EXPECTATIONS & REALITIES:

Directly applying the evidence for topical pain treatments

MEDS Conference

January 26, 2019

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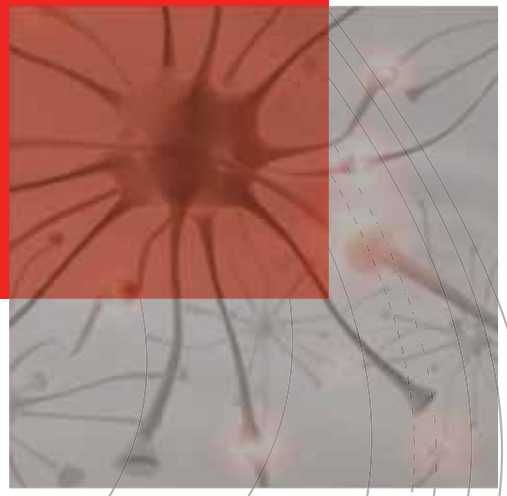


University of Manitoba

FACULTY/ PRESENTER DISCLOSURE

- **Faculty:** Jamie Falk
- **Relationships with commercial interests:** Not Applicable

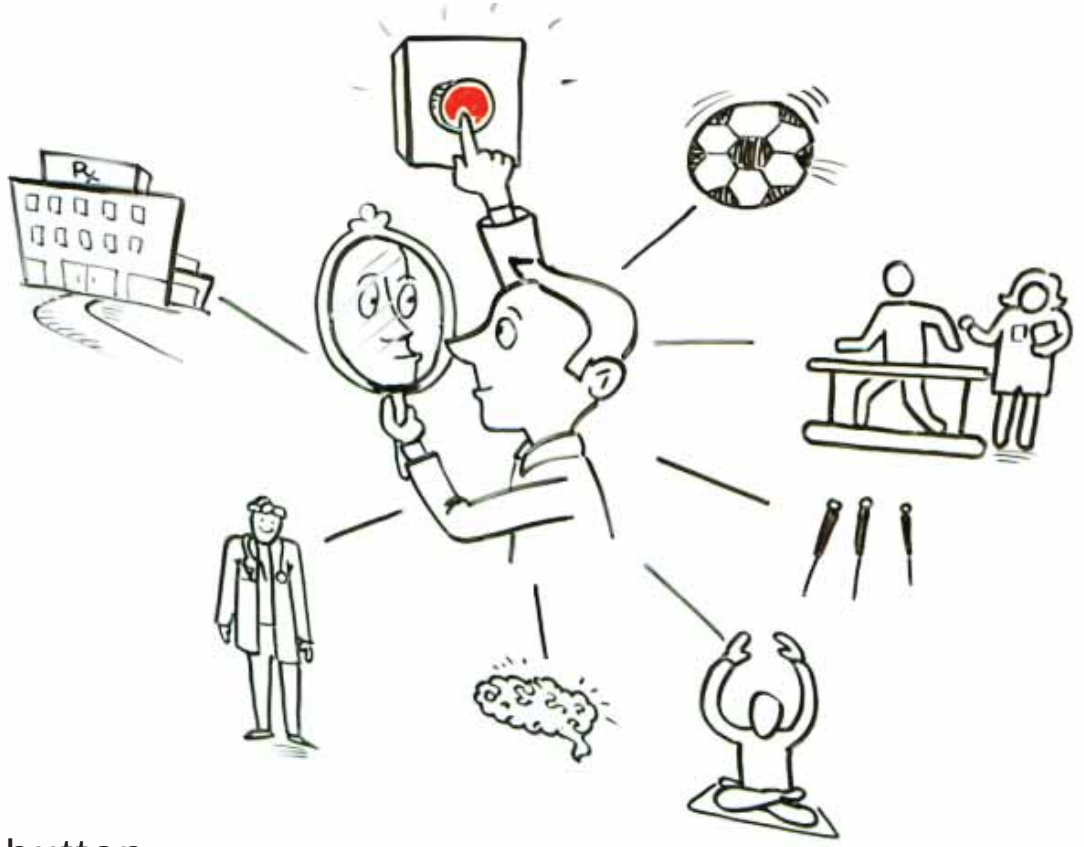
OUTLINE

1. Current state of chronic pain treatment
2. Current evidence for topical pain agents, covering…
   - → **various agents** including:
     - NSAIDs, lidocaine, capsaicin, amitriptyline, ketamine, gabapentin, combinations
   - → **main conditions** for today:
     - Osteoarthritis
     - Post-herpetic neuralgia
     - Diabetic neuropathy

WHAT I **WON'T** TALK MUCH ABOUT TODAY…

1. Compounding **vehicles & techniques**
   - Although practically important, actual clinically important comparisons on pain and function are sparse, if available at all
   - Others know a lot more than me about specific practical implications
2. What has worked for **my patients**
   - My patients may not be yours
   - n=1 trials are helpful for the individual patient, but not very useful for others (and tend to transform into folklore of profound benefit)

OUR **ASSUMPTION** TODAY…



WE:

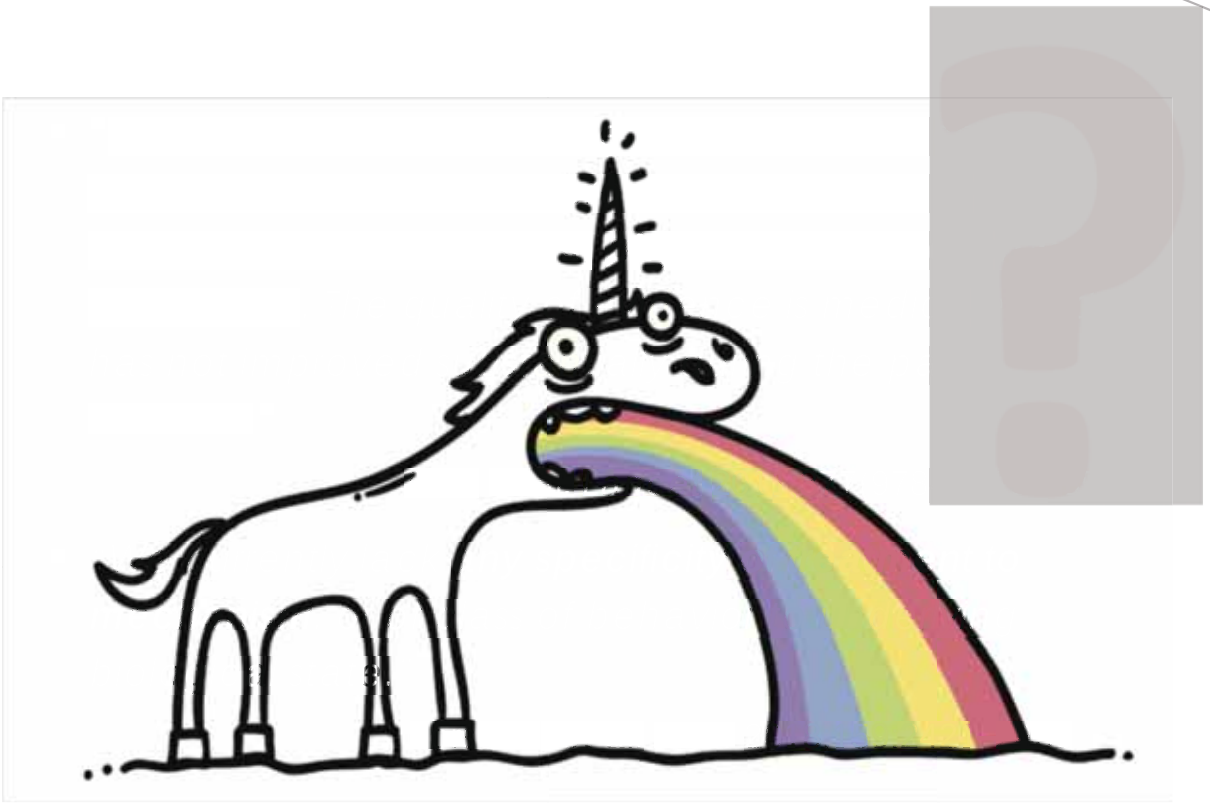
… pressed the reset button

… continue to reset the stage

… address frustration, hopelessness, coping ability

… are reflecting on our/the patient's approach to the pain experience

THE CURRENT **STATE OF THINGS**



Oral pain meds for chronic pain:

- NNT for ≥ 30-50% **pain** = ~**6-8**
- Uncertain **functional/QoL benefit**
- Up to 80% will get at least one side effect

WHAT DO WE NEED?

Effective options with **minimal side effects**

MAYBE WE ALREADY HAVE THE ANSWER…

Referring to lidocaine patches…

“These things are fantastic. If I could wrap myself in one like a big numb burrito, I would.”

LET'S LOOK AT SOME REAL EVIDENCE

Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews (Review)

CDSR 2017, Issue 5. Art. No.: CD008609

Derry S, Wiffen PJ, Kalso EA, Bell RF, Aldington D, Phillips T, Gaskell H, Moore RA

n = 30,700 in 206 studies

(**NSAID** n = **21,088**)

TOPICAL NSAIDs

- **ADVANTAGE:** major adverse effects **comparable to placebo**
  - ***WHY?*** → **2-10%** (likely **<5%**) systemically available
- Disadvantage: local skin reaction (NNH = 16), "stickiness" → NNH (withdrawal) = 50
- **WHICH NSAIDS & HOW MUCH?**
  - Diclofenac and ketoprofen have the best quality studies and most reliable NNTs
  - Diclofenac **1% -1.5%** solution or gel most commonly studied, dosed BID-TID
  - Does ↑ **%** work better**????**

Speaking of NNTs…

CDSR 2016, Issue 4. Art. No.: CD007400

TOPICAL NSAIDS: **OA**

- ***vs.* oral NSAIDs** for OA of hands & knees: **=**
- ***vs.* placebo** for OA, tendonitis (*BMJ* 2004;329:324-6):
  - ≥ 50% pain⇩@ week 1 → 74 vs. 44%
    week 2 → 92 vs. 58% } **NNT=3**
    week 4 → 55 vs. 57%
- ***vs.* placebo** for OA (*CDSR* **2017** Issue 5. Art.No.: CD008609):
  - ≥ 50% pain⇩@ **< 6 weeks** → NNT = **5**
    weeks 6-12 → NNT = **7-10**

i.e. can it help your patient get physical

WHAT ABOUT **FUNCTION** ?

YES, with (small) effect sizes similar to those seen for pain reduction

J Pain Palliative Care Pharmacother 2012;26:18-23
Br J Sports Med 2018;52:642–650
CDSR 2016, Issue 4. Art. No.: CD007400

TOPICAL NSAIDS: **OTHER CONDITIONS**

- **Acute pain** (sprains, strains, overuse injuries)**:**
  - Diclofenac or ketoprofen **vs. placebo** (CDSR 2015, CD007402)**:**
    - ≥ 50% pain relief @ **1week** → **NNT 2-2.5**

- **Back pain, neuropathic or widespread pain:**
  - no evidence to support use

READING A LITTLE FURTHER …

Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews (Review)

Derry S, Wiffen PJ, Kalso EA, Bell RF, Aldington D, Phillips T, Gaskell H, Moore RA

Other than NSAIDs…

"We judged evidence of efficacy for other therapies as ***low or very low quality***"

CDSR 2017, Issue 5. Art. No.: CD008609

"OTHER" TOPICAL THERAPIES

How clear is the evidence?

WHAT DO **PRACTICE GUIDELINES** SAY?

International Association for the Study of Pain

IASP

2015;23(4)

Treating Herpes Zoster and Postherpetic Neuralgia

Second-Line Agents According to the NeuPSIG Guidelines

Lidocaine patches (5%), capsaicin patches (8%), and tramadol are recommended as a second line of treatment. The reason for their being second-line is a low quality of evidence (lidocaine), a relatively small effect size (topical capsaicin), or lower tolerability or safety (tramadol).

Diabetic Neuropathy: A Position Statement by the American Diabetes Association

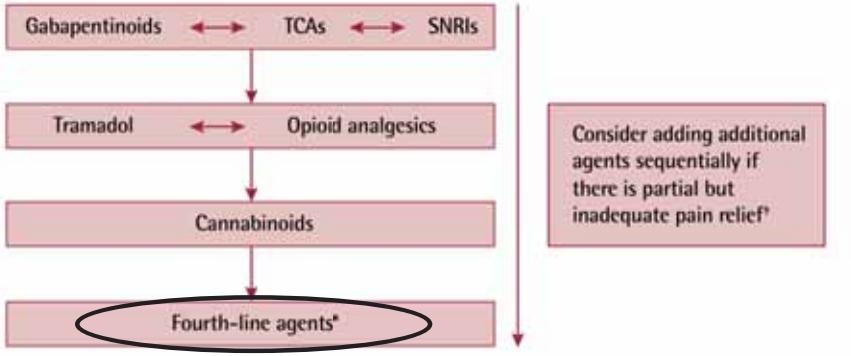
Diabetes Care 2017;40:136–154 | DOI: 10.2337/dc16-2042

- No mention of topical agents for PDN

Pharmacologic management of chronic neuropathic pain

Review of the Canadian Pain Society consensus statement (2014)

Figure 1. Algorithm for the pharmacologic management of neuropathic pain



*Fourth-line agents include topical lidocaine (second-line for postherpetic neuralgia)

†There is limited randomized controlled trial evidence to support add-on combination therapy.
Adapted from Moulin et al.[1]

Can Fam Physician 2017;63:844-52

Neuropathic pain in adults: pharmacological management in non-specialist settings

NICE 2013

Consider capsaicin cream[8] for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.

Additional research recommendations

- What is the clinical and cost effectiveness of lidocaine patches for localised peripheral pain?

"OTHER" TOPICAL THERAPIES: **RATIONALE** FOR USE

- Theory
- Extrapolation
- Clinical evidence

LIDOCAINE

Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews (Review)

Derry S, Wiffen PJ, Kalso EA, Bell RF, Aldington D, Phillips T, Gaskell H, Moore RA

"evidence does not exclude beneficial effects in a small percentage of people"

Topical lidocaine for neuropathic pain in adults (Review)

CDSR 2014, Issue rt. No.: CD010958

- 12 studies (n=508); PHN most common
- **no evidence from good quality RCTs** to support use, although 3rd tier studies indicated effectiveness for relief of pain ?
- no clear evidence of an effect on the incidence of adverse events or withdrawals ✓

2 commonly cited studies:

1. Rowbotham (1996)) (**5% patch vs. placebo**) n= 35
   → better pain scores at all time points
   → ~12mm difference (0-100) @ 12 hrs
2. Baron (2009) (**5% plaster vs. pregabalin**) n= 137
   → 30% pain⇩: **NNT = 8 for PHN** (lidocaine better), **no difference for PDN**
   → stopping due to side effects: **NNH = 6** (i.e. pregabalin worse)

CAPSAICIN

- **Low**-dose cream (0.025%, 0.075%)
  - *CDSR* 2012, Issue 9. Art. No.: CD010111:
    - 7 RCTs (n = 449) with various NeP conditions
    - * ***"Unlikely that low-concentration (< 1%) capsaicin provides any useful pain relief*** *in NeP conditions"* over 6-8 wks

    AND… Adverse event withdrawals 15% vs. 3% (placebo) → **NNH 8**
  - *Neurology* 2017;88:1958–67
    - 3 RCTs (n = 109) with **PDN** → SMD -0.46 [95% CI -0.95 to 0.03])
      - * **i.e. → Not effective, Low quality evidence**
- **High**-dose patch (8%) (with medical supervision)

  - *CDSR* 2017, Issue 1. Art. No.: CD007393:
    - **NNT = 11** for ≥ 30-50% pain reduction @ 8-12 wks

WHAT'S ON THE MB FORMULARY ?

Information for Pharmacists

Notice – Approved Compounds for Pain Management

January 19, 2018

Clinically effective concentrations for drugs that are benefits on the Manitoba Drug Benefits Formulary are as follows and MUST be present in clinically effective concentrations for the compound to be eligible:

- Ketamine (5 - 15%)
- Amitriptyline (2 - 10%)
- Ketoprofen (>5%)
- Baclofen (2 - 5%)
- Clonidine (0.1 - 0.3%)
- Nifedipine (2 - 16%)
- Amitriptyline (2 - 10%)
- Gabapentin (4 - 10%)
- Diclofenac (>5%) **Hmm, that's interesting**

Other active ingredients not listed above may be considered and will be evaluated as required.

1) What does this mean?
2) Who decided this?

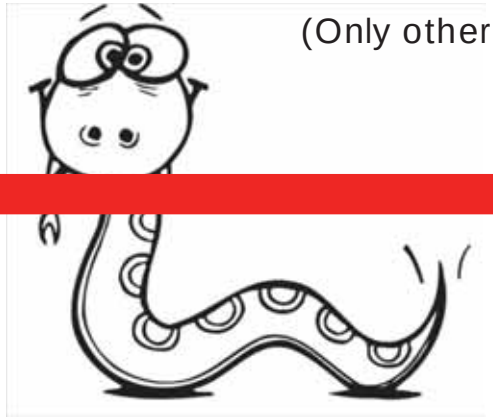
Let's dig deeper…

https://www.gov.mb.ca/health/pharmacare/profdocs/notice_pain_mgmt.pdf

GABAPENTIN:
Does it have a leg to stand on?

- Boardman, et al. (Obstet Gynecol. 2008 Sep;112(3):579-85)
  - **Who?** → n=51 women with vulvodynia → only 35 evaluable (no explanation)?
  - **What?** → Gabapentin 2-6% vs. nothing (no control grp)?
  - **Results** → 80% had ≥ 50% pain relief at 8 wks (37% on ? other therapies with no indication of start date)

(Only other study found: Letter to the Editor (*Br J Derm* 2015) n=23, no control grp)



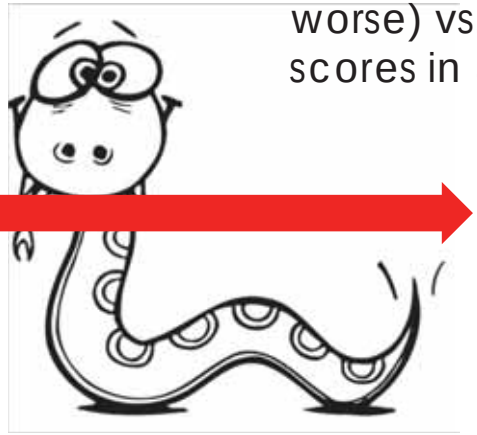
- **In theory**... maybe, but how?
- **Based on clinical evidence**... no, not really

(**recall MB Pharmacare:** "clinically effective concentrations... gabapentin 4-10%")

AMITRIPTYLINE:
Does it have a leg to stand on?

2 clinical trials exist:

1. Lynch (*Anesthesiology* 2005;103:140–6)
   - n = 92 (mixture of NeP types)
   - Amitriptyline **2%** → no better vs. placebo for pain scores @ 3 wks
2. Ho (*Clin J Pain* 2008;24:51–55)
   - n = 35 (mixture of NeP types)
   - Amitriptyline **5%** → no better (actually, statistically worse) vs. lidocaine 5% **AND vs. placebo** for pain scores in a 1-wk cross-over trial



- **In theory**… maybe (Na channel &/or adrenoceptor blockade?)
- **Based on clinical evidence**… no, not at all

(**recall MB Pharmacare:** "clinically effective concentrations… amitriptyline 2-10%")

DYNAMIC DUO?

- Let's **ADD KETAMINE…**
  - Lynch 2005:
    - → **no difference in pain scores** between **amit 2% + ket 1%** *vs.* placebo @ 3 wks
- Let's **INCREASE THE DOSE**…
  - Gewandter 2014:
    - n = **462**
    - amit **4%** + ket **2%** vs. placebo in CINP
    - → **no difference** in sensory symptoms @ 6 wks
- Let's **ADD BACLOFEN**…
  - Barton 2011:
    - n = **208**
    - amit **4%** + ket **2%** + **baclofen 1%** vs. placebo in CINP
    - → **no difference** in sensory symptoms @ 4 wks

The COMBO:
amitriptyline
+ ketamine

The

approach

Rx e.g. "ketoprofen 10%, amitriptyline 2%, gabapentin 2%, lidocaine 2% in Lipoderm"

The scientific method:

- What is the independent variable?
- What is the controlled variable?

Bottom line…

- without testing each variable (i.e. ingredient) in its own separate experiment, we won't know which is working (again, we have very little previous evidence that using any 2 ingredients together is better than 1)

Phrases to be **cautious** of:
→ "Synergistic effects"
→ "____ has worked well for my patients"

Open-label placebo treatment in chronic low back pain: a randomized controlled trial *Pain* 2016

"Compared to TAU, OLP elicited greater pain reduction (p< 0.001), with moderate to large effect sizes."

CDSR 2016, Issue 4. Art. No.: CD007400

Clinical success with carrier occurred in **~1/2** of those in studies lasting 6 - 12 weeks… response rates with carrier (topical placebo) are about twice those seen with oral placebo.

WHAT ABOUT THE **PLACEBO** EFFECT?

TABLE 2. Efficacy Outcomes in a Study of Diclofenac Sodium Gel in Patients With Osteoarthritis (Intent-to-Treat Population)

Outcome	DSG ($n = 207$)	Vehicle ($n = 212$)	Difference (95% CI)
WOMAC Pain at week 12[a] (0-20)			
Mean (SD)	6.1 (4.6)	7.1 (4.6)	
LS mean (SE)	6.1 (0.3)	7.2 (0.3)	1.2 (0.3–2.0)
Change from baseline	6.8 (4.5)	5.4 (4.5)	P = .008
WOMAC Physical Function at week 12[a] (0-68)			
Mean (SD)	21.7 (15.4)	25.7 (15.9)	
LS mean (SE)	22.0 (1.2)	26.1 (1.1)	4.1 (1.3–7.0)
Change from baseline	21.5 (15.3)	16.8 (15.7)	P = .004

J Pain Palliative Care Pharmacother 2012;26:18-23

If we suspected that at least some of the effect seen in a patient is a placebo effect, one could argue that this may be justifiable…

- **IF** we can be fairly certain there's no added safety concern with added medications, AND
- **IF** cost is not significantly different, AND
- **IF** the placebo effect is long-lasting **???**

"Few of them have reached a sufficient level of evidence to support systematic use as treatment options."

- Casale *et al, Curr Pain Headache Rep* 2017;21:15

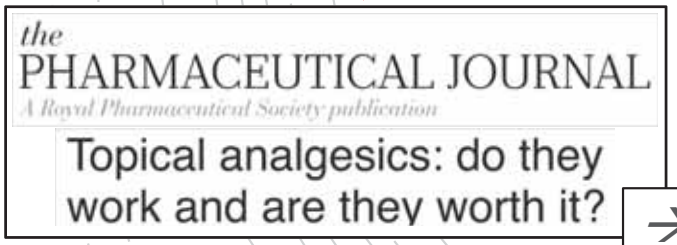
WHERE DOES THIS LEAVE US?

	BENEFIT?
NSAIDs 1-1.5% • OA • Acute MSK	
Lidocaine 5% plaster/patch • PHN • Other?	
Capsaicin <1%	
Gabapentin 2-6%	
Amitriptyline 2-5%	
Amitriptyline + ketamine 2-4%/1-2%	

Is it a dose thing?

→ i.e. have trials not gone high enough?

n = 1 TRIALS



Are individual patient trials **justifiable** when **evidence is not clear**

- *Maybe, but it depends on…*
  - The patient's adequately informed expectations and trade-off threshold
  - The patient's ability & willingness to pay
  - How scientific the approach is
    - **Not** the kitchen sink approach
    - **No assumptions** about higher concentration = better

i.e. each ingredient & each dose change is tested in the individual patient

→ *"Honest explanations to patients are vital"*

If I'm having **that** conversation, I'm starting to have **this** conversation…

CALLING IT QUITS
(pharmacologically)

How many tries are enough?

- Considering the trials themselves , follow-ups, re-assessments, costs…

When do we say,

"I don't think we have a <u>medication</u> solution"

?

WE: … continue to reset the stage

… **address frustration, hopelessness, coping ability**

… are reflecting on our/the patient's approach to the pain experience


QUESTIONS
?