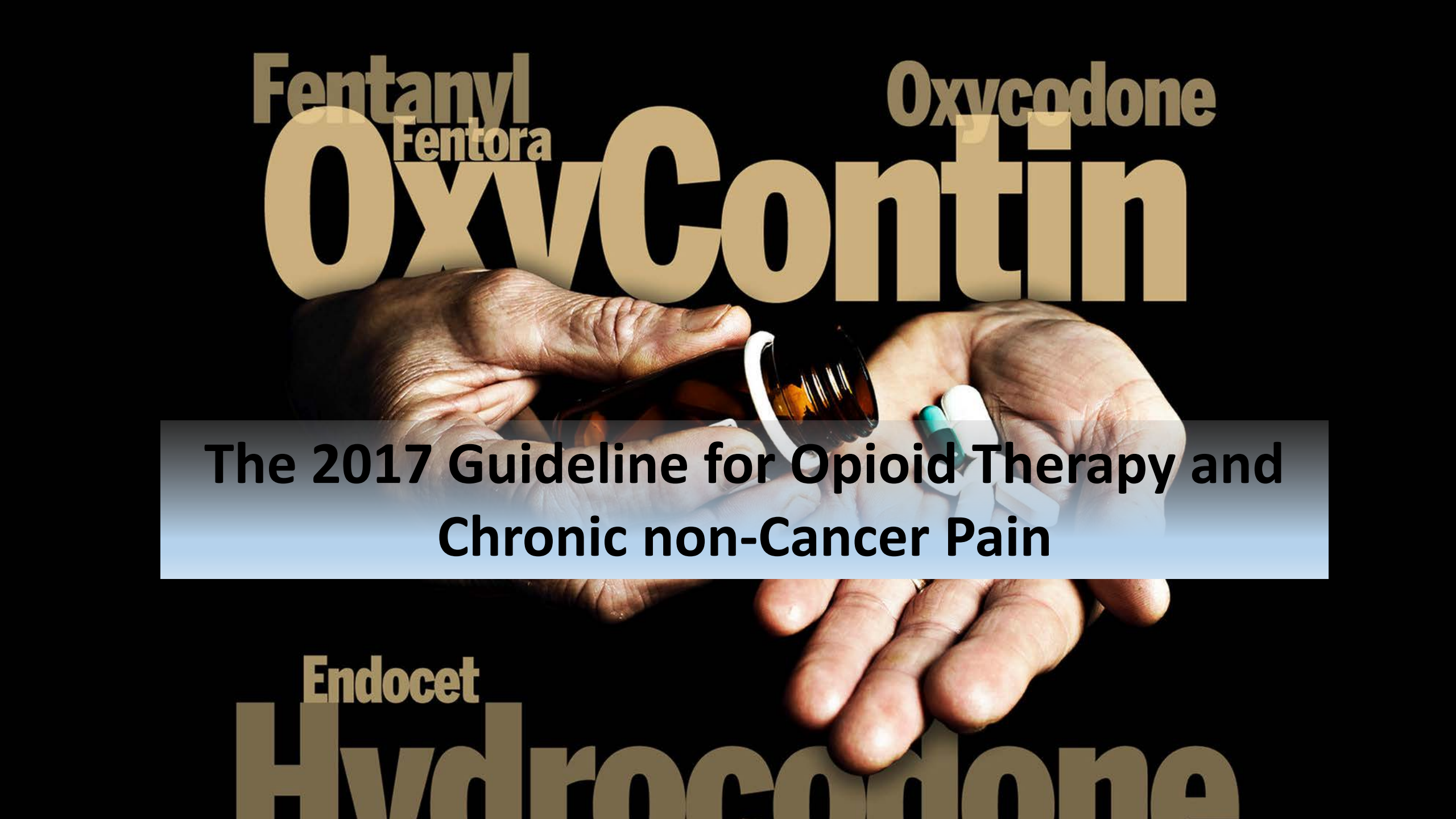


The 2017 Guideline for Opioid Therapy and Chronic non-Cancer Pain

Conflicts of Interest

- Our guideline efforts are supported by grants from the Canadian Institutes of Health Research & Health Canada

- I have no actual or potential conflicts of interest in relation to this presentation

Background

- Approximately 1 in 5 Canadians suffer from chronic non-cancer pain (CNCP), and opioids are often prescribed in this population

- North America, which represents 5% of the world's population, consumes 80% of all prescription opioids

- As rates of non-fatal and fatal opioid overdose have continued to rise, many have questioned whether the high use of opioids in North America represents evidence-based practice.

Background

- In March 2015 we were funded to update and revise the Canadian Guidelines for opioids and chronic non-cancer pain

- In consultation with clinical experts, methodologists, regulators, and patients living with chronic non-cancer pain we determined that the updated guideline should make 24 clinical practice recommendations

- Each recommendation was to be informed by 1 or more systematic reviews

Guideline Development Organization

- Steering Committee (n=4)
- Guideline Panel (n=15, including 2 patient representatives)
- Clinical Expert Advisors (n=13)
- Patient Representatives (n=16)
- A representative from Health Canada

Most Criticism has Focussed on the Guideline's Increased Restrictions for Opioids

PAIN NEWS NETWORK

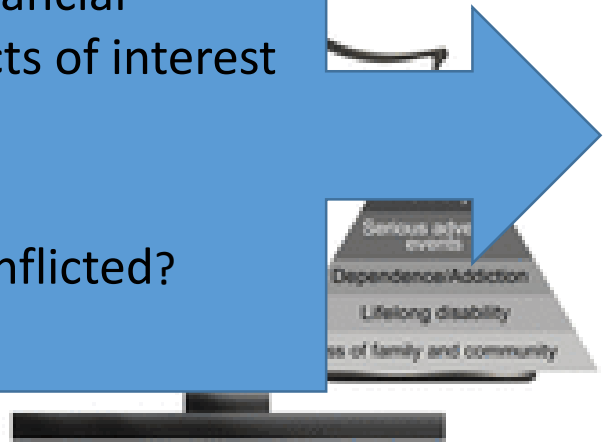
- Four advisory panels involving over 50 clinicians, academics, patients and "safety advocates" helped draft the Canadian guideline. Among them were three board members of Physicians for Responsible Opioid Prescribing (PROP), an anti-opioid activist group that played a key role in drafting the CDC guidelines: PROP Vice-President Gary Franklin, MD, Mark Sullivan, MD, and David Juurlink, MD.

Gary Franklin

- Opioids overuse is the “worst man-made epidemic in modern medical history…We are creating a lost generation of people whose lives are ruined by opioids,”

Gary Franklin has NO financial conflicts of interest

Is he unconflicted?



Opioids for chronic noncancer pain

Neurology 83 September 30, 2014

Gary M. Franklin, MD, MPH

Managing Conflict of Interest

- Two clearly defined camps
- Opioids are very useful for dealing with chronic non-cancer pain
  - The challenge is determining how to best use them
- Opioids have no role in the management of chronic non-cancer pain
  - Opioids kill and maim and should never be used
- We attempted to create a Guideline Panel in which no member could have important financial or intellectual conflicts of interest

GUIDELINE CPD

Guideline for opioid therapy and chronic noncancer pain

Jason W. Busse DC PhD, Samantha Craigie MSc, David N. Juurlink MD PhD, D. Norman Buckley MD, Li Wang PhD, Rachel J. Couban MA MISt, Thomas Agoritsas MD PhD, Elie A. Akl MD PhD, Alonso Carrasco-Labra DDS MSc, Lynn Cooper BES, Chris Cull, Bruno R. da Costa PT PhD, Joseph W. Frank MD MPH, Gus Grant AB LLB MD, Alfonso Iorio MD PhD, Navindra Persaud MD MSc, Sol Stern MD, Peter Tugwell MD MSc, Per Olav Vandvik MD PhD, Gordon H. Guyatt MD MSc

Cite as: *CMAJ* 2017 May 8;189:E659-66. doi: 10.1503/cmaj.170363

MAGIC app

https://www.magicapp.org/app#/guideline/1881

Scope
"This guideline does not address… treatment of opioid addiction or opioid use disorder"

THE GLOBE AND MAIL*

Opioid panel chair admits conflic

- review by The Globe of declara for all 28 medical experts, academics and patient advocat ho worked on the guidelines reveals that nine have received remuneration from drug companies, including Purdue Pharma, the pharmaceutical giant whose pain pill trigger anada's deadly opioi idemic. Two of the voted on the gu s and seven did
- D dered a to cond ent sc f th "tainte he influence of ind ,"

1 Panel member with a missed COI

1 Panel member previously received funds from a company that makes Suboxone

7 Clinical Expert Committee members declared a financial COI

Moving from Evidence to Recommendations

- Systematic reviews summarize the evidence, guidelines make clinical practice recommendations

- Results from our systematic reviews were provided to our guideline panel members

- We also conducted a systematic review of patient values & preferences, and focus group interviews of our Patient Advisory members to generate a values & preferences statement.

Patient Values & Preferences

- High value on small, but important, pain relief, and willing to trade rare, but serious harms
- Less value on avoiding addiction or physical dependence
- High concern regarding effects associated with dose reduction or cessation of opioid use
- We placed a high value on societal considerations of minimizing the risk of rare serious adverse events, but we also placed a high value on avoiding severe suffering that may accompany opioid reduction. We placed a high value on patient autonomy under these circumstances.

Recommendations

- We only voted on recommendations that could be informed by sufficient evidence
- We required 80% consensus to make a recommendation
- Recommendations could be ‘FOR’ or ‘AGAINST’, and ‘WEAK’ or ‘STRONG’

Recommendations

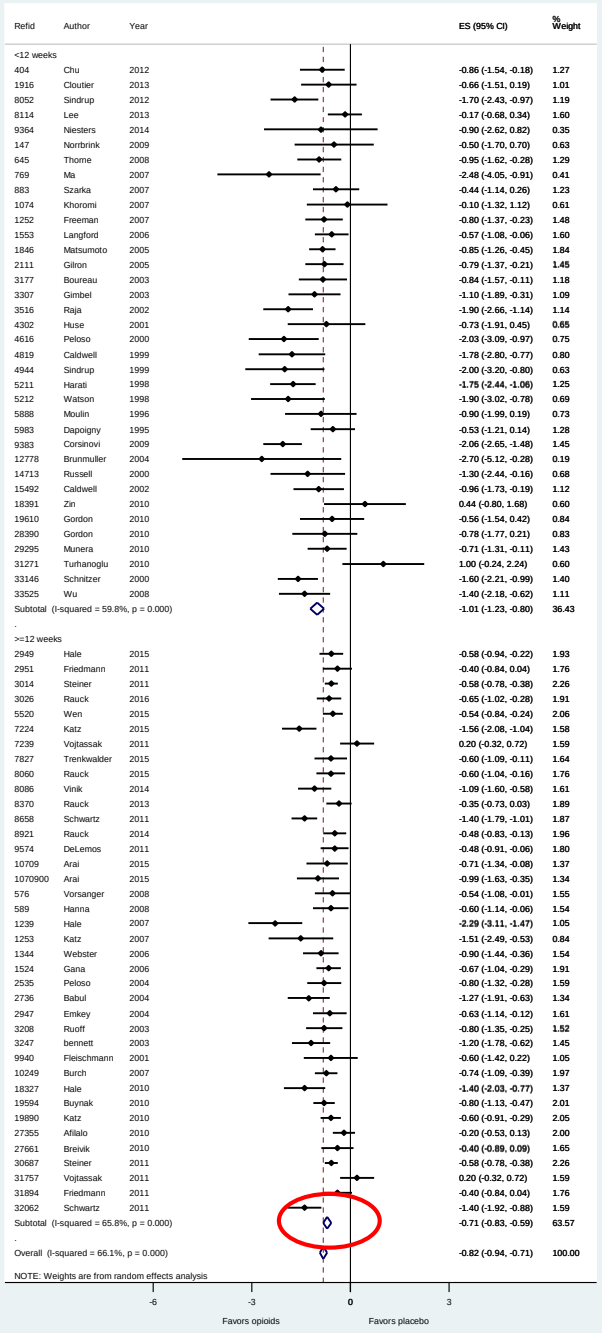
- **Strong recommendations** indicate that all or almost all fully informed patients would choose the recommended course of action, and indicate to clinicians that the recommendation is appropriate for all or almost all individuals.
  - Strong recommendations represent candidates for quality of care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

Recommendation #1

- When considering therapy for patients with chronic non-cancer pain, we recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids (**Strong recommendation, Low quality evidence**)

- As first-line treatment for patients with chronic non-cancer pain, several non-opioid therapies may achieve a similar magnitude of improvement in pain and function (e.g. nonsteroidal anti-inflammatory drugs [NSAIDs], graduated exercise, cognitive behavioral therapy) but without the harms of dependence, addiction, and non-fatal or fatal overdose.



Opioids vs. Placebo for Pain Relief

WMD -0.71cm on a 10cm VAS for pain; 95%CI -0.57, -0.85

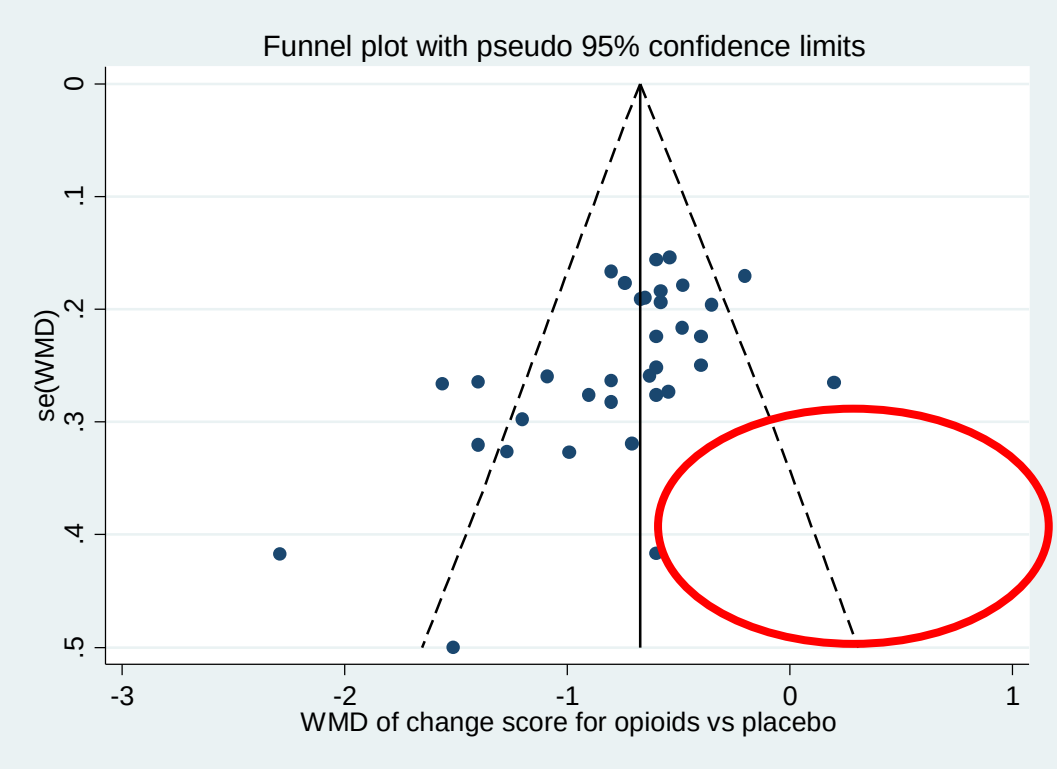
minimally important difference [MID] is 1cm

RR of achieving the MID = 1.29, 95% CI 1.23, 1.35

Risk Difference for achieving the MID = 12%, 95% CI 10%, 14%

Number Needed to Treat [NNT] = 8

Publication Bias



Egger's test: p=0.002

Outcome	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain Language Summary
		continuing established therapy without opioids	Opioid therapy		
Gastrointestinal side effects	Relative risk: 3.24 (CI 95% 2.69 - 3.89) Based on data from 17,463 patients in 54 studies Follow up 1-6 months	28 per 1000	91 per 1000	High	Opioid therapy worsens gastrointestinal side effects
		Difference: 63 more per 1000 (CI 95% 47 more - 81 more)			
Pain	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from 13,876 patients in 27 studies Follow up 3-6 months	Difference: MD 0.64 lower (CI 95% 0.76 lower - 0.53 lower)		High	Opioid therapy slightly improves pain
Pain (difference in patients who achieve the MID or greater)	Relative risk: 1.29 (CI 95% 1.24 - 1.34) Based on data from 13,876 patients in 27 studies Follow up 3-6 months	424 per 1000	547 per 1000	High	Opioid therapy increases the proportion of patients who will achieve a 1 cm reduction of pain on a 10 cm VAS compared with placebo.
		Difference: 123 more per 1000 (CI 95% 102 more - 144 more)			
Physical function	Measured by: SF-36 physical component summary scale Scale: 0-100 High better Based on data from 12,058 patients in 33 studies Follow up 1-6 months	Difference: MD 2.16 higher (CI 95% 1.56 higher - 2.76 higher)		High	Opioid therapy slightly improves physical function
Physical function (difference in patients who achieve the MID or greater)	Relative risk: 1.24 (CI 95% 1.17 - 1.3) Based on data from 12,058 patients in 33 studies Follow up 1-6 months	424 per 1000	526 per 1000	High	Opioid therapy increases the proportion of patients who will achieve 5 point increase on the SF-36 physical component summary scale compared with placebo.
		Difference: 102 more per 1000 (CI 95% 72 more - 127 more)			
Addiction	Based on data from 22,278 patients in 9 studies [86-94] Follow up N/A	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)		Moderate Due to serious inconsistency	Opioid therapy increases the risk of addiction.
Fatal overdose	Based on data from 285,520 patients in 1 studies[34] Follow up median 30 months	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18%, and 0.23% in patients prescribed <20 mg MED/day, 20-49 mg MED/day, 50-99 mg MED/day, and >100 mg MED per day respectively.		High	Opioid therapy increases the risk of fatal overdose.
Non-fatal overdose	Based on data from 9,940 patients in 1 studies[95] Follow up 1-119 months	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg MED/d, 50 to 99 mg MED/d, and more than 100 mg MED/d of opioids, respectively.		Moderate Due to serious imprecision	Opioid therapy increases the risk of non-fatal overdose.
Diversion	Based on data from 472,200 patients in 1 studies[96] Follow up 12 months	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI, 4.58%-5.22%) in 2013.		Moderate Due to serious risk of bias	Opioid therapy probably increases the risk of diversion.

Recommendation #2

- For patients with chronic non-cancer pain, without current or past substance use disorder and without other current psychiatric disorders, who experience persistent problematic pain despite optimized non-opioid therapy, we suggest adding a trial of opioids rather than continued therapy without opioids. (**Weak recommendation, Moderate quality evidence**)

- Opioids, when added to non-opioids achieve, on average, modest improvements in pain and function. Adverse effects include relatively frequent constipation, nausea and vomiting, addiction, and rare cases of unintentional overdose, which can be fatal or non-fatal

Recommend

Patients with an active substance use disorder are not represented in RCTs

- For patients with chroni active substance use disorder, we recomm use opioids (**Strong recommendation, Low**).

- Compared to individuals without active substance use disorder, patients with chronic non-cancer pain and active substance use disorder are at higher risk for opioid addiction (risk increases from 5.5% to 8.9%), non-fatal overdose (risk increases from 0.2% to 0.9% at <20 MED/day, with increasing risk at higher doses) and fatal overdose (risk increases from 0.1% to 0.5% at <20 MED/day, with increasing risk at higher doses)

Recommend

Patients with a current mental disorder are not represented in RCTs

- For patients with chron current psychiatric disorder whose non-op been optimized, and who experience persistent p we suggest stabilization of the psychiatric disorde ing a trial of opioids (**Weak recommendation, Low quality evidence**).

- Compared to individuals without mental illness, patients with chronic non-cancer pain and mental illness are at higher risk for opioid addiction (risk increases from 5.5% to 8.0%), non-fatal overdose (risk increases from 0.2% to 0.3% at <20 MED/day, with increasing risk at higher doses) and fatal overdose (risk increases from 0.1% to 0.15% at <20 MED/day, with increasing risk at higher doses).

Recommend

Patients with a history of substance use disorder are not represented in RCTs

- For patients with chroni history of substance use disorder, whose non as b n optimized, and who experience persistent pr ve suggest continuing non-opioid therapy rather th ds (**Weak recommendation, Low quality evidence**).

- Compared to individuals without prior substance use disorder, patients with chronic non-cancer pain and prior substance use disorder are at higher risk for non-fatal overdose (risk increases from 0.2% to 0.8% at <20 MED/day, with increasing risk at higher doses) and fatal overdose (risk increases from 0.1% to 0.4% at <20 MED/day, with increasing risk at higher doses).

Recommendation #6

- For patients with chronic non-cancer pain beginning opioid therapy, we recommend restricting the prescribed dose to under 90mg morphine equivalents daily rather than no upper, or a higher limit on dosing (**Strong recommendation, Moderate quality evidence**).

- On average, there is little to no difference in pain relief or functional improvement at different doses of opioids; however, there is likely an increase in the risk of non-fatal opioid overdose: 0.2% for <20mg MED/day, and 1.8% for ≥100mg MED/day. There is an increased risk of non-fatal opioid overdose with higher doses: 0.1% for <20mg MED/day, and 0.23% for ≥100mg MED/day.

Recommendation #7

- For patients with chronic non-cancer pain beginning opioid therapy, we suggest restricting the prescribed dose to under 50mg morphine equivalents daily (**Weak recommendation, Moderate quality evidence**).

- On average, there is little to no difference in pain relief or functional improvement at different doses of opioids; however, there is likely an increase in the risk of non-fatal opioid overdose: 0.2% for <20mg MED/day, and 0.7% for 50-99mg MED/day. There is an increased risk of non-fatal opioid overdose with higher doses: 0.1% for <20mg MED/day, and 0.18% for 50-99mg MED/day.

Recommendation #8

- For patients with chronic non-cancer pain currently using opioids, with persistent problematic pain and/or problematic side-effects, we suggest rotation to other opioids rather than keeping the opioid the same (**Weak recommendation, Low quality evidence**).

- Opioid rotation may result in a large improvement in pain and physical function. Rotation probably has little or no effect on the outcomes of addiction or diversion. It is uncertain whether rotation affects the incidence of gastrointestinal side effects.

Recommendation #9

- For patients with chronic non-cancer pain currently using 90mg morphine equivalents of opioids per day or more, we suggest tapering opioids to the lowest effective dose, potentially including discontinuation, rather than no change in opioid therapy (**Weak recommendation, Low quality evidence**).

- Reduction in opioid dose may reduce adverse effects, including cognitive impairment and the likelihood of non-fatal or fatal unintentional overdose.

- Some patients are likely to experience significant increase in pain or decrease in function that persist more than one month after a small dose reduction; tapering may be paused and potentially abandoned in such patients.

Recommendation #10

- For patients with chronic non-cancer pain using opioids and experiencing serious challenges in tapering, we recommend a formal multidisciplinary program (**Strong recommendation, Moderate quality evidence**).

- Studies provide moderate quality evidence that, in patients desiring a reduction or discontinuation of opioid therapy but experiencing serious challenges in tapering or discontinuing therapy, multi-disciplinary programs can substantially increase the likelihood of successful reduction or discontinuation.

- Recognizing the cost of formal multidisciplinary opioid reduction programs and their current limited availability/capacity, an alternative is a coordinated multidisciplinary collaboration including several health professionals.

Where's the Rest???

- Separate recommendations based on clinical condition?
- Co-prescribing of sedatives?
- Immediate vs. controlled release opioids?
- Risk mitigation strategies?
- Total dose dispensed at one time?

College of Physicians and Surgeons of British Columbia

Professional Standards and Guidelines

Safe Prescribing of Drugs with Potential for Misuse/Diversion

Standards

Physicians must:

- 4. Advise patients that long term opioid therapy is not indicated for certain medical conditions including headache disorders, fibromyalgia and axial low back pain.

What conditions do opioids work for?

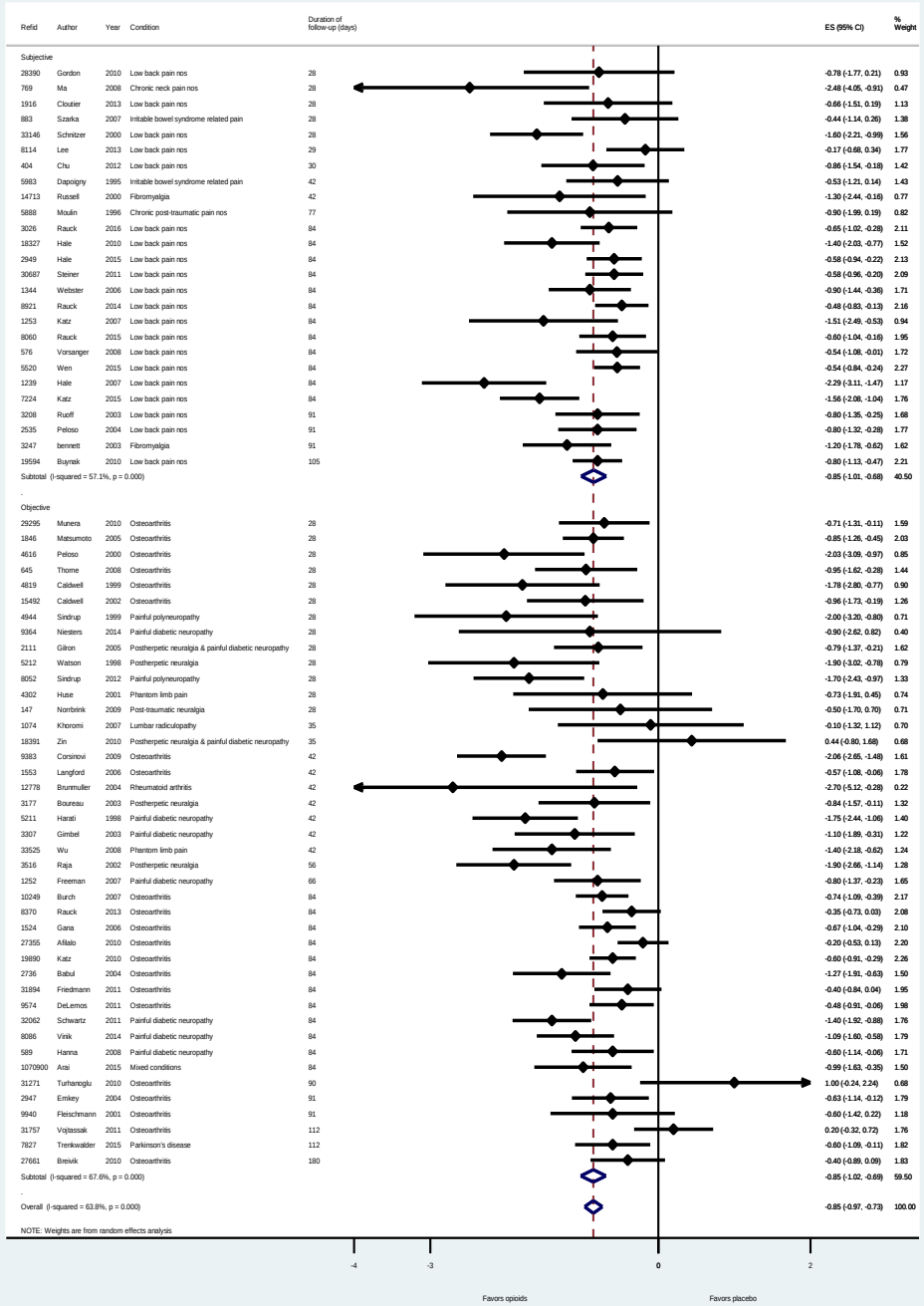
- It is neither feasible nor appropriate nor useful to review the evidence separately, and make a separate recommendation, for every known non-cancer chronic pain condition.

- The issue then becomes one of subgroup or effect modification: in the randomized trials that have addressed the impact of opioids on non-cancer pain, can one identify groups of conditions in which there is a greater or lesser impact on pain and function?

What conditions do opioids work for?

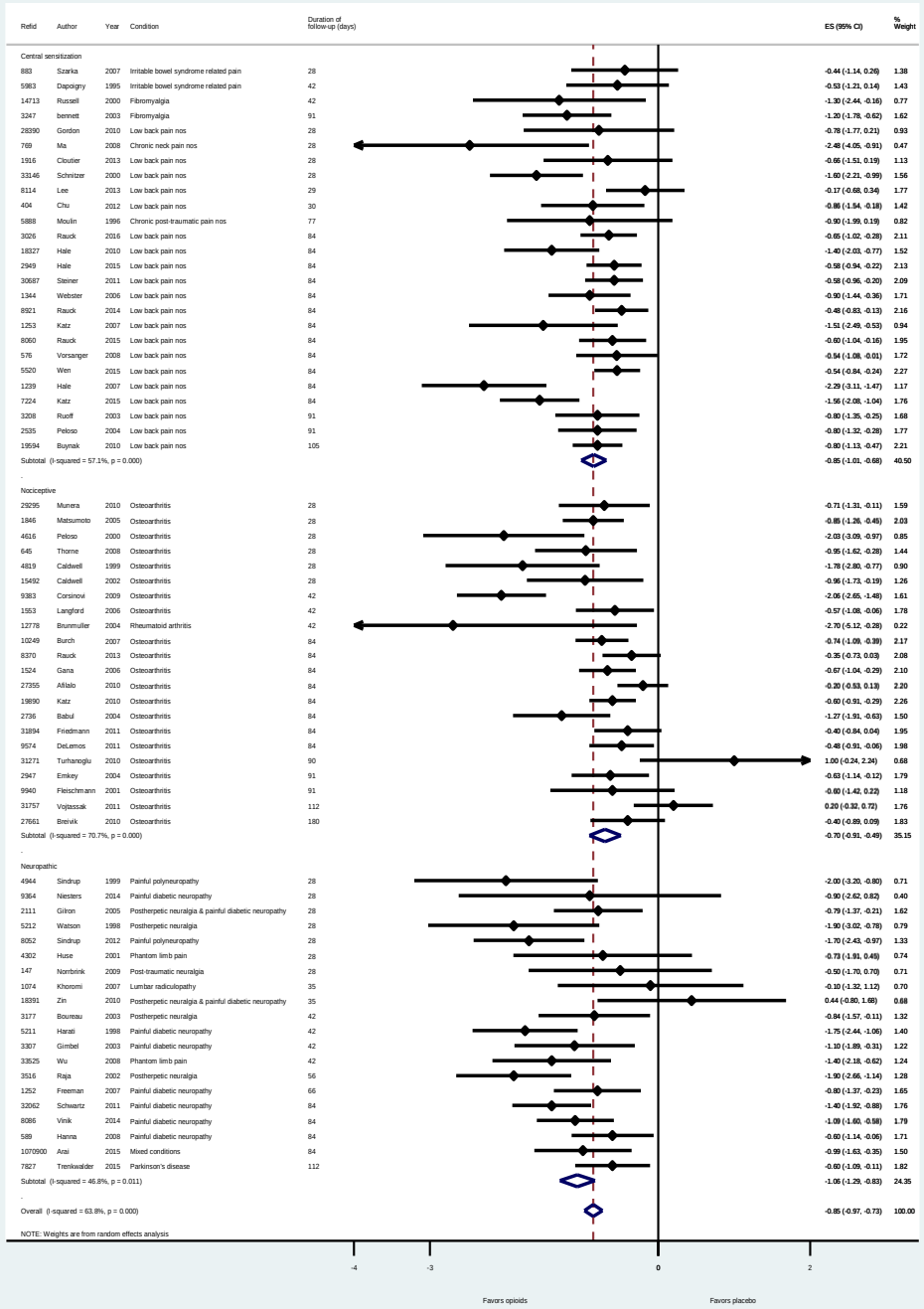
- Our Expert Committee members ended up advocating for 3 strategies of clustering clinical conditions (they were unable to come to agreement on a single approach):

1. Objective vs. subjective conditions
2. Neuropathic vs. nociceptive vs. central sensitization
3. Neuropathic vs. non-neuropathic



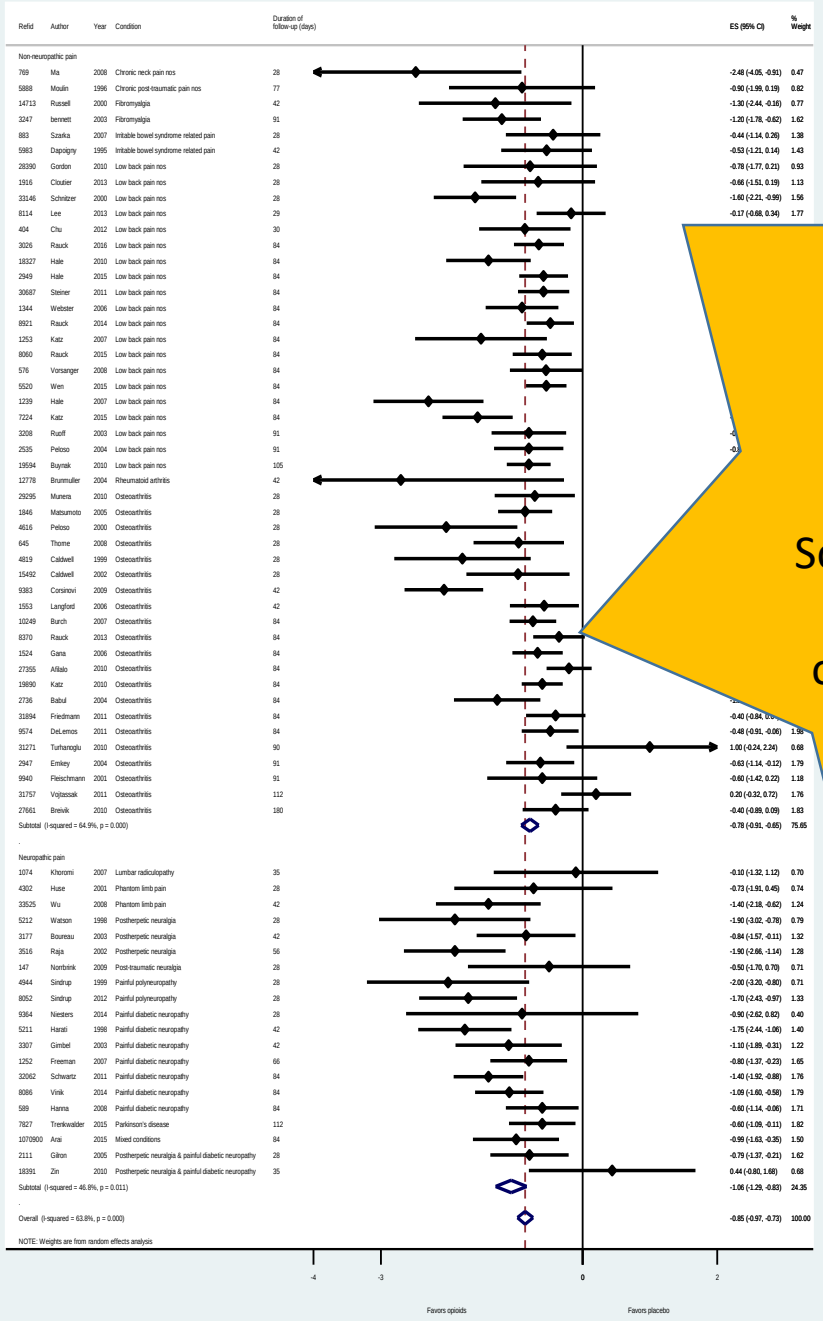
Subgroup analysis of pain reduction when comparing opioids with placebo: objective vs. subjective conditions

(68 studies, interaction p= 0.89)



Subgroup analysis of pain reduction when comparing opioids with placebo: neuropathic vs. nociceptive vs. central sensitization

(68 studies, interaction p=0.63)



No evidence for a subgroup effect based on clinical condition.

So, why are there Standards of Practice restricting use of opioids for some conditions?

Subgroup analysis of pain reduction
hen compared opioids with
lacebo: neuropathic vs non-
neuropathic

68 studies, interaction p= 0.08)

	No of studies*	p-value	adjusted R^2 (Proportion of between-study variance explained)
uropathic, excluding	68	0.08	12.26%
Length of follow-up (days)	68	0.009	17.49%
Multi-variable meta-regression	68		24.90%
Condition (neuropathic vs non-neuropathic, excluding mixed)		0.18	
Length of follow-up (days)		0.02	

Expert Guidance: Urine Drug Screening

- A baseline urine drug screen may be useful for patients currently receiving or being considered for a trial of opioids.

- Clinicians may repeat urine drug screening on an annual basis and more frequently if the patient is at elevated risk or in the presence of any aberrant drug-related behaviours.

- Approximately 30% of urine drug screening will demonstrate aberrant results, largely because of prescribed opioid non-detection and tetrahydrocannabinol.

Expert Guidance: Urine Drug Screening

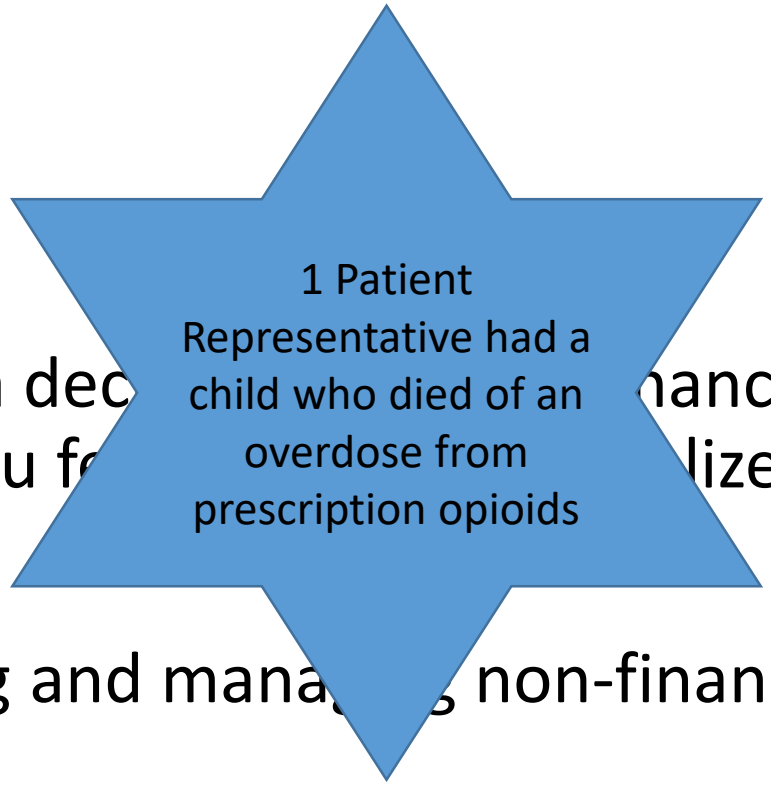
Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain Language Summary
		no UDT	UDT		
Opioid overdose	Relative risk: 1.36 (CI 95% 0.79 - 2.34) Based on data from 179,385 patients in 1 studies Follow up median 159 days	2 per 1000	3 per 1000	Very Low Due to serious imprecision	We are uncertain whether urine drug screening increases or decreases the risk of opioid overdose
		Difference: 1 more per 1000 (CI 95% 0 fewer - 3 more)			

Expert Guidance for Risk Mitigation

- Our Clinical Expert Committee felt, in general, that prescribers of opioids for chronic non-cancer pain may wish to consider implementation of risk mitigation strategies to potentially reduce harm.

- The alternative perspective is that prescribers adopting potentially ineffective risk mitigation strategies may become less concerned about possible opioid-related harms, and more willing to prescribe opioids for chronic non-cancer pain.

COI Issues



- 1 of 15 Panel members has a dec nancial COI. This presents a risk of bias. Do you fe lized?
- Should we bother identifying and mana s non-financial COI?
- Should anyone with a financial COI be allowed anywhere near a guideline, even if they are restricted from voting?

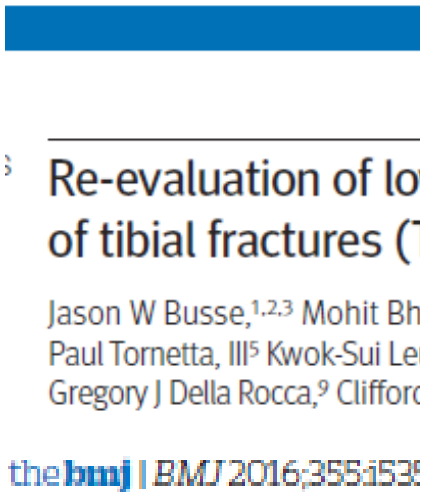
McMaster University
Inspiring Innovation and Discovery

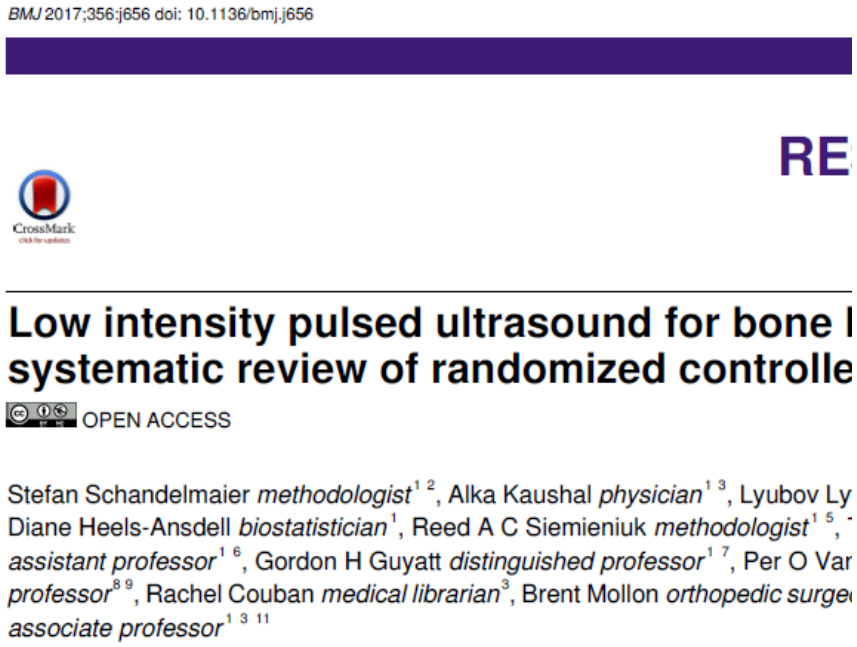
Michael G. DeGroote
INSTITUTE FOR PAIN RESEARCH AND CARE

Summary

- It is essential to involve individuals with vested interests in guideline development

- We think that both financial and intel
and man


Re-evaluation of lo
of tibial fractures (
Jason W Busse,[1,2,3] Mohit Bh
Paul Tornetta, III[5] Kwok-Sui Le
Gregory J Della Rocca,[9] Clifford
the bmj | BMJ 2016;355:i53


BMJ 2017;356:j656 doi: 10.1136/bmj.j656
RE
CrossMark
Low intensity pulsed ultrasound for bone
systematic review of randomized controlle
OPEN ACCESS
Stefan Schandelmaier *methodologist*[1,2], Alka Kaushal *physician*[1,3], Lyubov Ly
Diane Heels-Ansdell *biostatistician*[1], Reed A C Siemieniuk *methodologist*[1,5],
assistant professor[1,6], Gordon H Guyatt *distinguished professor*[1,7], Per O Var
professor[8,9], Rachel Couban *medical librarian*[3], Brent Mollon *orthopedic surge*
associate professor[1,3,11]

Study Team

Guideline Steering Committee
- Gordon H. Guyatt (Chair), McMaster University, Canada
- Norm Buckley, McMaster University, Canada
- Jason W. Busse, McMaster University, Canada
- David Juurlink, University of Toronto, Canada

Guideline Panel Members
- Jason W. Busse (Chair), McMaster University, Canada
- Thomas Agoritsas, University Hospitals of Geneva, Switzerland
- Elie Akl, American University of Beirut, Lebanon
- Alonso Carrasco-Labra, McMaster University, Canada
- Lynn Cooper, Canadian Pain Coalition, Canada
- Chris Cull, Inspire by Example, Canada
- Bruno da Costa, Florida International University, USA
- Joseph Frank, VA Eastern Colorado Health Care System, USA
- Gus Grant, College of Physicians and Surgeons of Nova Scotia, Canada
- Gordon H. Guyatt, McMaster University, Canada
- Alfonso Iorio, McMaster University, Canada
- Navindra Persaud, University of Toronto, Canada
- Sol Stern, private practice, Canada
- Peter Tugwell, University of Ottawa, Canada
- Per Olav Vandvik, Innlandet Hospital Trust-Division Gjøvik, Norway

Clinical Expert Committee
- Norm Buckley, Donna Buna, Gary Franklin, Chris Giorshev, Jeff Harris, Lydia Hatcher, Kurt Hegmann, Roman Jovey, David Juurlink, Priya Manjoo, Pat Morley-Forster, Dwight Moulin, Mark Sullivan

Patient Advisory Committee*
- Brian Barns, Lynn Cooper, Chris Cull, Ada Giudice-Tompson, Deborah Ironbow, Pamela Jessen, Andrew Koster, Sue Mace, Tracy L. Mercer, Kyle Neilsen, Ian Tregunna, Jen Watson

* 4 members did not provide written consent to be listed

Evidence Synthesis Team
- Samantha Craigie, Jason W. Busse, Li Wang, Rachel Couban, Vahid Ashoorion, Mahmood AmniLari, Yaping Chang, Kayli Culig, Kyle De Oliveria, Anna Goshua, Justin Ho, Patrick Hong, Alka Kaushal, Regina Li, Veena Manja, Curtis May, Yasir Rehman, John J. Riva, Stephanie Ross, Nicole Vogel, Raad Yameen, Madison Zhang

External Review Committee
- Paul Glasziou (Chair), Pablo Alonso Coello, Miranda Langendam