=15, n=948), PDN, PHN: ↓ pain NNT=4 but benefit may be overestimated as based on poor quality trials; ↑withdrawal due to AE NNH=14 vs placebo; majority of studies included amitriptyline [NICE'13(updated'17; 1st line, Strong Recommendation)] (average dose 25-100mg/d, range 10-200mg/d) but nortriptyline (25-100mg/d), desipramine, & imipramine also studied.[51,52,53,54,55] Limited data; however, head-to-head studies suggest similar benefit among TCAs, and nortriptyline may be better tolerated.[56,57]
One RCT (n=83) reported similar benefit among amitriptyline 50-75mg/d, duloxetine 60-120mg/d, & pregabalin 300-600mg/d.[58]
SNRIs: [CPS'14(1st line)] duloxetine [NICE'13(updated'17; 1st line, Strong Recommendation)] meta-analysis (N=8, n=2718), PDN: duloxetine 40-120mg/d ↓ pain NNT~6, ?↑ global response (20mg/d NS); but ↑withdrawal due to AE NNH=10 (120mg/d) & NNH=20 (60mg/d) & ↑AE, especially nausea, dry mouth, dizziness & somnolence vs placebo (generally ≤30mg/d was NS). Harms appear greater with 120mg/d vs 60mg/d but not benefits.[51,59] ✓(Health CND indication- PDN)
One study (n=83) RCT reported similar benefit among duloxetine 60-120mg/d, amitriptyline 50-75mg/d, & pregabalin 300-600mg/d.[58] In addition duloxetine 60mg/d was shown to be non-inferior to pregabalin 300mg/d in one RCT (N=407) and superior in an exploratory analysis of another RCT (N=804).[60] May consider venlafaxine 150-225mg/d or desvenlafaxine 200-400mg/d; however, less data & less robust (e.g. small sample size) vs duloxetine.[51,61]

V Gabapentin & Pregabalin: *appear effective.* [CPS'14 (1st line), NICE'13(updated'17; 1st line, Strong Recommendation)]
Gabapentin: meta-analysis (N=37 RCTs, n=5914), gabapentin 900-2400-3600mg/d vs placebo; PHN: ↓ pain NNT~7 & ↑global response NNT~10; PDN: ↓ pain NNT=6-10 & ↑global response NNT=5-10; but ↑D/C due to AE NNH=30, ↑AE (dizziness, ataxia/gait disturbance, somnolence, peripheral edema) NNH=8-20.[62] No clear dose-response. In 2 RCTs (n≤75), gabapentin (1500-2700mg/d) had a similar effect on pain and less AEs vs TCAs (nortriptyline 75mg/d,[63] amitriptyline 50-75mg/d).[64] Pregabalin: meta-analysis (N=25, n=5940), pregabalin 75-300mg BID vs placebo in PHN & PDN ↓ pain NNT~8 ↑global response NNT=5; but ↑D/C due to AE NNH=14, ↑AE dizziness, somnolence NNH=4-8 as well as peripheral edema. Potentially greater response with 600mg/d vs lower doses.[51,65] ✓(Health CND indication- PDN, PHN, SCI)
One RCT (n=83) reported similar benefit among pregabalin 300-600mg/d, duloxetine 60-120mg/d, amitriptyline 50-75mg/d.[58] In addition, duloxetine 60mg/d was shown to be non-inferior to pregabalin 300mg/d in 1 RCT (N=407) and superior in an exploratory analysis of another RCT (N=804).[60]

VI Tramadol: *may consider during an acute exacerbation* [NICE'13(updated'17, Weak Recommendation)] *or when other therapies are ineffective* [CPS'14(2nd line;)]*; watch DIs (5HT & seizure risk)*. Meta-analysis (N=6, n=438), 300-400mg/day vs placebo ↓ pain NNT=5, but ↑D/C due to AE NNH=9, ↑AE NNH~5 (dizziness, fatigue, dry mouth, constipation, nausea).[51,66]
Tapentadol: limited RCTs with mixed results.[51]
Buprenorphine: lacks RCTs.[67]
Strong opioids: *role is unclear; may consider during an acute exacerbation or when other therapies are ineffective.* [CPS'14(2nd line), NICE'13(updated'17; avoid unless under specialty care, Weak Recommendation)]
Meta-analysis, morphine & oxycodone vs placebo ↓ pain NNT=5; however, inconsistent results among individual trials (e.g., 4/8 trials were beneficial [mean dose: 45-91 MED/d; max dose: 90-240 MED/d], 4/8 trials were neutral [max dose: 15-180 MED/d]) and ↑D/C due to AE NNH=12.[51,68,69] Majority of data with a positive outcome was with MED/d ≤90.
Other opioids: inconclusive as limited data based on recent Cochrane systematic reviews: methadone (N=3, n=105) dose range studied: 10-80mg/d;[70] fentanyl (N=1, n=258) dose range studied: 12.5-50mcg/h;[71] hydromorphone (N=1, n=117) dose range studied: 12-64mg/d.[72]

VII Cannabinoids: *role unclear.* [CPS'14(3rd line), NICE'13(updated'17; avoid unless under specialty care, Weak Recommendation)]
Inconclusive evidence; **SATIVEX** THC:CBD buccal spray may be associated with favourable short-term patient outcomes, including reduced levels of perceived pain & good tolerability.[73] However, another systematic review (N=9, n=1,310) largely assessing **SATIVEX** THC:CBD buccal spray found generally negative results and ↑D/C due to AE NNH=13.[51]
SATIVEX THC:CBD ✓(Health CND- MS-related central neuropathic pain)
Inhaled cannabis (25mg of 9.4% vs 0% tetrahydrocannabinol) was beneficial in 1 RCT (n=21).[74]

VIII Carbamazepine: *1st line for trigeminal neuralgia.* [CPS'14]
Topical: lidocaine 2nd line for localized PHN [CPS'14]; most studies with lidocaine patch [USA, not CND].[75,76,77] May be useful in superficial neuropathic pain (lidocaine [XYLOCAINE 5% Ointment, MAXILENE 4 & 5% Cream, & capsaicin Cream]).[78] Compounded options usually in penetration enhancing vehicles.
May consider nitrate spray (apply to legs or bottom of feet HS) in PDN.[ADA'13]
Botulinum toxin A: 4th line option.[CPS'14]
Combo pharmacotherapy: *if partial, but inadequate pain relief with monotherapy may consider combinations of 1st and 2nd line agents.* [CPS'14] The following regimens have variable effect on pain/function and typically ↑AEs; however, may allow for dose reduction: gabapentinoid + TCA; gabapentinoid + duloxetine; opioid + gabapentinoid or TCA or duloxetine (average opioid dose 15-60 MED/day, max 120 MED/day).[51,79,80]

D Fibromyalgia [81 EULAR'17,82 CDN'12,83] (e.g. chronic widespread pain, central sensitized pain syndrome)

D I Non-drug treatment: patient education of diagnosis, treatment, expectations, credible info sources. Physical exercise [CND CNCP'17(moderate), EULAR'17(Ia,strong)] (moderate intensity 20-30min, 2-3d/wk): meta-analysis (N=13 RCTs, n=839), ↓ pain NNT=4, ↑ function NNT=6, & fatigue; studied up to ~4 years (persistent effects for pain).[84] Consider giving patient an exercise prescription. Physiotherapy (i.e. electric stimulation, acupuncture, whole-body vibration, massage, resistance training, acupoint stimulation, aquatic physical therapy) ↓ pain ±↑ function.[85] Also consider sleep hygiene, CBT, and self-management support (e.g. emotional awareness & expression therapy [226]).

II Acetaminophen: *generally not recommended; however, may be useful in some patients.* [CDN'12(Expert Opinion)] No RCTs of monotherapy in fibromyalgia available. (**see D-VIII** for **TRAMACET**).

III NSAIDs: *generally not recommended;* [EULAR'17(weak)] *however, may consider if comorbid pain disorder (e.g. OA).* [CDN'12(expert)] Meta-analysis (N=6 RCTs, n=292), NSAIDs (e.g. ibuprofen 2400mg/d, naproxen 1000mg/d) did not reduce pain compared to placebo.[86]

IV TCAs & SNRIs: *may be used;* [CDN'12(1A)] *amitriptyline (potentially nortriptyline) or duloxetine may be preferred.* [EULAR'17(Ia,weak)]
Amitriptyline: meta-analysis (N=9, n=649), 25-50mg/d vs placebo ↓ pain NNT=4, effect on other outcomes (e.g. function, QOL, mood, fatigue) either limited ± conflicting; withdrawal due to AEs were no different compared to placebo (RR 1, 95% CI 0.5 to 2.2), but ↑AEs NNH=4 (especially: dry mouth, fatigue, drowsiness, somnolence); studied up to 6 months.[52,87]
Nortriptyline: limited data, RCT (n=188) ↑ function & global improvement vs baseline (pain

		score not recorded), similar to amitriptyline.[88] Duloxetine: meta-analysis (N=6, n=2,249), 60-120mg/day ↓ pain NNT~8; 30mg/d was NS (RR 1.01 95% CI 0.75 to 1.35); improved global effect (change of ~3.5/10 vs baseline; absolute difference -0.5 ?clinical significance); ↑SF-35 mental score (all doses); but ↑ withdrawals due to AE (dose-dependent) NNH=9 (120mg/d), NNH=18 (60mg/d) & ↑AE (all doses) NNH~9 (esp nausea, dry mouth, dizziness, somnolence); studied up to 6 mos.[59] ✓(Health CND indication) Venlafaxine: limited data, no RCTs; however, may provide possible benefit.[89] SSRIs: *may consider; however, role is unclear.* *CDN'12(1A), EULAR'17 (weak recommendation against)* Meta-analysis (N=7, n=383), which included citalopram, fluoxetine, paroxetine ↓ pain NNT 10 (however, 95% CI 5-100), ↑ global improvement NNT=7, ↓ depression NNT=13; withdrawal due to AE similar to placebo.[90] Mirtazapine: recent (2016) RCT (n=430), 30mg/d ↓ pain NNT=7, ↑ function; but ↑AE NNH=9 (including somnolence, ↑LFTs, ↑ weight [~2kg]).[91]
	V	Pregabalin: *appears effective and may be a preferred option.* *EULAR'17(Ia,weak)* Meta-analysis (N=8 RCTs, n=4147), pregabalin 300-600mg/day vs placebo ↓ pain NNT~10 and improved global impression NNT~12; 150mg/d was NS. ?improvements in fatigue and anxiety/depression. Dose-related ↑ AE with >150mg/d (e.g. withdrawals due to AE NNH 6-17; any AE NNH=6-9; weight gain NNH=8); all doses: ↑ dizziness, somnolence, peripheral edema NNH 4-19.[92] Efficacy and safety data up to 1 year.[93] If ↑ daytime AE, consider dosing daily HS as 1 RCT (n=177) reported similar benefit and ?↓ AE vs BID dosing.[94] ✓ (Health Canada indication) Gabapentin: *limited data*.[95] RCT (n=150), gabapentin 1,800mg/d (1,200 - 2,400mg/d) ↓ pain NNT=5, ↑global improvement NNT=4; but ~2x ↑D/C due to AE & ↑AE NNH=5-13 for dizziness, sedation, lightheadedness, weight gain.[96]
	VI	Tramadol: *may consider during an acute exacerbation or when other therapies are ineffective.* *CDN'12(D), EULAR'17(Ib,weak)* In one RCT (n=69), tramadol ~200-300mg/d vs placebo ↓ pain NNT=4, but no difference in function (p=0.371); AE similar, but run-in period prior.[97,98,99] Strong Opioids: *use is discouraged.* *EULAR'17(strong) CDN'12(D)* No RCTs of strong opioids (e.g. oxycodone) in fibromyalgia available[100] and prospective observational data suggests worse pain & function outcomes vs non-opioid therapy; also, risk of harms.[101,102,103,104]
	VII	Cannabinoids: *limited data*. Nabilone 0.5-2mg had conflicting effects on pain and function in 2 RCTs (both studies had <50 subjects), but ↑AE (e.g. 1.5x) vs comparator.[105,106,107]
	VIII	Cyclobenzaprine (TCA-like): *may consider;* *EULAR'17(Ia,weak)* *however, limit to short-term use.* Meta-analysis (N=5 RCTs, n=312), 10-40mg/d divided BID-TID ↓ pain ~35% vs baseline at 4 weeks, but no difference > 4 weeks; ↑ patient rated global "improvement" NNT=5 over 1-3 months.[108] NNH=4.[109] Naltrexone (4.5mg/d[not commercially available; 50mg scored tablet available CDN]): RCT (n=31), may ↓pain and improve general satisfaction in women, but ↑headache & vivid dreams (NNH=5-8).[110] Combo pharmacotherapy: *may be required,* *CDN'12(D* *but limited data; consider following regimens* (variable effect of pain/function and typically ↑AEs): -SNRI/SSRI am + pregabalin HS or divided BID: e.g. duloxetine (average dose 100mg/d) + pregabalin (average dose 380mg/d)[111] or paroxetine 25mg am + pregabalin 75mg HS[112] -SNRI/SSRI am + TCA HS: e.g. fluoxetine 20mg am + amitriptyline 25mg HS[113] -TRAMACET 325/37.5mg 1-2 tabs QID (average 4 tablets/day)[114]
E		**Other Pain, Chronic**
E	I	Non-drug treatment: including education, goal setting, pacing, etc are important! Findings from a review of evidence-based guidelines found the following: 1) physical and exercise therapy: "11 evidence-based guidelines included recommendations about the use of physical therapy interventions for the management of chronic, non-cancer pain. Overall, guidelines supported the use of physical & exercise therapy, manual therapy (i.e. spinal manipulation therapy & mobilization techniques), acupuncture, massage, & yoga. However, guidelines were typically limited with respect to the optimal frequency and duration of treatment & sometimes provided contradictory recommendations."[115] 2) behavioural and psychological interventions: "CBT was recommended across all guidelines. Other psychological interventions, including hypnosis, relaxation, biofeedback and mindfulness, were also recommended in several guidelines."[116] 3) multidisciplinary treatment programs: "showed modest improvement for specific outcomes measured. No relevant cost effectiveness studies of multidisciplinary treatment programs, for patients with chronic, nonmalignant pain in outpatient settings, were identified."[117]
	II	In dementia, acetaminophen often 1st choice due to effectiveness & safety.[118,119,120]
	III	NSAIDs: *provide value in MSK pain over the short term; less benefit with longer term use.*
	IV	Amitriptyline: 75mg/d may be beneficial in post-stroke pain based on 1 RCT (n=15).[121,122] Duloxetine: possibly effective for pain in major depressive disorder. Duloxetine 60mg/d improved pain (50% reduction) at 12 weeks in a meta-analysis (N=3, n=1359) RR~1.3.[59]
	VI	Opioids: adding opioids to non-opioid therapy results in a reduction in pain, and an increase in function vs continuing established therapy without opioids.[1] Given 1000 patients with chronic pain treated over ≤6 months opioid therapy compared to continuing previous care: - Pain: 112 more patients would have a pain reduction of 1/10 on a VAS - Function: 102 more patients would have a small but important improvement There is no evidence of a dose-response effect for pain (p=0.49) or function (p=0.22).[1] Of note, based on observational data, although use of prescription opioid increased dramatically in the USA (104%, 2000-2010), this has not been accompanied by improvement in disability or health status metrics.[123] Opioids not recommended in some specific pain types such as chronic pelvic pain.[Choosing Wisely] **SUBOXONE**: based on 2 non-randomized studies & 1 retrospective study, an evidence-based guideline suggests **SUBOXONE** as being "effective, safe, unlikely to be misused, and highly useful for the treatment of chronic pain. It is also effective for hyperalgesia & addiction".[124]
	VII	Cannabinoids: Pain in General: limited evidence with mixed results; some may see improvement: meta-analysis (N=9) found patients more likely to report ≥30% improvement in pain (RR 1.43), but no difference when limiting to higher quality studies (i.e., longer duration and larger sample size). Additionally, a wide variation in product formulation and dosing complicated generalizability of results.[125] Spasticity: some benefit in MS with both **SATIVEX** THC:CBD buccal spray and smoked cannabis; however, also significant harms. (**see U-VII** Tolerability) Nabilone: some positive benefit & limited harms (studied dose range: 0.5-6mg/day).[126] Studies included MS, fibromyalgia peripheral neuropathy, post chemo- & radio-therapy, & medication overuse headache.
	VIII	Lamotrigine: 200mg/d possibly effective in post-stroke pain based on 1 RCT (n=30).[127 128] Limited data on other anticonvulsants and not routinely recommended.[129,130]
F		**Sleep** [131]
F	I	Non-drug measures may include: sleep hygiene, sleep restriction, positioning & supportive supplies (e.g. pillows, splints), light therapy, daytime activity/exercise, bedtime routine, CBT (may improve pain, too). {Note: *quality* of sleep more important than *quantity* of sleep.}
	II-III	Acetaminophen & NSAIDs: may have some benefit on sleep if pain that is disrupting sleep.
	IV	Amitriptyline: had some benefit on sleep vs duloxetine, but less than pregabalin. However, it was better tolerated and had fewer discontinuations due to adverse events.[58] Nortriptyline is an alternative to amitriptyline with potentially less AEs. Doxepin **SILENOR** 3-6mg (very low dose), is indicated for insomnia. Mirtazapine: 7.5-15mg may be an option for those with poor appetite, mood & sleep.[132] Trazodone: 25-100mg is potentially helpful in PDN & fibromyalgia. If SNRI (e.g. duloxetine) disrupts sleep, give early in day.
	V	Pregabalin: improved sleep vs duloxetine, but had worsening function & more discontinuations due to adverse events (RCT in PDN at 4 weeks).[58]

	VI	Opioids: sometimes problematic; at doses > 100 MED/d, opioids appear to cause sleep disturbance[133]; sleep apnea & additional mental health problems also a concern.[134]
	VII	Selective cannabinoids (dronabinol [no longer available in CDN], nabilone, **SATIVEX** THC:CBD buccal spray) may have positive effect on sleep.[135] Cannabidiol (CBD) may have potential benefit in insomnia; however, delta-9 tetrahydrocannabinol (THC) may decrease sleep latency & impair sleep quality long-term.[136] Nabilone 0.5-1mg HS effective alternative to amitriptyline 10-20mg HS (1 RCT in fibromyalgia patients found sleep quality improved; preference for nabilone NNT=11).[107]
	VIII	Other: adjuncts may be considered. (**see** RxFiles Sleep/Sedatives Chart)
G		**Overdose Risk**
G	II	Acetaminophen: generally considered safe at recommended doses (≤4g/day); overdose possible with: a) acute ingestion of a high dose (≥ 200mg/kg or 10g); b) repeated supratherapeutic ingestion (over a 48 hour period: 150 mg/kg or 6 g/day (whichever is less) c) in the presence of risk factors (e.g. alcoholism, prolonged fasting/malnutrition, isoniazid use) overdose may present with repeated exposure to lower doses (100 mg/kg daily or ≤4 g/day). Unintentional overdose common due cumulative exposure from ingestion of multiple &/or **combination OTC products** containing acetaminophen. (**see K** Hepatic Risk) Note: some recent guidance, especially from the USA, suggests a max of ≤3g/day for chronic use.
	III	NSAIDs: higher doses associated with higher risk of AEs.
	IV	Antidepressants: TCAs such as amitriptyline are potentially fatal in overdose; however, inadvertent overdose less common than currently seen with opioids. Uncertain, but venlafaxine may also be associated with increased risk of fatal overdose.[137,138]
	V	Gabapentin: associated with severe respiratory depression without concomitant opiates in up to 1 out 1000 patients based on post-marketing studies.[MHRA'17]
	VI	Opioids:[1] patients with CNCP who are on opioids are at risk of an overdose. The risk is greater for those with active depression; SUD (substance use disorder, active or history of), or on high MED regimens (e.g. >100 MED/day). Concurrent use of CNS depressants (e.g. alcohol, cannabinoids, BZ) also increases risk. Inadvertent overdose is a prominent current concern (*opioid crisis*).Evidence for dose-dependent harms (**see Questions Surrounding the Recent CDN Opioid Guidelines**, Questions 7-9)[1]:

Opioid Dose	FATAL Overdose Rate	Non-Fatal Overdose Rate
<20 MED/d	0.1%	0.2%
20-49 MED/d	0.14%	na
50-99 MED/d	0.18%	0.7%
>100 MED/d	0.23%	1.8%

Other overdose risk factors:
- altering route of delivery (e.g., crushing, smoking or snorting pills, or injecting)
- obtaining opioids illicitly
- resuming opioid use after a period (e.g. 7+ days) of not consuming (e.g. after incarceration, during a taper), as previous tolerance is lost.

Tramadol: additional potential harms with overdose include seizures & 5HT syndrome.

	VII	Cannabinoids: overdose may present as drowsiness/impairment which may result in hospitalization. The ↑ potency of edible cannabinoids or THC oil products has led to an ↑ in overdose as well, especially but not exclusively in children.[139,140,141]
H		**Mortality Risk**
H	II	Acetaminophen: mortality secondary to overuse is rare overall & primarily associated with acute overdose. Overuse may be inadvertent due to multiple products with acetaminophen, or overuse of an acetaminophen/codeine combination (e.g. Tylenol #1) when attempting to get codeine component.
	VI	Opioids: risk of all cause mortality appears higher for CNCP patients on opioids than for those on anticonvulsants or antidepressants.[142] There is an ↑ in non-fatal overdose risk (9x) in those at doses >100 MED/day, and overdose more likely to be fatal.[1,143] Deaths due to opioid related overdose (2016 Canada): 2,458.[144]
	VII	Cannabinoids: no RCT data. Cohort data unclear due to confounders. However, good evidence that cannabis use increases the risk of motor vehicle accidents.[145]
I		**Addiction / Substance Use Disorder (SUD) Risk**
I	V	Gabapentin: sometimes abused (snort or inject high dose for euphoria), or used to ease withdrawal from alcohol, cocaine. Some reports/concerns regarding opioid & gabapentin cross-abuse (potentiation of opioid; relaxed euphoria).[146] More likely with doses >3000mg/day Pregabalin: potential for abuse is a concern. MHRA (UK) has planned to move these agents to controlled drug status. FDA currently has pregabalin scheduled. Canada is aware, but has not changed schedule status.
	VI	Opioids: Hx of alcohol use disorder ↑ risk of opioid overdose, accidents, & injury rates.[147] CDN Guideline Meta-analysis (9 studies, n=22,278 patients): risk of opioid addiction was 5.5% even when taking opioids as prescribed.[1] Addiction risk did not appear to be related to dose; but greater in those with active SUD or unstable psychiatric disorders. Tamper-Resistant or Abuse-Deterrent designed formulations are available (see Table 8, Pg 23 of Pain Mini-book); however, evidence regarding their value and role vary. May have some potential to reduce misuse & abuse (e.g. injection use); however, none can deter abuse through oral ingestion of many tablets.[148,149] Tramadol: lower potency opioid but no evidence of less addiction risk/abuse[150]; misuse/abuse increasing in USA {about 250%, 2005 -2011 (6256 to 21,640 visits)}[151] Tapentadol: potential for abuse similar to μ-opioid analgesics, such as morphine & hydromorphone; underestimation/low incidence due to limited availability & use.[152]
	VII	Cannabinoids: due to recreational use/abuse & high potency, medicinal marijuana may be problematic. Risk of developing dependence to cannabis was ~ 9% in one study.[153]
J		**Gastrointestinal (GI) Risk**
J	III	NSAIDs: GI risk well appreciated in those with risk factors. Greater risk with higher doses, longer term therapy, & concomitant therapy with other drugs that increase bleeding. Consider prophylaxis (e.g. with standard dose PPI) in those at high risk. Topical NSAIDs associated with less risk than oral NSAIDs due to lower systemic levels.
	VI	Opioids: GI adverse event risk is increased.[154] One observational OA trial in older adults saw an ↑ bowel obstruction with opioids vs NSAIDs (HR=4.87). Constipation common!
	VII	Cannabinoids: while some cannabinoids (i.e. nabilone) are indicated for severe nausea/vomiting from cancer chemotherapy, trials paradoxically often show an increase in nausea versus placebo (e.g. rates of nausea, vomiting, or diarrhea were 30% in the cannabis group and 21% in the control group after 1 year in the **COMPASS** trial). As well, *Cannabinoid Hyperemesis Syndrome* is a rare but serious adverse effect.[155]
K		**Hepatic Risk**
K	II	Acetaminophen: (**see G** Overdose Risk) for those with chronic pain at ↑risk, consider monitoring LFTs (e.g. every 3-6 months). ↑risk if chronic/extensive alcohol use (≥ 3 drinks /day), those with liver disease, those who are malnourished, or others risk factors for hepatic disease.[156] Avoid or limit acetaminophen use (e.g. ≤2g/day) in those with cirrhosis.
	III	NSAIDs: hepatic risk uncommon with most; ↑ LFTs/risk with diclofenac & sulindac.[157]
	IV	Amitriptyline & Nortriptyline: hepatically metabolized; use with caution in hepatic dysfunction (no dosing adjustments specified in monograph). Venlafaxine: reduce dose by ~50% in mild to moderate hepatic impairment. Duloxetine: avoid in hepatic impairment.
	VI	Tramadol: IR (**ULTRAM**): if cirrhosis max dose recommended is 50mg q12h; ER (**ZYTRAM XL**, **TRIDURAL**, **RALIVIA**): avoid use if Child Pugh Class C; use caution if Child Pugh Class A or B. Opioids: drug exposure increases in cirrhosis, monitor and adjust dose as necessary.
	VIII	Cyclobenzaprine: caution in mild hepatic impairment (~doubles drug exposure); consider

		starting at lower dose and/or less frequent dosing; avoid if moderate/severe impairment.
L		**Renal Risk**
L	III	NSAIDs: may use if CrCl ≥30mL/min or if dialysis; avoid if CrCl <30mL/min (unless dialysis) & in transplant patients. Choosing Wisely Canada: don't prescribe NSAIDs in individuals with chronic kidney disease of all causes, including diabetes.[158]
	IV	Amitriptyline & Nortriptyline: renally eliminated; use with caution (no dosing adjustments specified in monograph). Venlafaxine: ↓ total daily dose by 25-50% dose if GFR ≤70mL/min. Duloxetine: avoid if CrCl <30mL/min or in dialysis.
	V	Pregabalin & Gabapentin: reassess dose if CrCl <60mL/min.
	VI	Tramadol: IR (**ULTRAM**): <30mL/min q12h dosing (max 200mg/d); ER (**ZYTRAM XL**, **TRIDURAL**, **RALIVIA**): <30mL/min avoid use. Morphine: metabolites may accumulate, causing AEs if CrCl <30mL/min. This is less of an issue at low doses; however, monitor & switch (e.g to hydromorphone) if problematic side effects.
M		**Cardiovascular (CV) Risk[159]**
M	III	Concern with all NSAID/COXIB: consider benefit/harm & select patients carefully; use lowest effective dose. - ↑ risk: diclofenac ≥150mg/day, indomethacin, celecoxib >200mg/day, meloxicam. - risk appears neutral[PRECISION]: naproxen ≤750mg/day, celecoxib[CONCERN] ≤200mg/day & ibuprofen ≤1200-?<2400mg/day.[160,161] **Choosing Wisely Canada**: don't prescribe NSAIDs in individuals with hypertension.[158]
	IV	TCA: ↓ BP, ↑HR, widen QRS (overdose), prolong QT interval. Venlafaxine: ↑ BP and HR, prolong QT interval.
	VI	Opioids: ↓ HR; tramadol & methadone at higher doses – may prolong QT.[162]
	VII	Cannabinoids: generally ↑ HR; variable effect on BP; inhaled marijuana associated with cardiovascular risk (may trigger an acute event).[163,164]
N		**Heart Failure (HF) Risk**
N	III	Oral NSAIDs: can exacerbate HF & lead to hospitalization due to Na^+ & water retention, ↑ systemic vascular resistance, ↑ BP, worsening renal function & diuretic resistance.[165,166,167] - Several heart failure guidelines recommend avoiding NSAIDs,[ESC'16 (IIIB), 168 ACCF/AHA '13 (IIIB)] or to use with caution.[CCS'06 (IB)] – **Choosing Wisely Canada**: don't prescribe NSAIDs in individuals with HF.[158] – The risk appears to be dose-dependent & can occur within days.[169] Topical NSAIDs: may also cause acute HF, but less likely compared to oral NSAIDs due to lower systemic levels. May use, but monitor HF status, weight, etc. – Only 6% of topical diclofenac is systemically absorbed (note: heat ↑absorption).[170] – Topical diclofenac does not appear to ↑ CV risk.[171,172] In an open-label RCT with 947 patients, topical diclofenac 1% 4g/day x 12 months did not ↑CV risk compared to placebo (10.2% had history of cerebrovascular or cardiovascular disease at baseline).[196]
	IV	TCAs: may cause postural hypotension, which can limit the titration of ACEI, ARBs or ARNI target doses. These agents also have negative inotropic & proarrhythmic properties. Reversible upon discontinuation.[189] SNRIs: there are 2 case reports of venlafaxine & duloxetine worsening HF;[173] however, a 2014 observational study in Ontario found that low to moderate doses of venlafaxine were not associated with an increased risk of HF compared to sertraline.[174]
	V	Gabapentinoids: can cause dose-dependent peripheral edema. An observational study from Ontario[2017] did not find an ↑ risk of HF with pregabalin use, compared to gabapentin.[175] Monitor weight/fluid status, & use with caution in patients with NYHA Class III or IV HF.
	VI	Opioids: sleep disordered breathing (e.g. sleep apnea) in HF patients increases the risks of opioids & other centrally sedating medications.[176]
	VIII	Gout is common in HF; avoid NSAIDs; consider corticosteroids or colchicine in acute gout.[177]
O		**Seizure Risk[178,179,180,181]**
O	III	NSAIDs: mechanism is unclear; NSAIDs potentially ↓prostaglandins which ↓seizure threshold. Reports with oral: indomethacin (50mg x1), ASA (500mg x1 or in overdose ?secondary to metabolic acidosis), diclofenac, mefenamic acid (toxic dose ≥60mg/kg).[182,183,184]
	IV	Antidepressants: low risk at therapeutic doses (exceptions are: clomipramine & bupropion), but ↑ risk with overdose[185,186] e.g. venlafaxine dose dependent risk (≥900mg).[187,188]
	V	Gabapentinoids: low risk; unless abrupt withdrawal in epileptic patients. Taper to stop.
	VI	Opioids: all may ↑seizure risk; but especially tramadol (associated with seizures at therapeutic & toxic doses e.g. seizure in 8% of patients >500mg).
	VII	Cannabinoids: cannabidiol likely effective in refractory pediatric Dravet syndrome to ↓ seizures.[189] In other seizure types, conflicting reports for both improving & worsening seizures.[190] Possibly increased seizure risk with increased potency.[191]
	VIII	Baclofen: associated with seizure upon withdrawal (including status epilepticus).[192] Cyclobenzaprine: seizures rare; however, structurally similar to TCAs.
P		**Falls and/or Fracture Risk**
P	IV	Antidepressants (especially TCAs): may result in ↑ falls/fractures due to BP drop (greatest with amitriptyline), and/or CNS & ACh side effects (e.g. ↓ alertness, balance, dizzy).
	VI	Opioids: have been associated with increased falls[193] & fractures[194,195] in observational studies. Those on ≥50 MED/d appear most at risk (HR=2). One OA study in older adults saw an ↑ in hip, humerus, pelvis, and wrist fractures (HR=4.47; NNH=26/yr) vs NSAIDs.[196] The first 2 weeks following initiation is a particularly high risk period for fractures.[197]
	VIII	Caution with 3+ CNS drugs. CNS effects additive & ↑ falls, especially in elderly.[198,199] Review potential drug causes and explore non-drug fall prevention measures.
Q		**CNS Adverse Effects (AE) - alertness, drowsy, dizzy, coordination, balance**
Q	III	NSAIDs: reports of cognitive dysfunction, esp in elderly. Most reports with indomethacin.[200]
	IV-VIII	Antidepressants, gabapentinoids, opioids, cannabinoids, muscle relaxants: all notable for CNS AEs. Start low, go slow; use lowest effective dose; caution with polypharmacy (**see P-VIII** Falls and/or Fracture Risk); consider giving larger portion of daily dose in evening/HS; evaluate patient & adjust dose/regimen. Counsel patients that AEs diminish over ~3-10d when dose/regimen stabilized. Allow for adequate trial to assess tolerability.
R		**ACh Adverse Effects (Anticholinergic Adverse Effects)**
R	-	A common AE, especially with TCAs (amitriptyline > nortriptyline). May manage dry mouth with a) non-pharmacological options, b) OTC saliva substitutes, or c) pilocarpine rinse.
S		**DIs (Drug Interactions)**
S	III-VIII	Many of these medications have similar AE profiles and combinations may lead to potentiation of these AE, for example: CNS: TCAs, SNRIs, gabapentinoids, opioids, cannabinoids ACh: TCAs, opioids Weight gain: TCAs, gabapentinoids, cannabinoids 5HT (i.e. serotonin syndrome): TCAs, SNRI, SSRIs, tramadol QT prolongation: TCAs, ?SNRI, methadone, tramadol GI bleeds: NSAIDs, SSRIs
T		**Weight Gain**
T	I	Non-drug treatment: interventions (e.g. exercise, dietary, ↑ activity) will help limit the weight gain often seen in deconditioned patients, or with drug therapy.
	IV	TCAs: notable for weight gain, especially amitriptyline. Duloxetine may result in weight gain or weight loss.[201]
	V	Gabapentin & Pregabalin: weight gain common with both agents.[202]

DI: Ibuprofen/naproxen & ASA for CV prevention: consider alternate NSAID, or give NSAID 30 minutes after, or 8hrs before ASA.

	VI	Opioids: potential for weight gain or weight loss (particularly in overuse/abuse); when used at usual doses for pain, weight gain is seldom an issue.
	VII	Cannabinoids: weight gain possible side effect (? due to ↑ appetite). Deconditioning is common in CNCP patients; give attention to diet & exercise.
U		**Tolerability**
U	III	Topical NSAIDs: are very well tolerated, with AE rates similar to placebo.
	IV	Antidepressants: all except nortriptyline escalating doses of 25-100mg/day had AE>placebo.[203] Duloxetine: may be associated with a higher rate of discontinuation due to AE especially at >60mg/d (**see A-IV** LBP, **C-IV** Neuropathic Pain, & **D-V** Fibromyalgia). AEs of antidepressants reversible & NOT associated with any structural organ damage. RCT with amitriptyline 75mg/day, duloxetine 120mg/day, pregabalin 600mg/day & placebo in PDN found equal analgesia, but differences in tolerability (equal QOL; pregabalin worse for daytime functioning, ↑D/C due to AEs, but better effect on sleep per polysomnograph).[58]
	V	Gabapentinoids: CNS side effects, especially dizziness & somnolence, are common. Pregabalin: may be associated with a higher rate of discontinuation due to AE especially at >300mg/d (**see D-V** Fibromyalgia).
	VI	Opioids: as doses increases, serious harms also increase.[204] A systematic review of predominately uncontrolled trials ≥6 months found ~30% of oral opioid users discontinued therapy due to AE or lack of benefit.[205] **Set Functional Goals & Monitor!**
	VII	Cannabinoids: numerous formulations available with varying potency and toxicity. Common dose dependant AEs: dizziness, sedation, confusion, dissociation, euphoria. - Potential increase risk of:[206] motor vehicle collisions, mania in non-bipolar population, psychosis, ? cognitive dysfunction. Other, serious uncommon AE: ↑ infectious disease complications (e.g. aspergillosis).[207,208] **Set Functional Goals & Monitor!**
V		**Psychiatric Disorders**
V	I	Non-drug treatment: several non-drug therapies (e.g. CBT, mindfulness) are effective & valuable in treating psychiatric disorders.
	III	NSAIDs: indomethacin & potentially sulindac are associated with acute disorientation, paranoia, or hallucinations, which is more common in elderly.[209]
	IV-VII	These drug classes have significant CNS & anticholinergic AEs and extra vigilance is warranted in elderly due to the potential for these drugs to cause delirium.
	VI	Opioids: low quality evidence suggests ↑risk of very serious AEs (non-fatal overdose & death) in patients with serious psychiatric disorder.[1] Addiction risk also ↑.[1] Stabilizing psychiatric disorder advised before considering an opioid trial.[1] Depression/anxiety/mood disorder: common comorbidity in opioid users;[210] caution necessary when prescribing opioids in this population.
	VII	Cannabinoids: data from the one year **COMPASS** trial showed a 27% risk of psychiatric disorders (vs 11% in control group, NNH = 6), including depression, anxiety, euphoria, panic attack, paranoia, apathy, & hallucination.[155] Evidence for benefit in post-tramatic stress disorder (PTSD) is inconclusive.[211]
W		**Pregnancy/Lactation** (Risk symbols from RxFiles Comparison Charts)[212]
W	II	Acetaminophen: P L possible association with behavioural & hyperkinetic disorders.[213]
	III	Oral NSAIDs:[214,215,216] P_1, P_2, P_3 ? block implantation, miscarriage, malformations, premature ductus arterious closure, cryptorchism, inhibit labour, fetal renal toxicity. L ibuprofen (preferred), naproxen, celecoxib. Topical NSAIDs: likely safe.
	IV	TCA: P L more experience vs SNRIs; ↓ levels in breastmilk (<10% maternal dose); SNRI: P L
	V	Gabapentinoids: P L limited data (more with gabapentin vs pregabalin). Monitor baby for drowsiness, poor feeding/weight gain if breastfeeding. Risk of fetal malformations and intrauterine death similar to general population, but associated with low birth weight.[217,218]
	VI	Opioids:[219] $P_{1,2}$ codeine, tramadol; P for other commonly used opioids. Third trimester and ≥30 days of use may cause neonate depression & withdrawal. Abrupt D/C may cause premature labour & spontaneous abortion. Taper to lowest effective dose. ▪ L codeine, tramadol –↑toxicity in ultra-rapid CYP2D6 metabolizers (FDA warning);[220] oxycodone. Monitor baby for limpness, difficulty breathing/feeding, or ↑ sleep. ▪ L morphine, hydromorphone, methadone, fentanyl.
	VII	Cannabinoids: P L associated with impaired neurodevelopment, ?stillbirth, & ?↓ fetal growth. Lactation: insufficient data. Discourage use during preconception, pregnancy, lactation.[221] ACOG'15 (ungraded)
X		**Cost / month:** see Pain Medication – Trial Dosages, Regimen Options & Costs Chart
X	I	Non-drug treatment: some can be inexpensive & built into routine/lifestyle. Others can be quite costly. Success requires availability, affordability & coordination. Multidisciplinary team approaches are part of many successful interventions; unfortunately this type of support is not always available (or affordable).
	II	Acetaminophen: acetaminophen 650mg q6h ($5); ER TYLENOL ARTHRITIS 1.3g q8-12h ($20)
	III	Oral NSAID: Naproxen 375mg BID ($20) Topical NSAID: OTC diclofenac ($26) 2x150g Prescription diclofenac $26-92
	IV	Antidepressants: Amitriptyline 75mg HS ($23) Venlafaxine 150mg daily ($22); Duloxetine 60mg daily ($42)
	V	Gabapentinoids: Gabapentin 600mg TID ($42); Pregabablin 150-225mg BID ($48-76)
	VI	Opioids: Tramadol ($45-167) (**TRIDURAL** - **ZYTRAM XL**); Morphine SR 30mg q12h ($33), 60mg q12h ($51); Hydromorphone SR 6mg q12h ($81), 12mg q12h ($133)
	VII	Cannabinoids: Nabilone ($112); **SATIVEX** ($240/vial) *CanniMed*(SK dispensary): **Dried**: 1.5g/d ($200-400)avg dose 2.5g/d in COMPASS **Vaporizers**: ($229-669) **Oil**: 60mL bottle ($129-169) [may last some on low doses e.g. 0.5mL/d up to 3 months]
Y		**Other**
Y	I	Non-drug treatment: ▪ Pain reduction and improved function, not pain elimination, is the goal of drug therapy. Those with CNCP must be helped to refocus on positive, incremental gains. Dedicated therapists &/or CNCP programs are helpful. ▪ Address Fear/Avoidance of Physical Activity: fear-avoidance beliefs hold a stronger relation to disability & poor pain rehabilitation outcomes than does pain intensity. ▪ Education, behavioural, psychosocial, physical & other therapies (e.g. music) are essential for successful long-term management. **Encourage "self-help" approaches.** ▪ {Consider role of concomitant: exercise, pacing, heat, ice, TENS, CBT, relaxation, spiritual, ♫ music therapy, acupuncture, yoga, massage, tai chi etc.} ▪ Multidisciplinary interventions may ↓ drug requirements. Programs that simultaneously address physical, psychological & functional aspects may be needed for some.
	V	Gabapentinoids: combining a gabapentinoid (e.g. gabapentin) with a TCA (e.g. nortriptyline) or an opioid (e.g. morphine) in neuropathic pain may be more efficacious than either drug alone; however, overlapping AE profiles including CNS AEs may adversely affect function.[222,223]
	VI	Opioids: several potential dose dependent AEs with higher-dose, long-term use. Hyperalgesia, where there is a central sensitization to pain, may result in loss of effectiveness. Effectiveness may return after deprescribing the opioid. High doses (e.g. ≥120 MED/d) of opioids associated with lower testosterone & need for treatment if symptomatic.[224] Opioid patient education: - Navigating Opioids for Chronic Pain: https://www.cpd.utoronto.ca/opioidprescribing/navigating-opioids/ - Best Advice for People Taking Opioid Med (Doc Mike Evans): www.youtube.com/watch?v=7Na2m7lx-hU FDA warnings (opioids in general): • Opioids can interact with antidepressants and migraine medicines to cause serotonin syndrome. Patients taking an opioid along with a serotonergic medicine should seek medical attention immediately if they develop symptoms such as agitation; hallucinations; rapid heart rate; fever; excessive sweating; shivering or shaking; muscle twitching or stiffness; trouble with coordination; and/or nausea, vomiting, or diarrhea • Taking opioids may lead to a rare, but serious condition in which the adrenal glands do not produce adequate

		amounts of cortisol. Patients should seek medical attention if they experience symptoms of adrenal insufficiency such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure. • Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility.

▼on NIHB ☎ =EDS Sask ✆=prior NIHB ✗ =Non Formulary SK ⊗ = not covered by NIHB **#**=fracture **2°** =secondary **5HT**=serotonin activity **ACh**=anticholinergic **ACP**=American College of Physicians **AE**= adverse events **am**=morning **ANRI**=angiotensin-receptor neprilysin inhibitor **BID**=twice daily **BP**=blood pressure **BZ**=benzodiazepine **CBD**=cannabidiol **CBT**= cognitive behavioural therapy **CDN**=Canadian **CNCP**=chronic non-cancer pain **CNS**=central nervous system **COXIB**=selective cyclooxygenase 2 inhibitor **CPS**=Canadian Pain Society **CrCl**=creatinine clearance **CV**=cardiovascular **d**=day **D/C**=discontinue(d) **DI**=drug interaction **ER**=extended release **esp**=especially **EtOH**=alcohol **EULAR**=European League Against Rheumatism **FDA**=Food & Drug Administration **Fx**=function **GI**=gastrointestinal **GFR**=glomerular filtration rate **HF**=heart failure **HR**=heart rate or hazard ratio **HS**=bedtime **Hx**=history **IBS**=irritable bowel syndrome **K+**=potassium **LBP**=low back pain **LFT**=liver function test **MED**=morphine equivalent dose **MMD**=major mood disorder **mo(s)** =month(s)**MS**=multiple sclerosis **MSK**=musculoskeletal **N**=number of studies **n**=number of subjects **NICE**=National Institute for Health & Clinical Excellence **NNH**=number needed to harm **NNT**=number needed to treat **NRS**=numeric rating scale **NS**=non-significant **NSAID**=non-steroidal anti-inflammatory drug **OA**=osteoarthritis **OTC**=over the counter **PDN**=painful diabetic neuropathy **PHN**=post-herpetic neuralgia **PPI**=proton-pump inihibitor **PTSD**=post traumatic stress disorder **QID**=four times daily **RCT**=randomized controlled trial **RD**=risk difference **Rx**= prescription **SCI**=spinal cord injury **SNRI**=serotonin norepinephrine reuptake inhibitor **SR**=sustained release **SSRIs**=selective serotonin reuptake inhibitor(s) **SUD**=substance use disorder **sx**=symptoms **TCA**=tricyclic antidepressant(s) **THC**= delta-9-tetrahydrocannabinol **TID**=three times daily **TN**=trigeminal neuralgia **tx**=treatment **UDS**=urinary drug screen **VAS**= visual analogue scale **wk(s)**=week(s) **Wt**=weight

References – Chronic Pain Outcomes Comparison Chart - www.RxFiles.ca (Duplicates to be removed in future printing)

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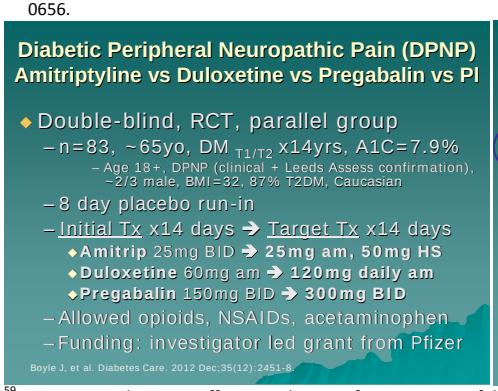

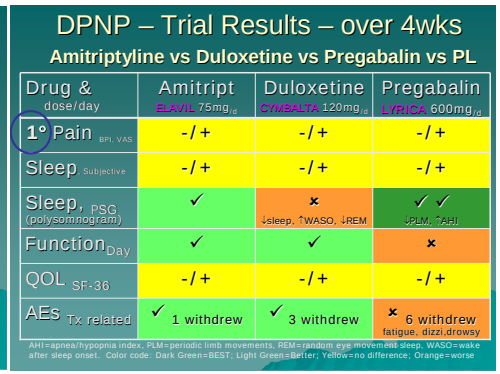

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Prescribing Opioids Safely in Chronic Pain [1]

A Crawley BSP, L Regier BSP © www.RxFiles.ca Nov 2017

It is impossible to predict which patients will run into trouble with their opioids. One effective practice is to apply "universal precautions" to all opioid patients - which also reduces stigma.[10]

Table 1: Quick Checklist for Opioid Prescribing

Useful Opioid Manager Tool: nationalpaincentre.mcmaster.ca/opioidmanager

SET UP (Steps ❶❷❸❹)

- ❑ Non-opioid approaches are being optimized
- ❑ Check electronic health records (i.e. PIP in SK)
- ❑ Baseline urine drug screen
- ❑ No initial red flags? (see Table 2)
- ❑ Assess risk of adverse effects
- ❑ Assess risk of overdose, addiction
- ❑ Patient understands opioid prescribing is a trial
- ❑ Obtain Treatment Agreement & Informed Consent

MONITORING (Step ❺)

- ❑ Check electronic health records & random urine drug screens
- ❑ Non-opioid approaches continue
- ❑ Opioid is providing benefit?
- ❑ Risk of overdose remains low?
- ❑ Calculate morphine equivalent dose (MED)
- ❑ Adverse effects are tolerated?
- ❑ No ongoing red flags? (see Table 4)

EXIT (Step ❻)

Discuss opioid trial/course in terms of resulting pain/functional status. Taper &/or discontinue opioid as appropriate. Monitor & follow-up.

❶ Optimize non-opioid interventions first.

CDN Guidelines Strong Recommendation

Opioid prescribing is [sometimes] a surrogate for inadequate pain management resources.[4]

- **A non-pharmacological approach** to pain management is essential for successful long-term management. This may include: **exercise** (NNT 4-8)[5], **behavioural tx** (an excellent patient-led approach available through Positive Coping with Health Conditions www.comh.ca/pchc), multidisciplinary rehab, acupuncture, mindfulness, acceptance & commitment tx, stress reduction, tai chi, yoga, sleep hygiene, psychosocial interventions, hypnosis, music tx, TENS, RICE (rest, ice, compression, elevation), low level laser tx, heat/cold, positioning, massage tx ...
- **Non-opioid pharmacotherapy** for pain includes acetaminophen, ASA/NSAIDs (oral/topical), TCAs, SNRIs, anticonvulsants, capsaicin topical, etc. (see Chronic Pain Tx Considerations chart). Trial requires adequate dose & adequate duration.

❷ Prevent issues by assessing patients carefully.

It's OK to say "no" to prescribing an opioid if harm likely to outweigh benefit (see Table 7 - ways to say "no").

- **Confirm through electronic health records** (e.g. PIP in Saskatchewan) and a **baseline urine drug screen** that your "opioid-naïve" patient really is opioid-naïve. Watch for red flags for drug-seeking behaviour (Table 2). Ask for photo ID if patient is unfamiliar.
- **Assess risk of harm** (adverse effects, overdose, and addiction):[6]
  - ➢ Check for other agents that can affect the CNS: e.g. **alcohol**, **benzodiazepines/sedatives**, marihuana, cocaine, anticholinergics ...
  - ➢ Comorbidities which ↑ risk of overdose: elderly, renal impairment, hepatic impairment, COPD, sleep disorders e.g. sleep apnea.
  - ➢ Psychiatric comorbidities: guidelines recommend avoiding trials of opioids in patients with an active substance use disorder and suggest avoiding in patients with an unstabilized psychiatric disorder.[1] Low quality evidence shows a higher addiction risk in these patient groups (~8% vs 5.5% risk).[1] Involvement of a mental health practitioner can be extremely useful in patients needing concurrent psychiatric care (e.g. issues of central dysregulation of pain, impulsiveness, or somatization).
  - ➢ Addiction risk can be assessed with the Opioid Risk Tool (ORT): nationalpaincentre.mcmaster.ca/opioid/cgop_b_app_b02.html
  - ➢ Older/Frail Adults: Assess risk of delirium, dementia, and falls. Adjust therapy and follow-up accordingly.

Table 2: Red Flags for Drug-Seeking Behaviour

- "Allergies" to weak opioids or NSAIDs.
- Knows clinical terms/street names for drugs.
- Requests specific drugs & has perfect story.
- Signs of intoxication or abuse.
- Patient is from outside the local area.

Seek collaborative information.
Set boundaries.
Caution if pressured to cross boundaries.
Accept, but don't fall for "the compliment" or other emotional manipulation.

❸ Prevent issues by setting expectations early.

- Patients should expect opioid prescribing to be in the context of a **trial**.
  - ➢ Some, but not all pain patients benefit from opioids. If an opioid is not working (i.e. function not improving; pain scores still high), then "*it may not be right for you*".

10 people given opioids & supporting care for 3-6 months[1]

~ 4 people: no response	**~ 1** person: response to opioid & supporting care	**~ 5** people: response, but also would have responded to continuing previous care

- Advise of the **potential opioid harms, emphasizing those associated with higher doses**.
  "You may get some pain relief, but that may come with drowsiness, constipation, sweating ..."
- Advise patients that opioid use comes with **responsibility**.
  "That's why I routinely discuss important information, obtain informed consent/treatment agreement, and obtain a baseline & periodic urine drug screens for all my patients on opioids." See Step 4 below.

Table 3: Aspects of a Practical Opioid Trial in Chronic Non-cancer Pain (CNCP)

Ensure non-pharm approaches are simultaneously pursued throughout opioid trial!

- **Trial Duration**: Perhaps 3 months; consider an additional 3 months if more info needed.
- **Initiation**: Low dose e.g. morphine ≤5mg po Q6H (or weak opioid e.g. tramadol), with a small quantity of tabs. Note: Generally avoid PRNs in CNCP unless targeted at incident pain.
- **Goals of Therapy**: Individualize. Consider how pain affects the physical, psychological, social, & spiritual aspects of the patient's life. Goals may include improvement in function and/or pain. Functional goals should be specific and emphasized more than pain scores.
- **Assessment Interval**: Early (e.g. in 3 to 14 days), then monthly for tolerability and benefit.
- **Assessment Parameters**: Goals of therapy; red flags (see Table 4); adverse effects (e.g. nausea, constipation, drowsiness, itch); calculate total daily morphine equivalent dose; urine drug screen (baseline and at least once during trial period). See Step 5 below.
- **Dose Increases**: Limit number of dose escalations to 2–3x during the trial (this also facilitates staying within maximum recommended doses from the 2017 guidelines).
- **Exit Strategy**: Discuss up-front & define expectations early. Reassure. See Step 6 below.

❹ Reinforce expectations by using a *Treatment Agreement* and obtaining *Informed Consent*.

⇒ Treatment Agreements with Informed Consent will formalize and clarify the expectations outlined in Step 3.
e.g. necessity of engagement in non-pharm approaches; use of one pharmacy; use of one doctor; safe disposal & storage of the medication (lock box); taking opioids only as prescribed; avoidance of illicit substances; urine drug testing; no driving if sedated or decreased alertness (usually with new opioid initiation or dose increases)

⇒ Share the Treatment Agreement with all involved parties (including the patient's community pharmacy).

Visit www.RxFiles.ca for samples of customizable *Treatment Agreements with Informed Consent* (search "agreement").

❺ Prevent issues through ongoing monitoring and documentation.

Useful Opioid Manager Tool for documentation: nationalpaincentre.mcmaster.ca/opioidmanager

- Assess early (e.g. in 3-14 days), then monthly, then adjust frequency to patient.
- DOCUMENT all encounters and especially all red flags (Table 4) to help identify patterns.
- Communicate plan to all team members (e.g. pharmacy, multidisciplinary team members).
- Prevent forgery through best practice prescribing (Table 6).

What to assess at each visit:

- **Check the electronic health record** (e.g. PIP in SK) for fill dates, double doctoring, and multiple pharmacy use. Order **urine drug screens** as indicated: www.rxfiles.ca/rxfiles/uploads/documents/members/Urine-Drug-Screening-UDS-QandA.pdf **(NOTE: Random screens most effective as they make it much harder to manipulate the test result.)**
- **Calculate current morphine equivalent dose (MED)**. Guidelines suggest that for most new patients, little additional benefit is gained with doses greater than 50-90mg MED/d, while risk of adverse effects and overdoses rises.[1] Referral for a second opinion may be valuable if escalating the dose beyond 90mg morphine equivalents.
- **Are non-opioid interventions still optimized?** Continue emphasis on non-opioid/non-drug tx.
- **Is the opioid providing benefit?** e.g. progress on functional goals, original diagnosis still valid
- **Are adverse effects tolerated?** e.g. GI issues, drowsiness, itch, hypogonadism, hyperalgesia
- **Are there any red flags for aberrant prescription drug use?** e.g. see Table 4.
- **Is the risk of overdose still low?** e.g. no new comorbidities, no new CNS depressants.

Table 4: Red Flags for Aberrant Prescription Drug Use

- Rapid ↑ in doses / frequent changes needed / unsanctioned dose increases.
- Refusal to engage in non-pharm or non-opioid therapy ("*nothing else works*").
- Requests for replacement Rx for lost, stolen, or spilled opioids.
- Frequent requests for early refills ± dramatic stories.
- Requests for brand name (instead of generic) or short-acting (instead of long-acting) products. [These products have a higher street value.]
- Missed follow-up assessments.

Table 5: When are naloxone kits (for overdose prevention) recommended?[1]

- Anyone who may come in contact with an opioid overdose situation.
- Those with risk factors for opioid overdose, including: opioid use disorder, previous overdose history, high opioid doses (e.g. >90 MED/d), comorbidities (e.g. elderly, renal impairment, hepatic impairment, COPD, sleep apnea), or concomitant CNS depressants (e.g. benzos, alcohol) without judegement.
- Those who were on high opioid dosages and are tapering or have tapered their opioid use (as these patients may try to re-initiate opioids at their previous dose).

Universal Precautions

- treatment agreements
- informed consent
- urine drug screen: baseline & at least annually
- check electronic records (PIP)
- initial red flags (Table 2)
- concept of "trial" (Table 3)

Ongoing monitoring: more structure needed

e.g. ↑ lines crossed
e.g. ↑ red flags

Universal Precautions Plus

- Add/↑ random urine drug screens
- Adjust quantity limits
  e.g. biweekly → weekly → daily dispenses
- Potentially blister pack medications
- Naloxone to prevent overdoses (Table 5)
- Consider tamper-resistant formulations, 24hr formulations, random pill counts by pharmacy, and patch-exchange programs (Table 8)
- Engage exit strategy (Step 6)

Table 6: Ways to Prevent Forgery

- Avoid leaving space for alterations (e.g. "5mg"; not " 5 mg").
- Fill unused space on prescription with a pen stroke/scribble.
- Use numerical & written form for quantities. e.g. disp: # fifteen [15 only].
- Secure prescription pads to prevent theft, and number sequentially.
- Fax or electronically send (e.g. on PIP) prescriptions to the patient's pharmacy, rather than directly giving patients the prescription.

Sample Rx: Hydromorph Contin 3mg (three) po BID. **Mitte**: 56 (fifty-six) caps to be released in quantities of 28 (twenty-eight) every 14 days.

❻ Engage exit strategy when needed.

Exiting means a discontinuation or dose reduction of an opioid, and may occur when issues arise during routine monitoring.

- **Tapering** is important to prevent withdrawal and may have a high rate of success.[7,8] Rule of thumb: ↓ by 5-10% every 2-4 weeks (go slower as taper gets closer to finishing). Rotating to a lower dose of a different opioid may help. If exit was engaged after a failed trial, then important to fully exit. Template: www.rxfiles.ca/rxfiles/uploads/documents/Opioid-Taper-Template.pdf
- Take a multidisciplinary **team approach** whenever dealing with the problem of misuse & diversion of prescription drugs.[1,9] Consider referral to an addictions medicine specialist. Continue to pursue non-opioid strategies. If resistance to the exit, see Table 7. Note: some patients will report LESS pain after tapering.[7,8] *Ensure the patient doesn't feel abandoned!*

Additional Tips: ★ **Consider 7, 14, or 28 day fill intervals** to help avoid weekend dispenses when physicians are unavailable & pharmacies are closed. ★ **Consider avoiding codeine products**, since slow CYP2D6 metabolizers may get ↓effect, while hypermetabolizers may get toxic levels. ★ **Consider avoiding oxycodone products**, since oxycodone may have ↑ euphoria.[12] ★ **Avoid morphine in renal insufficiency** due to build-up of toxic metabolites. ★ **Select patients carefully for acetaminophen-opioid combo products** (e.g. TYLENOL #3, PERCOCET), as overdose/misuse can come with extra problems. Half of acetaminophen liver failures are from opioid combo products![11]

CNS=central nervous system **MED**=morphine equivalent dose **ORT**=Opioid Risk Tool **PIP**=Pharmaceutical Information Program **TENS**=transcutaneous electrical nerve stimulation

Table 7. My patient is pressuring me to start or continue opioids. How do I say "no" while maintaining a positive relationship?[6]

"If you feel starting a prescription for an opioid might not be a good idea for your patient at any point in a consultation, you have an opportunity to stop and communicate to the patient your concern and reasons around not initiating opioids. Although it may be uncomfortable at first to say no, in the long run you are doing your patient a great service and practicing compassionate, evidenced-based medicine." -Sarah Liskowich, MD, CCFP

Use active listening skills. Sit with the patient to bring you to the same level. Listen to the patient's story, and reflect his/her words back to show that you're listening. Ask questions with a neutral tone. Does he or she perceive a large benefit with opioids? Are his or her expectations unrealistic (e.g. a goal of "zero pain")? Do opioids provide an "escape" from difficult life circumstances? Is there fear of withdrawal, or fear of unmanageable pain? Ensure your patient knows that you care about him/her, and want him/her to do well.	*-It sounds like there's a lot of stress in your life right now.* *-You're saying the pain is making you feel desperate and edgy.* *-I know you're going through a tough time right now, and I'm really sorry about that.*
Where possible, gather objective facts. These may include: pain scores over time, assessment of changes in function, adverse effects, previous history, risk of overdose or addiction (e.g. calculation of ORT score). This is also where documentation of red flags (e.g. requests for early refills, see Table 4) is important. Involving a colleague for a second opinion can also bring in valuable information. In the absence of objective facts, consider no therapy changes for a short period (e.g. 3 months) with clear criteria for how a decision will be made after that time.	*-It is my professional responsibility, in providing the best possible patient care, to only prescribe medications when it can be done safely.* *-I cannot in good conscience prescribe a medication that could harm or kill you.* *-You've told me Dilaudid works, but what else have you tried?* *-Before moving ahead, I will need to obtain and consider the initial assessment report regarding your accident and resulting injuries.* *-I haven't met you before, and can't prescribe these types of drugs on the first visit before I have a full history.*
Use the patient's history +/- objective facts to explain your decision. Sometimes focusing on the safety issues of opioids can be valuable (e.g. risk of overdose, presence of adverse effects). It is also helpful to reframe the goal from "pain relief" to "function restoration". It's OK to be honest and straightforward about your reasons for wanting to stop or avoid opioids; in fact, the situation can be viewed as an opportunity to educate patients. **If you are feeling emotionally pressured, or threatened,** it's OK to excuse yourself from the room and/or confer with a colleague. Avoid responding to emotion with emotion, and avoid prescribing emotionally. Try to keep your feelings and the medical facts separated.	*-It looks like opioids just don't work well for you. I have noticed that...* *-This opioid seems to be doing more <u>to</u> you, than <u>for</u> you.* *-When we first started opioids, your pain was not controlled. Now you are on a high dose of opioids and having side effects ... but your pain is still not controlled. It might seem hard to believe, but if we pull back on the opioids you may actually feel better than you do now.* *-When I look at your medical history and other medical conditions, I worry that your risk of overdose with this medicine is just too high.* *-If we combined an opioid with your sleep apnea, it could slow down your breathing too much, even to the point of stopping.* *-From what you've told me, I think stress is adding to your pain, and an opioid is not the best way to treat that problem.* *-In the long run, opioids will actually change the way your brain perceives pain. Numbing the pain for a while will make it worse when you finally feel it.*
Provide an alternate plan to show that you still support your patient. Encourage non-pharmacological therapies; offer non-opioid medications. Potentially, advise the patient that the pain may resolve on its own without opioids. Referring to a colleague for a second opinion may be helpful. Refer to an addictions medicine specialist if necessary. If discontinuing an opioid, provide reassurance that the opioid will be tapered slowly to prevent withdrawal symptoms. Aim to be polite but firm!	*-We've talked about some options that may help you control your pain. Out of all those, what would you like to try?* *-There is a strong connection between feeling down and pain, so would you be willing to meet with our mental health specialist?* *-In the meantime, let's work together with your pharmacist on a gradual tapering plan.* *-I know you can do this, and I'll stick with you through it.*

Table 8: Formulations that were designed to help deter abuse[13]

- **Tamper-resistant formulations to deter injection**: **OxyNEO** (oxycodone), **NUCYNTA** (tapentadol), **TARGIN** (oxycodone/naloxone), **SUBOXONE** (buprenorphine/naloxone)
- **Once daily products to facilitate directly-observed therapy**: **KADIAN** (morphine), **JURNISTA** (hydromorphone)
- **Patches to couple with patch-exchange**: **DURAGESIC** (fentanyl), **BUTRANS** (buprenorphine)

References: Prescribing Opioids Safely: available online at www.RxFiles.ca
http://www.rxfiles.ca/rxfiles/uploads/documents/members/Prescribing%20Opioids%20Safely.pdf

Additional Useful Links / Phone Numbers

★ Canadian Clinical Guidelines: www.cfpc.ca/2017_canadian_guideline_opioids_chronic_non_cancer_pain
★ American CDC Clinical Guidelines: www.cdc.gov/drugoverdose/prescribing/guideline.html
★ Patient Handout: www.ismp-canada.org/download/OpioidStewardship/opioid-handout-bw.pdf
★ Pocket Guide for Tapering: www.cdc.gov/drugoverdose/pdf/clinical_pocket_guide_tapering-a.pdf
★ Drug Information service for Saskatchewan clinicians: medSask 306-966-6340 or 1-800-667-3425
★ Saskatchewan College of Physicians – Prescription Review Program 306-244-7355
★ Saskatchewan Provincial Lab – (Urine Drug Screens): 306-787-3383

RxFiles: OPIOID AND PAIN RELATED LINKS

www.RxFiles.ca

Available Via Subscription (Individual or Group) to *RxFiles Online* & Free to Health Professionals in SK

Chronic Pain Treatment Colour Chart – Pain Meds, Comparison of Benefits & Harms (New Nov 2017)
http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Pain-Tx-Outcomes-Colour.pdf

CNCP Treatment Overview Chart
http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Pain-Chronic-NonCa.pdf

Opioids Drug Comparison Chart (Updated Nov 2017)
http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Opioid.pdf

Opioid Related Constipation Chart
http://www.rxfiles.ca/rxfiles/uploads/documents/members/Opioid-Induced-Constipation-QandA.pdf

Pain Approaches Comparison – Acute/Palliative/CNCP (Updated Nov 2017)
http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-Pain-Approaches-Acute-Palliative-CNCP.pdf

Pain Overview, Q&A & Acute Pain Chart (Updated May 2017)
http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-PAIN-Acute-Tx.pdf

Prescribing Opioids Safely (New Sept 2017)
http://www.rxfiles.ca/rxfiles/uploads/documents/members/Prescribing%20Opioids%20Safely.pdf

Available Free

Patient Consent & Agreement - Opioid
http://www.rxfiles.ca/rxfiles/uploads/documents/Opiod-Informed-Consent-And-Agreement.pdf

Opioid Tapering (Updated Oct 2017) Chart and Template
http://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-Taper-Template.pdf

Opioid / Fentanyl Patch Exchange Tool
http://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-Patch-Exchange-Disposal-Tool.pdf

Opioid Clinic Policy - Sample
http://www.rxfiles.ca/rxfiles/uploads/documents/members/Opioid-Controlled-Substance-Rx-Clinic-POLICY.pdf

Pain Management in Older Adults

a) Geri-RxFiles Section: Pain Management in Older Adults – Updated Feb, 2017
http://www.rxfiles.ca/rxfiles/uploads/documents/GeriRxFiles-Pain.pdf

b) Q&A: http://www.rxfiles.ca/rxfiles/uploads/documents/GeriRxFiles-Pain.pdf

c) CFP Article (2011): http://www.cfp.ca/content/57/8/907

Flow Sheet – Opioids and Controlled Substances
http://www.rxfiles.ca/rxfiles/uploads/documents/Opioids-Controlled-Substance-RX-FLOW-SHEET.pdf

Urine Drug Screening Q&A
http://www.rxfiles.ca/rxfiles/uploads/documents/members/Urine-Drug-Screening-UDS-QandA.pdf

Opioids & Chronic Non‐Cancer Pain (CNCP) ‐ What Can Pharmacists Do to Better Address Both "Pain" & "Addiction/Diversion" Concerns?
http://www.rxfiles.ca/rxfiles/uploads/documents/Pain-Opioids-Pharmacists-QandA.pdf

RxFiles Pain Management and Opioids Newsletter – (New Nov 2017)
http://www.rxfiles.ca/rxfiles/uploads/documents/Opioids-Pain-2017-Newsletter.pdf

PainLinks: Resources for Those Living with Pain (For SK Residents) – (New Nov 2017)
www.RxFiles.ca/PainLinks

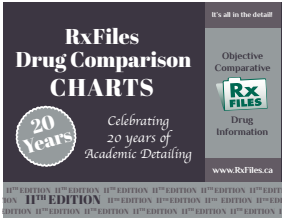
Other Links:

Chronic Non-Cancer Pain & Appendices – (March 2017) – thewellhealth (CEP)
https://thewellhealth.ca/wp-content/uploads/2017/03/CEP_CNCP_Main_V1.pdf
https://thewellhealth.ca/wp-content/uploads/2017/03/CEP_CNCP_Appendix_V1.pdf

ISMP - Opioid Pain Medicines; Information for Patients and Families
https://www.ismp-canada.org/download/OpioidStewardship/opioid-handout-bw.pdf

Opioid Manager Tool from 2011 (facilitate guideline implementation)
http://nationalpaincentre.mcmaster.ca/opioidmanager/

2017, May 08 - Canadian Guideline for Opioids for Chronic Pain
http://nationalpaincentre.mcmaster.ca/guidelines.html



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