If Not Opioids then what…

LEAH EDMONDS

CSHP OCTOBER 26, 2017

Disclosure

- Nothing to disclose

Objectives

Identify various non-opioid options for the treatment of **chronic non cancer pain**

Choose appropriate non-opioid therapy for the treatment for **chronic non cancer pain** based on available evidence in the medical literature

What is Chronic Non Cancer Pain?

Chronic non cancer pain includes any painful condition that persists for at least three months and is not associated with malignant disease

According to seven national surveys conducted between 1994 and 2008, 15%–19% of Canadian adults live with chronic non cancer pain.

What is Chronic Non Cancer Pain?

Neuropathic: damage or pathology to the central nervous systems (central or peripheral	• Trigeminal neuralgia • Diabetic peripheral neuropathy • Idiopathic Neuropathy • Post herpetic neuralgia • Post Stoke pain • Multiple Sclerosis
Nociceptive	• Osteoarthritis • Chronic low back pain • Inflammatory arthropathies • Fibromyalgia
Central Sensitization	• Complex regional pain syndrome

Should it ever be opioids?

2017 Canadian Guidelines For Chronic Non Cancer Pain

- **<u>Recommendation 2:</u>** For patients with chronic non cancer pain, without current or past substance use disorder and without other active psychiatric disorders, who have persistent problematic pain despite optimized nonopioid therapy, we suggest adding a trial of opioids rather than continued therapy without opioids **(weak recommendation)**

Should it ever be opioids?

- **Benefits of Opioid Therapy**
  - Small net benefit, moderate evidence
    - A large number of trials included were with tramadol (28%)
  - Clinical Question:

Population:	Patients with chronic non-cancer pain, without current or past substance use disorder and without other current serious psychiatric disorders, whose therapy is optimized with non-opioids with persistent problematic pain
Intervention:	Trial of opioids.
Comparator:	Continue established therapy without opioids.

  - Outcome
    - Pain: Difference in patients who achieved minimally important difference (MID) for greater in 3-6 months
      - MID defined as 1cm on a 10cm scale
    - Relative Risk for achieving MID= 1.29
    - NNT= 8

What is considered an opioid?

- 2017 Canadian Guidelines For Chronic Non Cancer Pain

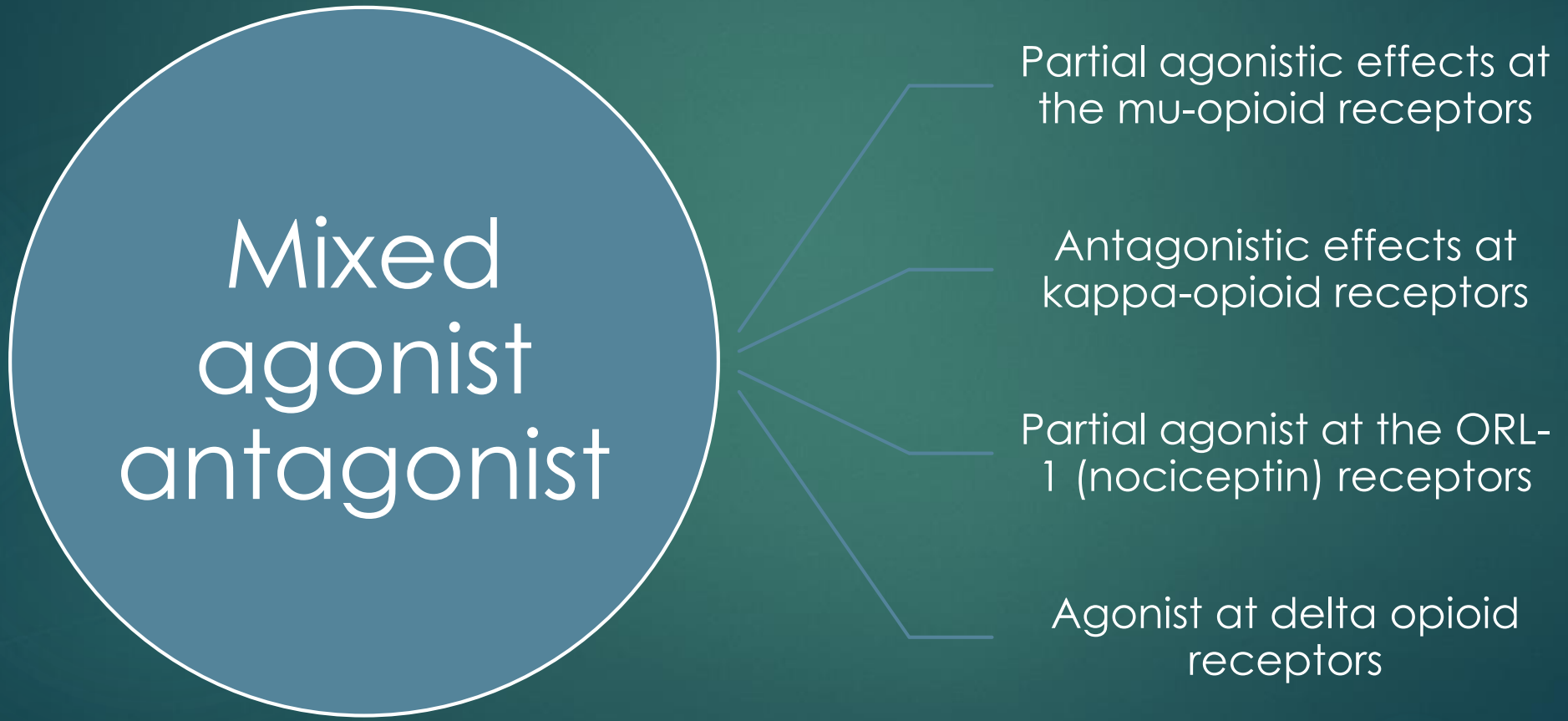
Opioid options for initiating a trial of therapy for patients with chronic non-cancer pain

Opioid	Comments
Morphine	Avoid in renal insufficiency
Oxycodone	~1.5x as potent as morphine. Available in a tamper-resistant formulation
Hydromorphone	~5x as powerful as morphine. Available in a tamper-resistant formulation
Oxycodone/Naloxone	Naloxone combination may minimize constipation and possibly act as an abuse deterrant
Buphrenorphine	Oral formulations preferred over transdermal for initial trial
Codeine	
Tapentadol	Available in a tamper-resistant formulation. Combined noradrenaline reuptake inhibitor and weak opioid
Tramadol	A prodrug (serotonin–norepinephrine reuptake inhibitor) that is converted to an opioid in a highly variable fashion.

Opioids that are not recommended for initiating a trial of therapy for patients with chronic non-cancer pain

Opioid	Comments
Methadone	Requires a specific Health Canada exemption to provide
Fentanyl (transdermal)	Not in opioid-naïve patients
Meperidine	Limited effectiveness; toxic metabolite accumulates in high doses or in renal insufficiency
Pentazocine	Limited effectiveness. High incidence of dysphoria

Buprenorphine



Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CEDAC FINAL RECOMMENDATION

BUPRENORPHINE TRANSDERMAL PATCH RESUBMISSION

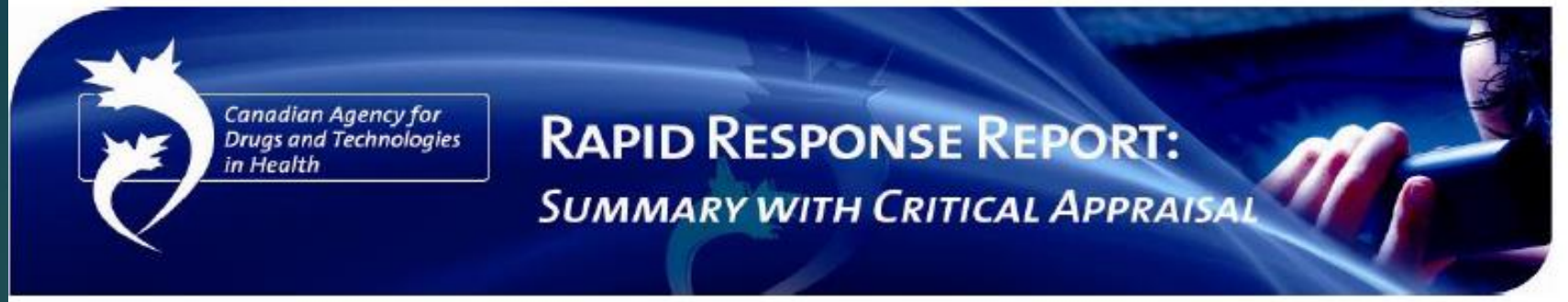
(BuTrans – Purdue Pharma)

Indication: Pain, Persistent (Moderate Intensity)

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that buprenorphine transdermal patch not be listed.

Reason for the Recommendation:
In the three randomized controlled trials (RCTs) included in the systematic review considered by CEDAC, buprenorphine transdermal patch did not provide statistically significantly greater reductions in pain compared with oral opioid formulations, and buprenorphine transdermal patch is more costly than many available opioid formulations.

Of Note:
The Committee noted that the frequency of gastrointestinal adverse events was similar between buprenorphine transdermal patch and the oral opioid comparators in the systematic review.



TITLE: **Buprenorphine for Chronic Pain: A Review of the Clinical Effectiveness**

DATE: 06 January 2017

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of buprenorphine for the treatment of adults with chronic pain?

2. What is the comparative clinical effectiveness of buprenorphine doses greater than 24 mg per day compared with daily doses of 24 mg or less?

3. What is the clinical effectiveness of buprenorphine when tapering opioid doses for adults with chronic pain?

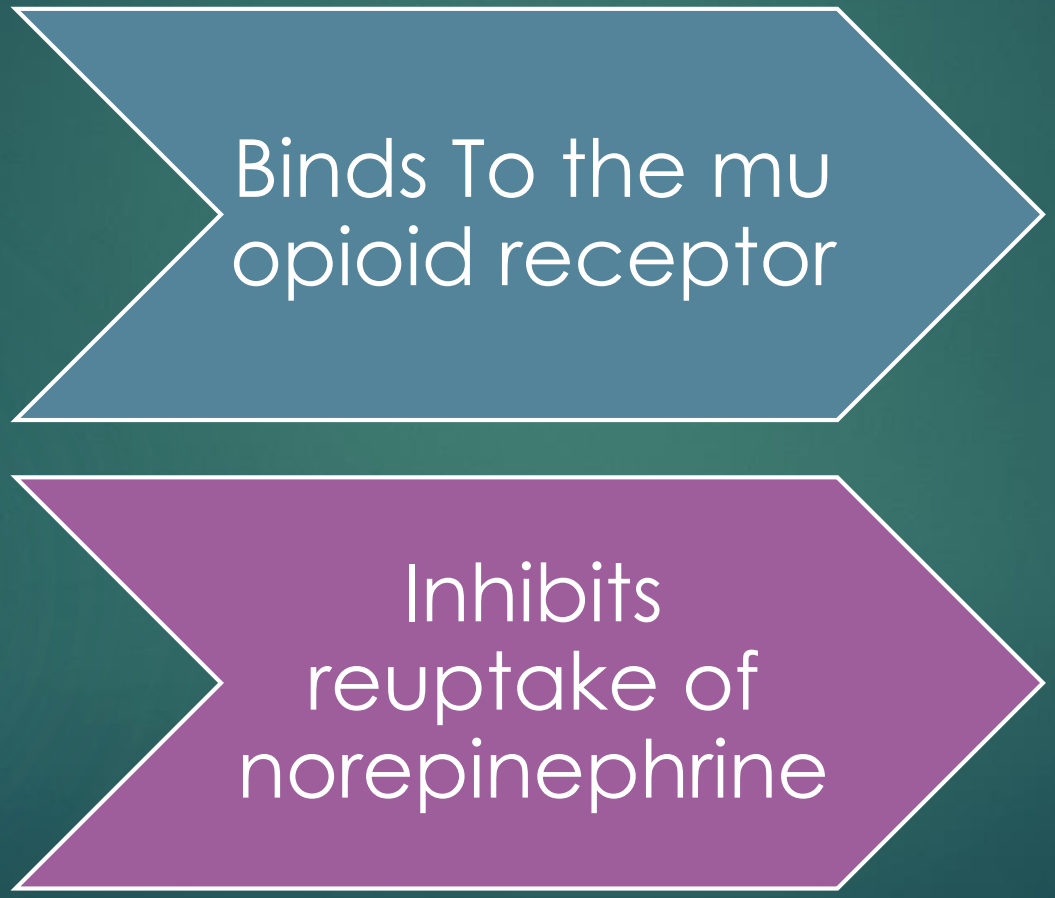
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The available evidence indicates that transdermal buprenorphine results in modest improvements in pain relative to placebo in patients with several types of non-cancer chronic pain. The improvements in pain relative to placebo did not meet a suggested standard for minimum clinical significance (>30% pain reduction) in some studies, but there was evidence from several studies that buprenorphine improved some domains of quality of life relative to placebo.

While one systematic review suggested that buprenorphine was inferior to morphine, the overall evidence does not suggest that other opioids are superior to buprenorphine with respect to pain reduction in chronic non-cancer pain. This needs to be investigated in further trials and high quality network meta-analyses that incorporate the most recent buprenorphine data.

While claims have been made that buprenorphine is associated with a lower risk of adverse events such as constipation, cognitive dysfunction and respiratory depression,[30] we did not identify any high quality evidence to support these claims in the context of chronic non-cancer pain. The available evidence is insufficient to assess the relative harms of buprenorphine to other opioids in patients with chronic non-cancer pain.

Tapentadol


Binds To the mu opioid receptor
Inhibits reuptake of norepinephrine

Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CEDAC FINAL RECOMMENDATION

TAPENTADOL
(Nucynta CR – Janssen Inc.)
Indication: Pain, Moderate to Moderately Severe

This document was originally issued on September 28, 2011. It was corrected on March 25, 2014. The price of hydromorphone has been corrected in the last paragraph on page three, under the heading "Cost and Cost-Effectiveness".

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that tapentadol controlled release (CR) not be listed.

Reason for the Recommendation:
The Committee considered the data from three active-controlled double blind randomized controlled trials (RCTs) to be insufficient to determine the relative efficacy of tapentadol CR compared with oxycodone CR, due to the high and unbalanced frequency of patient withdrawals (tapentadol CR range, 44% to 48%; oxycodone CR range, 60% to 65%), much of which occurred during the initial three-week titration phase.

Of Note:
There are no RCTs comparing tapentadol CR with less costly long-acting opioid formulations of codeine, morphine, or hydromorphone.

Tramadol

Low affinity binding for the mu opioid receptor

Inhibits reuptake of norepinephrine and serotonin

Tramadol

Mentioned as a treatment options in many guidelines

Based on the evidence efficacy appears to be comparable to low-dose or low potency opioids and NSAIDS.

Existing treatments have a number of drawbacks and contraindications:

- NSAIDS in renal failure, cardiac conditions, GI problems
- Other opioids may have greater abuse potential & more GI motility issues.

Tramadol provides an additional treatment option, with somewhat different adverse event profile and contraindications.

Potential for abuse is somewhat controversial, but at least some risk of abuse and diversion exists.

Many drug interactions

Serious adverse events have occurred with tramadol use, including seizures and serotonin syndrome

Possible Non Opioid Treatment Options

- Acetaminophen
- NSAIDS
- Marijuana
- Cannabinoids
- Tricyclic Antidepressants
- SNRIs (Duloxetine, venlafaxine)
- Gabapentin
- Pregabalin
- Ketamine
- Carbemazepine, oxcarbazepine
- Lamortigine
- Capsacin
- Botulism
- Mexilitine
- Levetracetam
- Cyclobenzaprine
- Magnesium

"This is only a placebo, but trust me, it works!"

Research Paper

PAIN®

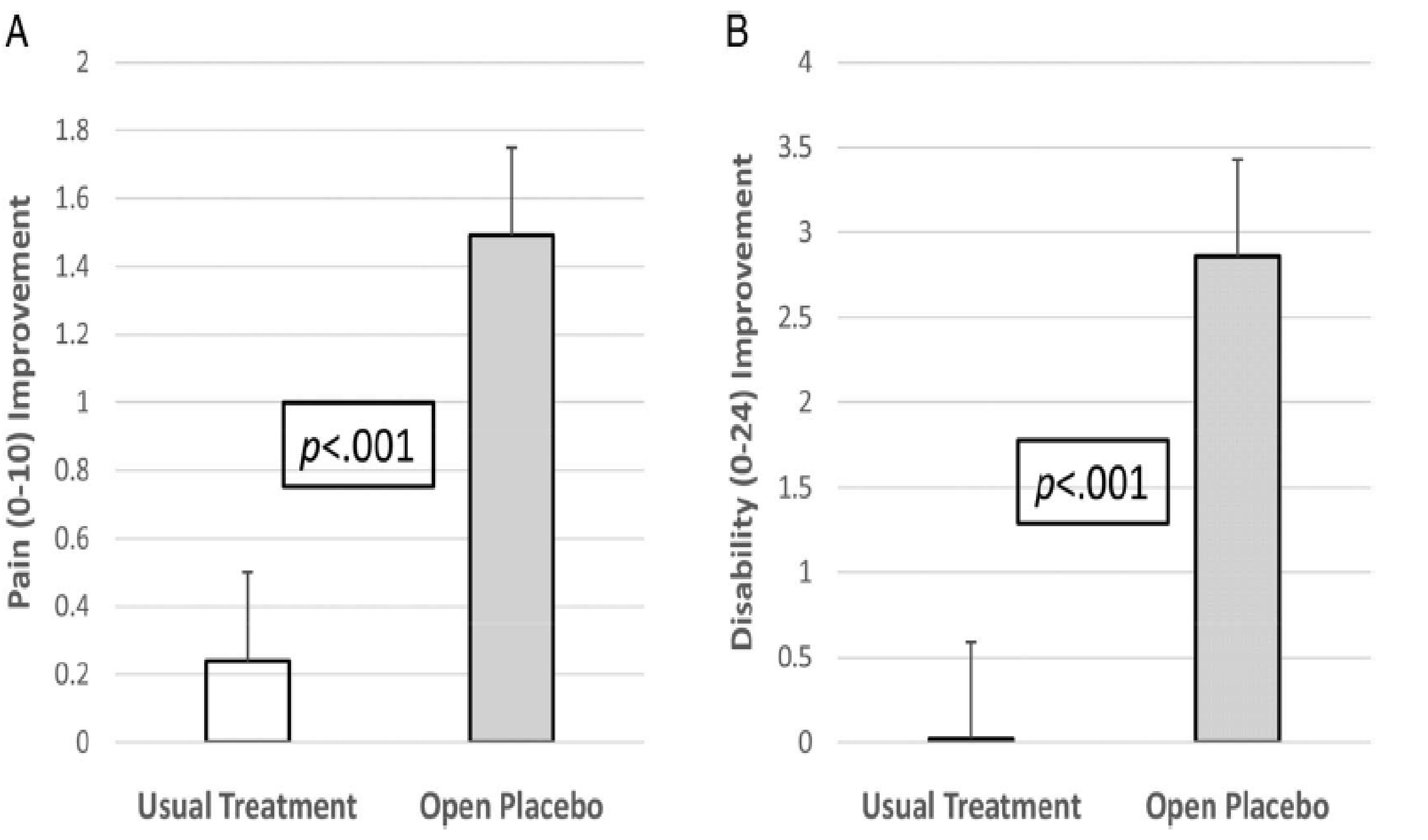
OPEN

Open-label placebo treatment in chronic low back pain: a randomized controlled trial

Cláudia Carvalho[a,*], Joaquim Machado Caetano[b], Lidia Cunha[c], Paula Rebouta[c], Ted J. Kaptchuk[d], Irving Kirsch[d]

Abstract

This randomized controlled trial was performed to investigate whether placebo effects in chronic low back pain could be harnessed ethically by adding open-label placebo (OLP) treatment to treatment as usual (TAU) for 3 weeks. Pain severity was assessed on three 0- to 10-point Numeric Rating Scales, scoring maximum pain, minimum pain, and usual pain, and a composite, primary outcome, total pain score. Our other primary outcome was back-related dysfunction, assessed on the Roland–Morris Disability Questionnaire. In an exploratory follow-up, participants on TAU received placebo pills for 3 additional weeks. We randomized 97 adults reporting persistent low back pain for more than 3 months' duration and diagnosed by a board-certified pain specialist. Eighty-three adults completed the trial. Compared to TAU, OLP elicited greater pain reduction on each of the three 0- to 10-point Numeric Rating Scales and on the 0- to 10-point composite pain scale ($P < 0.001$), with moderate to large effect sizes. Pain reduction on the composite Numeric Rating Scales was 1.5 (95% confidence interval: 1.0-2.0) in the OLP group and 0.2 (−0.3 to 0.8) in the TAU group. Open-label placebo treatment also reduced disability compared to TAU ($P < 0.001$), with a large effect size. Improvement in disability scores was 2.9 (1.7-4.0) in the OLP group and 0.0 (−1.1 to 1.2) in the TAU group. After being switched to OLP, the TAU group showed significant reductions in both pain (1.5, 0.8-2.3) and disability (3.4, 2.2-4.5). Our findings suggest that OLP pills presented in a positive context may be helpful in chronic low back pain.


A
Pain (0-10) Improvement
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
p<.001
Usual Treatment
Open Placebo
B
Disability (0-24) Improvement
4
3.5
3
2.5
2
1.5
1
0.5
0
p<.001
Usual Treatment
Open Placebo

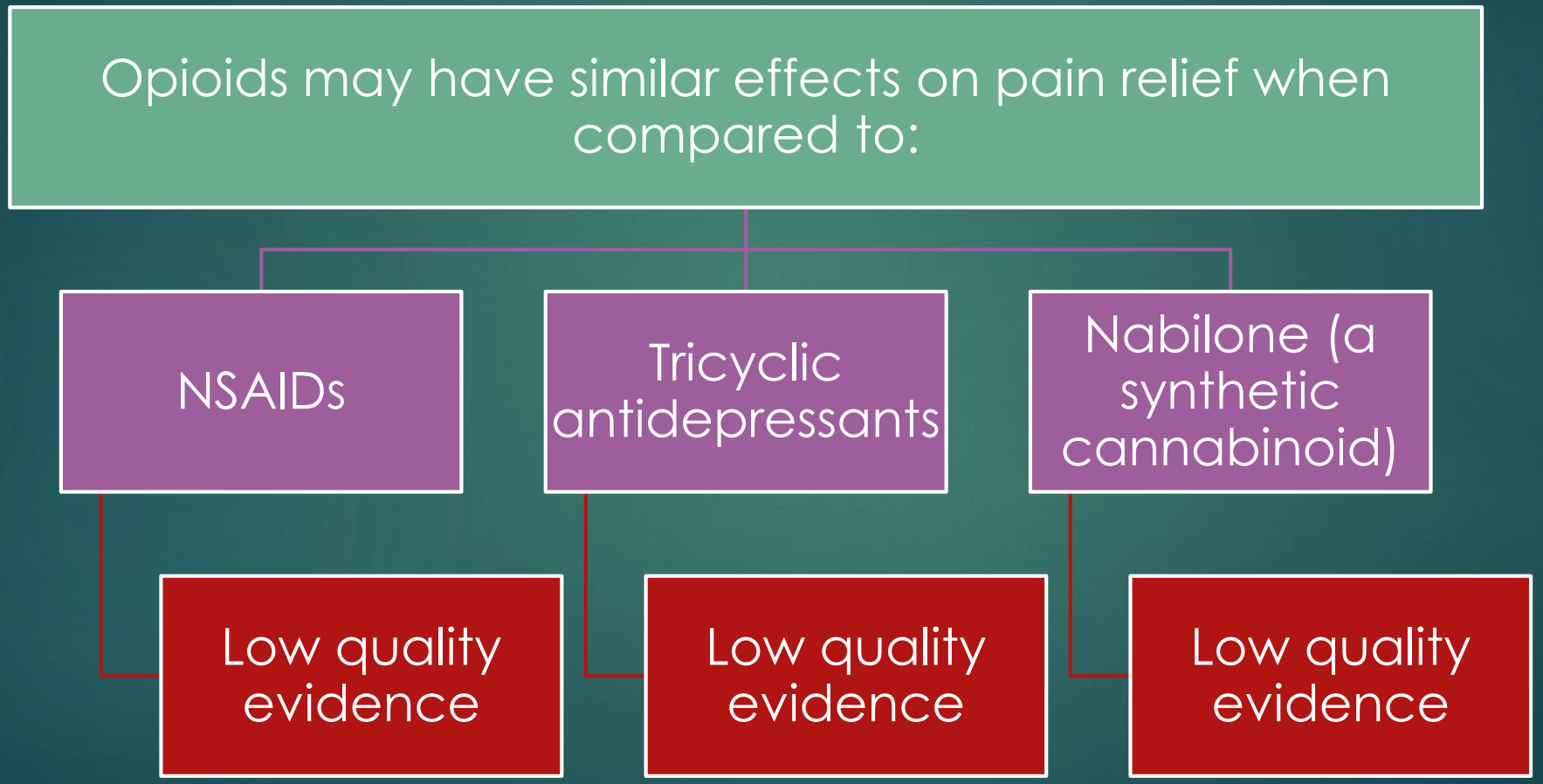
Recommendation 1: When considering therapy for patients with chronic non-cancer pain

Strong Recommendation

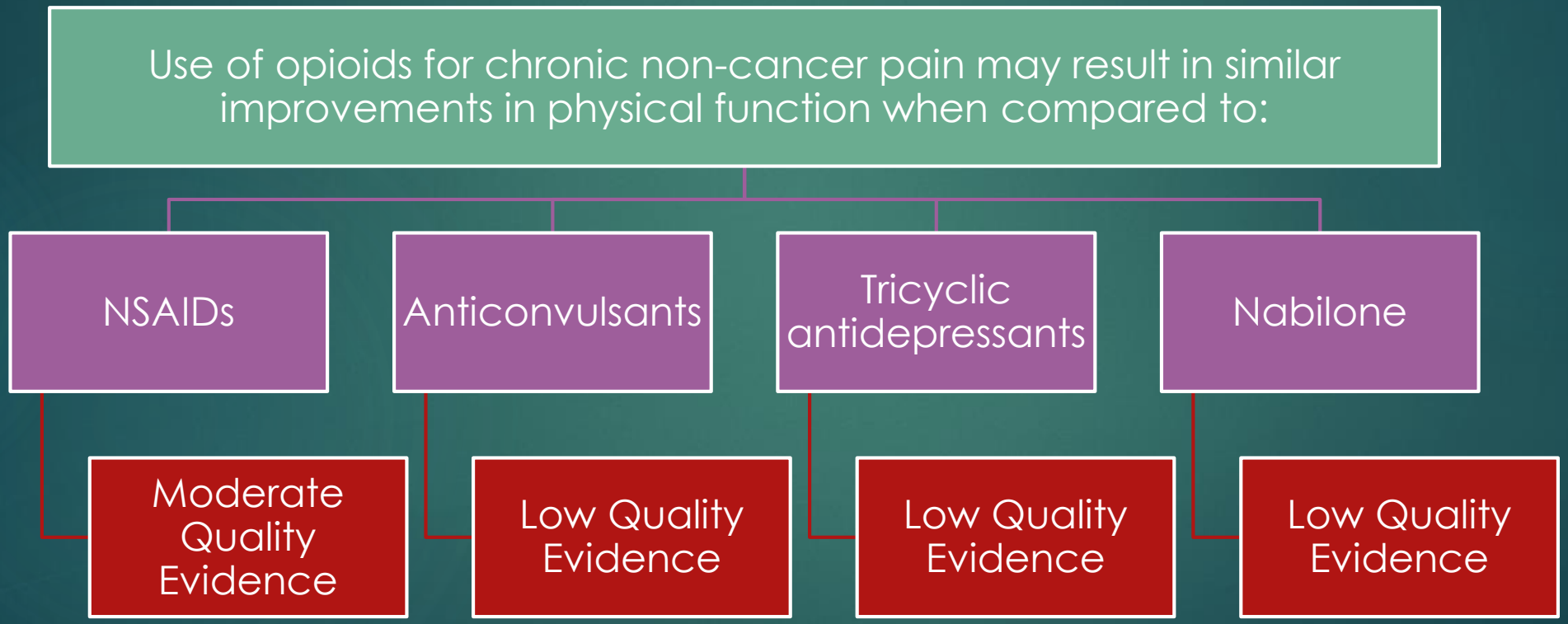
We recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids

Chronic non-cancer pain condition(s)	Quality of Evidence	Therapies with some evidence of effectiveness
Chronic low back pain	Moderate to high	NSAIDS, duloxetine, and benzodiazepines are more effective than placebo, sham, no treatment, usual care, or wait list*[41]*
Rheumatoid arthritis, osteoarthritis, fibromyalgia, low back pain, intermittent claudication, dysmenorrhoea, mechanical neck disorder, spinal cord injury, post-polio syndrome, and patellofemoral pain	Low	Physical activity reduced the severity of pain and improved physical function. Harms included muscle soreness.*[71]*
Fibromyalgia	Moderate	Regular physical exercise probably reduces pain in patients with fibromyalgia.*[168]*
Chronic low back pain	Low to moderate	Evidence of small to moderate short-term benefits for Tai chi, mindfulness based-stress reduction, exercise, multidisciplinary rehabilitation, spinal manipulation, massage therapy, and acupuncture. Effects on function were generally smaller than effects on pain.*[41]* *[40]*
Back pain, knee osteoarthritis, neck pain, fibromyalgia, severe headaches or migraines	Low or very low	Acupuncture, yoga, massage therapy, spinal manipulation, osteopathic manipulation, Tai Chi, and relaxation approaches may help some patients manage pain.*[149]*

2017 Canadian Guidelines For Chronic Non Cancer Pain



2017 Canadian Guidelines For Chronic Non Cancer Pain



TITLE: Cannabinoid Buccal Spray for Chronic Non-Cancer or Neuropathic Pain: A Review of Clinical Effectiveness, Safety, and Guidelines

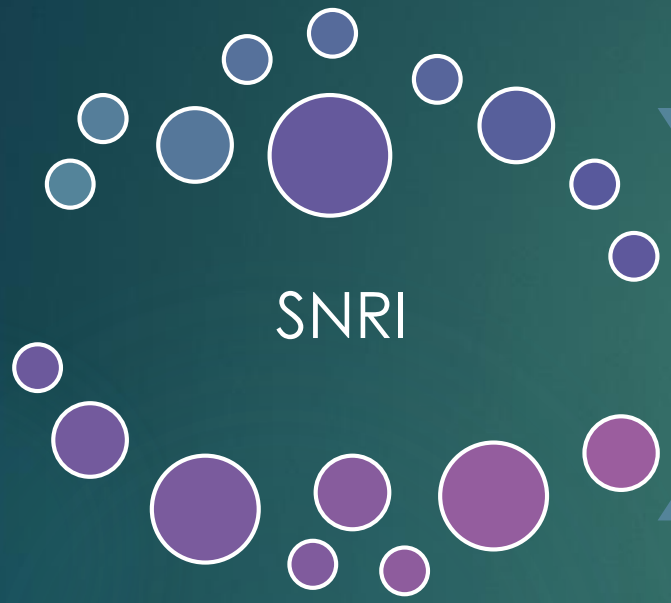
RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of delta-9-tetrahydrocannabinol/cannabidiol for the treatment of adult patients with chronic non-cancer pain or neuropathic pain?

2. What are the evidence-based guidelines relating to the use of delta-9-tetrahydrocannabinol/cannabidiol for adult patients with chronic non-cancer pain or neuropathic pain?

In brief, the available evidence comparing patient outcomes following THC:CBD treatment versus placebo appears insufficient to make well-founded conclusions about the clinical advantage and use of THC:CBD for the management of chronic neuropathic and non-cancer pain. Well-designed, prospective, randomized, active comparator-controlled trials with adequate follow-up, and adapted for the Canadian setting are needed to address this evidence gap.

Duloxetine



Selective Norepinephrine Reuptake Inhibitor

- Duloxetine (Cymbalta®, generics)
- Venlafaxine (Effexor®, generics)
- Desvenlafaxine (Pristiq®)

Introduced on the Canadian market in 2008

Original indications:

- Major Depressive Disorder
- Generalized Anxiety Disorder

Duloxetine

Health Canada Pain Indications			
Management of neuropathic pain related to diabetic peripheral neuropathy (2008)	Management of pain associated with fibromyalgia (2009)	Management of chronic low back pain (2011)	Management of chronic pain associated with osteoarthritis (OA) of the knee (2012)

Duloxetine: Evidence

CADTH	Antidepressant Indication	Recommendation	Do not list • Insufficient evidence that it offers any therapeutic advantage over cheaper alternatives
	Peripheral Diabetic Neuropathy	Recommendation	Be listed with criteria • For the treatment of neuropathic pain in diabetic patients who are unresponsive to adequate courses of two alternative agents, such as tricyclic antidepressants and anticonvulsants • Dose limited to a maximum of 60mg per day

Duloxetine: Evidence

Osteoarthritis

- Duloxetine reduces pain and improves function in patients with OA of the knee (level 1 [likely reliable] evidence)
  - Based on 3 RCTs
  - Two of the trials had limitations 1 with baseline differences and the other with a high dropout rates

Chronic Low Back Pain

- Duloxetine may improve lower back pain but magnitude of benefit unclear (level 2 [mid level] evidence)
  - Based on 3 RCTs
  - Trials had high drop out rates

Duloxetine: Evidence

Firbromyalgia

- Duloxetine may reduce pain in adults with fibromyalgia. (level 2 [mid-level] evidence)
  - Based on Cochrane review of trials with high dropout rates
  - Systematic review of 10 randomized trials comparing SNRIs vs. placebo for ≥ 4 weeks in 6,038 adults with fibromyalgia
- Duloxetine 60mg/day & 120mg/day may reduce pain severity in patients with fibromyalgia. (level 2 [mid-level] evidence)
  - Based on 2 systematic reviews limited by high dropout rates or incomplete quality reporting
- Duloxetine may improve pain, sleep, depressed mood and quality of life in patients with fibromyalgia. (level 2 [mid-level] evidence)
  - Based on systematic review with incomplete reporting of trial quality
- Duloxetine may improve pain and function across varying levels of tiredness at baseline in patients with fibromyalgia. (level 2 [mid-level] evidence)
  - Based on post hoc analysis of pooled data from 4 double-blind, placebo-controlled studies

Duloxetine Evidence

Neuropathic Pain

- Tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin appear to have moderate effectiveness in patients with neuropathic pain **(**level 2 [mid-level] evidence**)**

Gabapentin, Pregabalin, Tricyclic Antidepressants

Neuropathic Pain

- The evidence base for drug treatment of neuropathic pain is weak, due to the small magnitude of clinically meaningful effects and the high risk of bias in the RCTs
- Probably less than 1 in 10 patients achieve a meaningful reduction in pain
- Most patients experience some adverse side effects like somnolence, dizziness, nausea, dry mouth and constipation
- To identify patients who respond, a therapeutic trial with early assessment is essential. Reassessment of drug utility is needed to detect people with spontaneous remission or placebo response
  - Within the first week (usually within the first one or two days), some additional benefit seen at week 2
- Higher doses are unlikely to achieve greater pain reduction, but are more likely to cause harm.

Venlafaxine

Therapeutics Initiative

=

There are too few trials with too much bias to have sufficient evidence to comment on venlafaxine for neuropathic pain

Neuropathic Pain

Medication		NNT (95% CI)	NNH (95% CI)	Number of Trials
First-line	Tricyclic antidepressants	4 (3-4.4)	13 (9.3-24.4)	15
	Serotonin-noradrenaline reuptake inhibitors	7 (5.2-8.4)	11 (9.5-15.2)	10
	Pregabalin	8 (6.5-9.4)	14 (11.6-17.4)	25
	Gabapentin	7 (5-8.3) TI= 6-8	25 (15.3-78.6) TI=8	8
	Gabapentin extended release or enacarbil	9 (6.2-13)	32 (17.1-230)	6
Second-line	Tramadol	5 (3.6-6.7)	12 (8.4-25.3)	7
	Capsaicin 8% patches	11 (7.4-18.8)	Not reported	6
Third-line	Botulinum toxin A	2 (1.5-2.4)	Not reported	4
	Strong opioids	5 (3.4-5.8)	11 (8.4-19.3)	13

Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

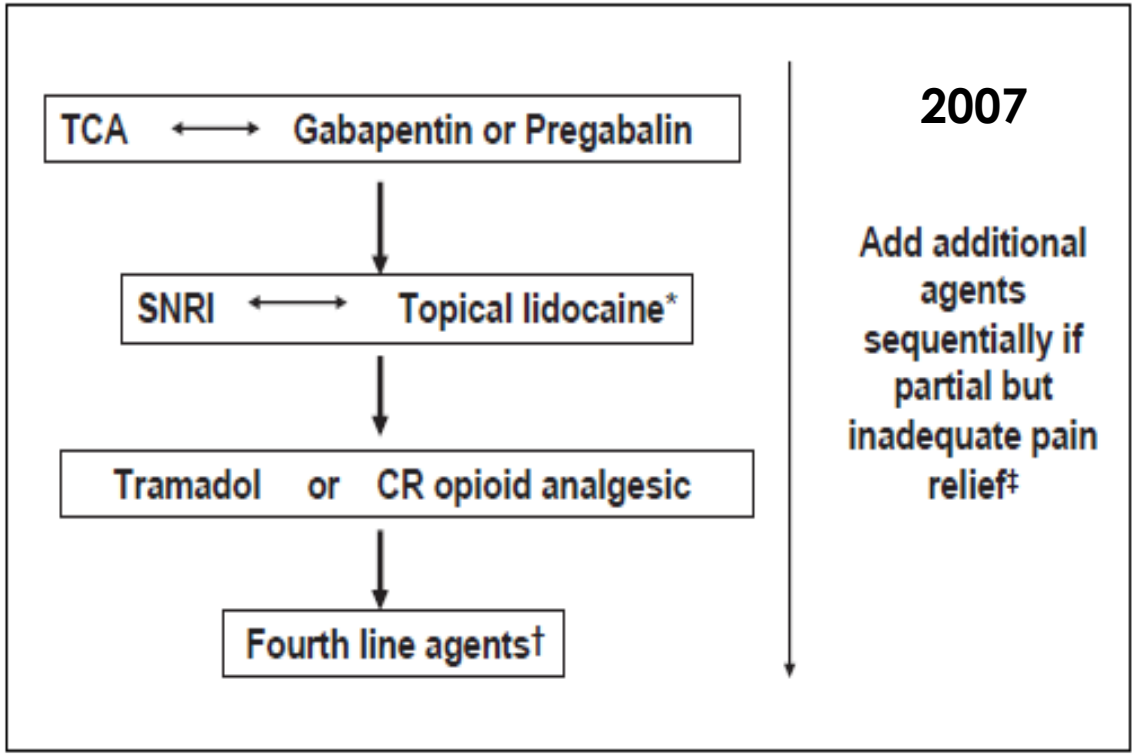


Figure 1) *Stepwise pharmacological management of neuropathic pain. *5% gel or cream – useful for focal neuropathy such as postherpetic neuralgia (the lidocaine patch is not available in Canada); †Cannabinoids, methadone, lamotrigine, topiramate, valproic acid; ‡Do not add serotonin noradrenaline reuptake inhibitors (SNRIs) to tricyclic antidepressants (TCAs). CR Controlled-release*

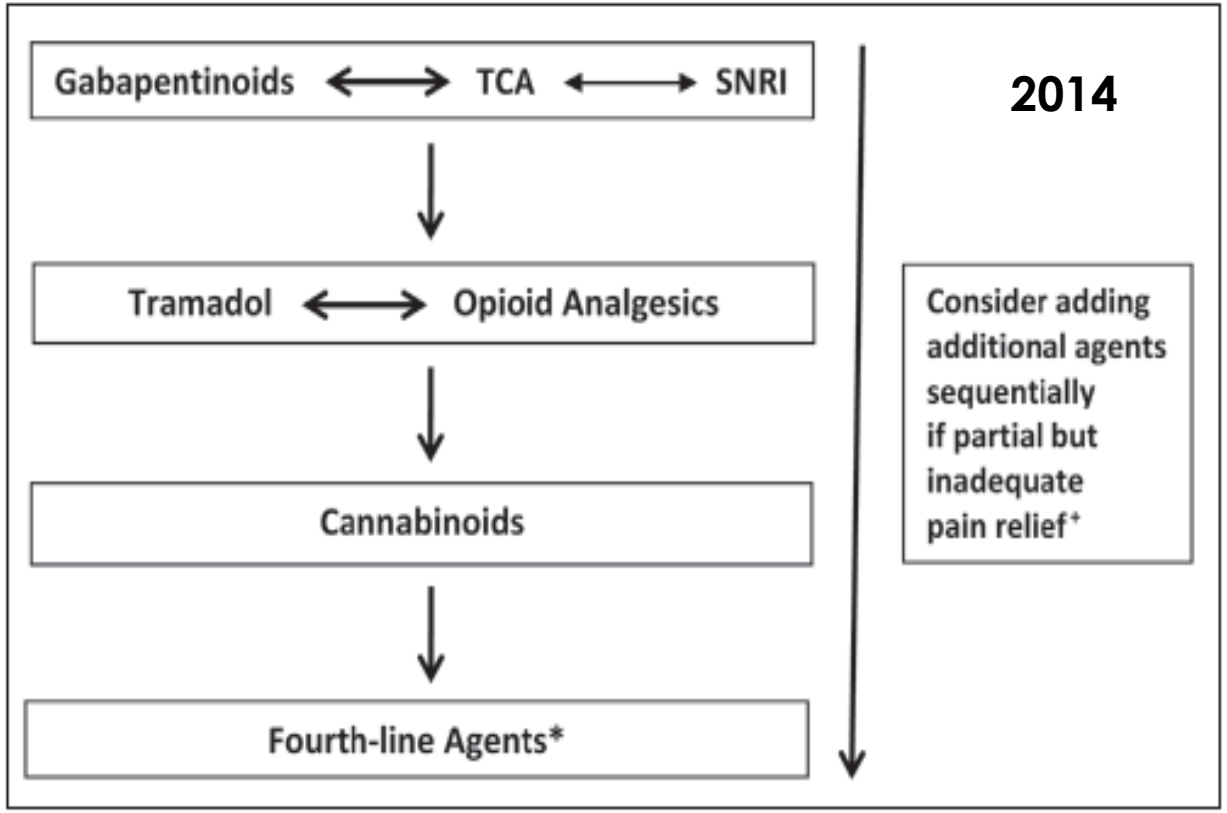


Figure 1) *Algorithm for the pharmacological management of neuropathic pain. *Topical lidocaine (second line for postherpetic neuralgia), methadone, lamotrigine, lacosamide, tapentadol, botulinum toxin; +Limited randomized controlled trial evidence to support add-on combination therapy. TCA Tricyclic antidepressants; SNRI Serotonin noradrenaline reuptake inhibitors*

Treatment Guidelines Chronic Low Back Pain

NICE

- Consider oral non-steroidal anti-inflammatory drugs (NSAIDs) for managing low back pain, taking into account potential differences in gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age.
- When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment.
- Prescribe oral NSAIDs for low back pain at the lowest effective dose for the shortest possible period of time.
- Consider weak opioids (with or without paracetamol) for managing acute low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective.
- Do not offer paracetamol alone for managing low back pain.
- Do not routinely offer opioids for managing acute low back pain.
- Do not offer opioids for managing chronic low back pain.
- Do not offer selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors or tricyclic antidepressants for managing low back pain.
- Do not offer anticonvulsants for managing low back pain.

Toward Optimized Practice

Evidence-Informed Primary Care Management of Low Back Pain

Clinical Practice Guideline | December 2015

3rd Edition – minor revision 2017

Pain Type	Medication		Dosage Range
Acute and sub-acute low back pain or flare-up of chronic low back/ spinal pain	**1st line**	Acetaminophen	Up to 1000 mg QID (max of 3000 mg/day long-term)
	2nd line NSAIDs (consider PPIs if >45 years of age)	Ibuprofen	Up to 800 mg TID (max of 800 mg QID)
		Diclofenac	Up to 50 mg BID
	Add: Cyclobenzaprine for prominent muscle spasm		10 to 30 mg/day; Greatest benefit seen within one week; therapy up to 2 weeks may be justified
	If already on a controlled release opioid: add a short-acting opioid or increase controlled release opioid by 20 to 25%		See opioids below
Chronic low back/spinal pain	**1st and 2nd lines**	See acute pain, above	
TRICYCLICS AND OPIOIDS	**3rd line** Tricyclics (TCAs)	Amitriptyline Nortriptyline* *fewer adverse effects	10 to 100 mg HS
	3rd line Weak Opioids	Codeine	30 to 60 mg every 3 to 4 hours
		Controlled release codeine	50 to 100 mg Q8h, may also be given Q12h
	4th line Tramadol**		Slow titration max 400mg/day. Note: Monitor total daily acetaminophen dose when using tramadol - acetaminophen combination
	5th line Strong Opioids** (controlled release)	Morphine sulfate	15 to 45 mg BID
		Hydromorphone HCl	3 to 10 mg BID
		Oxycodone HCl	10 to 30 mg BID
		Fentanyl patch	12.5 to 25 mcg/hr Q3 days

**for carefully selected patients with documented functional goals to monitor for improvement

CLINICAL GUIDELINE

ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians

Ann Intern Med. 2017;166:514-530. doi:10.7326/M16-2367

Amir Qaseem, MD, PhD, MHA; Timothy J. Wilt, MD, MPH; Robert M. McLean, MD; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians*

- **Recommendation 3:***In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, clinicians and patients should consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or **tramadol or duloxetine as second-line therapy**. Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients. (Grade: weak recommendation, moderate-quality evidence)*

Nova Scotia Formulary Benefit Status

Buprenorphine	• Not a benefit
Tapentadol	• Not a benefit
Tramadol	• Not a benefit
Tricyclic Antidepressants	• Full benefit
Nabilone	• Full benefit
Cannabinoid Buccal Spray	• Not a benefit

Nova Scotia Formulary Benefit Status

Duloxetine	• Restricted • For the treatment of neuropathic pain in diabetic patients who are unresponsive to adequate courses of two alternative agents, such as tricyclic antidepressants and anticonvulsants (dose limited to a maximum of 60mg per day)
Gabapentin	• Restricted • For the treatment of neuropathic pain (e.g. diabetic neuropathy, postherpetic neuropathy) in patients who have failed a trial of a tricyclic antidepressant (e.g. amitriptyline, desipramine, imipramine, nortriptyline).
Pregabalin	• Restricted • For the treatment of neuropathic pain (e.g. diabetic neuropathy, postherpetic neuropathy) in patients who have failed a trial of a tricyclic antidepressant (e.g. amitriptyline, desipramine, imipramine, nortriptyline)