Tom Perry, MD, FRCPC

UBC Therapeutics Initiative (ti.ubc.ca)

- Independent academic group
- budget $550 K
- no conflicts of interest
- reputation for integrity, accuracy

therapeutics letter

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

therapeutics letter
May - June 2016

Questioning the basis of approval for non-insulin glucose lowering drugs

Glucose lowering drugs are commonly prescribed in British Columbia, and 46% of adults with type 2 diabetes are receiving more than one drug (see Table). Annual spending on non-insulin glucose lowering drugs in Canada was $748 million in 2013.[1] When these drugs are taken, the underlying unproven assumption is that by lowering glucose they will prevent the complications of diabetes: premature death, myocardial infarction, stroke, amputation, neuropathy, renal failure and blindness. **This Letter documents that approval of new drugs is not based on these clinically important outcomes.**

Number of patients dispensed 1 or more different glucose lowering drugs in the same calendar month		
1 drug	119,287 patients	55.9%
2 drugs	64,966 patients	30.5%
3 drugs	23,176 patients	10.9%
≥ 4 drugs	5,885 patients	2.8%

*Pharmafile medication dispensing records; 213,577 people aged 40 and older. Estimate includes all insulin and non-insulin glucose lowering products approved by Health Canada as of February 2016 and excludes people dispensed insulin only between 2015 to 2016.

How does Health Canada assess non-insulin glucose lowering drugs?

In 2007, Health Canada issued the following guidance for clinical trials in type 2 diabetes: *"Clinical practice guidelines ensure the best standard of care based on current science and consensus in the medical and scientific communities. From the regulatory perspective, they are one of the measures against which the safety of the subjects is assessed during the review of clinical trial applications."*[2] Health Canada claims that adherence to Canadian Diabetes Association (CDA) guidelines *"will contribute to the safety of subjects"* and emphasizes a recommendation for *"more aggressive management of type 2 diabetes … tailored to aim for glycemic targets as close to normal as possible, and as early as possible, with the target HbA1c attained within 6 to 12 months"*.[3]

On this basis, non-insulin glucose lowering drugs approved since 2007 include (by date of approval): sitagliptin (Januvia), saxagliptin (Onglyza), liraglutide (Victoza), exenatide (Byetta), linagliptin (Trajenta), alogliptin (Nesina), canagliflozin (Invokana), dapagliflozin (Forxiga), albiglutide (Eperzan), empagliflozin (Jardiance), dulaglutide (Trulicity) and exenatide extended-release (Bydureon).[4] Health Canada's Summary Basis of Decision website presents its interpretation of the benefits and harms of drug therapies which *"reflects the information available to Health Canada regulators at the time a decision has been rendered"*.[5,6] As an example, Health Canada states that two 26-week studies supported a judgment on the clinical efficacy of liraglutide (Victoza), based on the surrogate outcome, change in HbA1c from baseline.[5] Health Canada's safety review identified the following signals: thyroid C-cell hyperplasia, thyroid C-cell tumors (animal studies), heart rate increase, PR interval prolongation, pancreatitis, hypoglycemia, gastrointestinal adverse events, immunogenicity, and injection site reactions.[5] Health Canada approved liraglutide in 2010 noting that *"Given the uncertainty regarding human risk for MTC [medullary thyroid cancer], the rejection of this product was considered; however, the clinical benefit of Victoza® as first-in-class in Canada for the treatment of Type 2 diabetes should also be considered and deemed worthwhile to balance the unknown human risk. Although there are several classes of products currently marketed in Canada for the treatment of Type 2 diabetes, there are still many patients with Type 2 diabetes (45% in the United States) who do not achieve the HbA1c target (< 7%) indicating that there is still an unmet need for new medications."*[4]

What are the potential benefits and harms of "more aggressive management of type 2 diabetes"?

A 2013 Cochrane systematic review identified 28 randomized controlled trials (RCTs) in which

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COI declaration

Thomas L. Perry, M.D., FRCPC

- **Consultant to a number of lawsuits against drug companies**
- **no relationship with pharmaceutical companies**

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Outline

- B.C. experience with evidence-based provincial drug plan since 1994
- National Pharmacare must be based on best evidence to get best results
- Evaluation of drugs must be independent of industry
- Harder than it looks
- First, a reminder why drugs are not always good

Who ensures drug safety and value?

The experiences of two women will help us understand why this is an important question (videos to be shown live at conference only)

Consider the many factors that determine benefits vs. harms of drugs …

Watch carefully - if you recognize patient, respect her confidentiality

Should we try to minimize what first video showed?

Health Canada's role

- Approves drugs for use in Canada
- Does not control how prescribers use them
- Standard is reasonable safety and some "benefit"
- New **NOT** better than old, just better than placebo for **something**
- Long term safety unknown
- Approval often on basis of surrogate outcomes

Example

Vortioxetine (antidepressant)

- Application 2012, Notice of Compliance 2014
- Efficacy for acute treatment of depression demonstrated in at least 1/11 short-term RCT
- No comparison with other antidepressants

Can you tell from this whether YOU would want to take vortioxetine (Trintellix) for depression?

Vortioxetine (latest antidepressant)

Would YOU would want to take it for depression?

What if you learn it is **less efficacious** than 2 other antidepressants?

"Some readers might ask: *'How could the FDA and EMA approve a new drug that appears to be less effective than other available antidepressants, and which failed to be more effective than placebo in a substantial subset of trials?*' The short answer is that regulatory standards for efficacy are not as strong as prescribers or the public may think: efficacy is defined in terms of a chosen effect, which may or may not be clinically relevant."

- Cosgrove L et al (including Barbara Mintzes). Under the Influence: The Interplay among Industry, Publishing, and Drug Regulation. Accountability in Research 2016. http://dx.doi.org/10.1080/08989621.2016.1153971

UBC Therapeutics Initiative - History

- 1973: B.C. Pharmacare established
- 1989: costs rising at 16%/y
- 1994: more drugs, higher costs, large budget deficit. Ministry of Health needs scientific review of new drugs
- TI starts - $450K budget

- No conflicts of interest
- Scientific review of evidence
- Government makes courageous funding decisions based on available evidence
- Role includes education and impact evaluation

Elements for success

1. Clarify scientific evidence, free from bias

2. Report it accurately

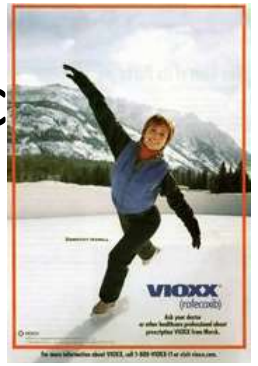
1. Basis for government funding policy is evidence, not opinion

1. Adequate funding to maintain and rejuvenate academic group ($1 M/y)

Results by 2007

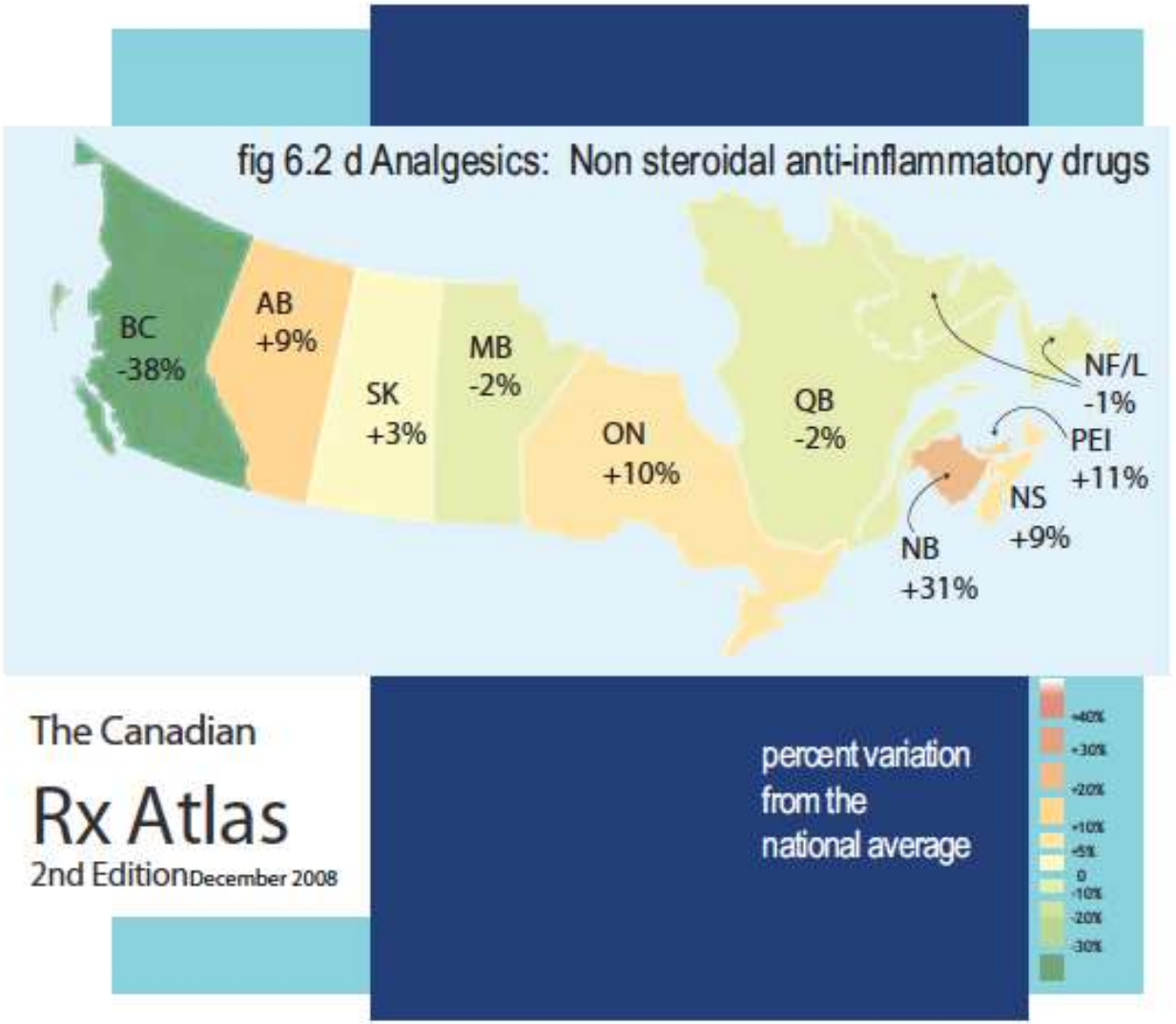
- B.C. drug costs $701 M/y < Canadian mean
- $208 M/y savings from lower cost drugs
- Some expensive drugs not covered; e.g.: donepezil (Aricept), celecoxib (Celebrex), rofecoxib (Vioxx), rosiglitazone (Avandia)
- No evidence of harm – probably saved lives
- Precedent for Common Drug Review at national level

Example 1: new NSAIDS licensed 1999 -



- celecoxib (Celebrex), rofecoxib (Vioxx), valdec (Bextra), meloxicam (Mobicox), lumiracoxib (Prexige)
- promoted as “safer” than traditional NSAIDs
- **Real evidence** showed they were not safer; some **more dangerous** (valdecoxib, rofecoxib, lumiracoxib soon removed from market)
- **Pharmacare did not pay for them routinely**

2007 per capita NSAIDs << Canada

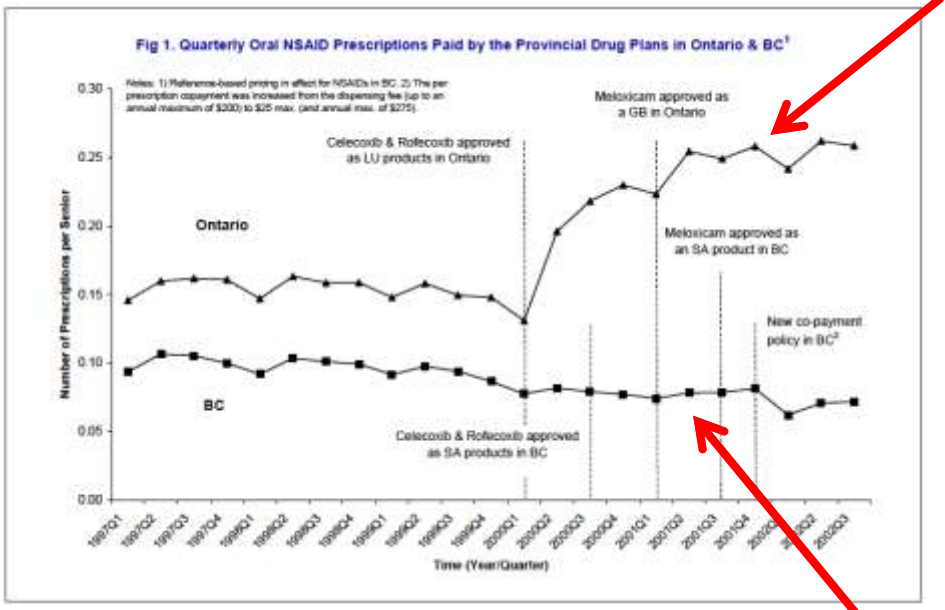


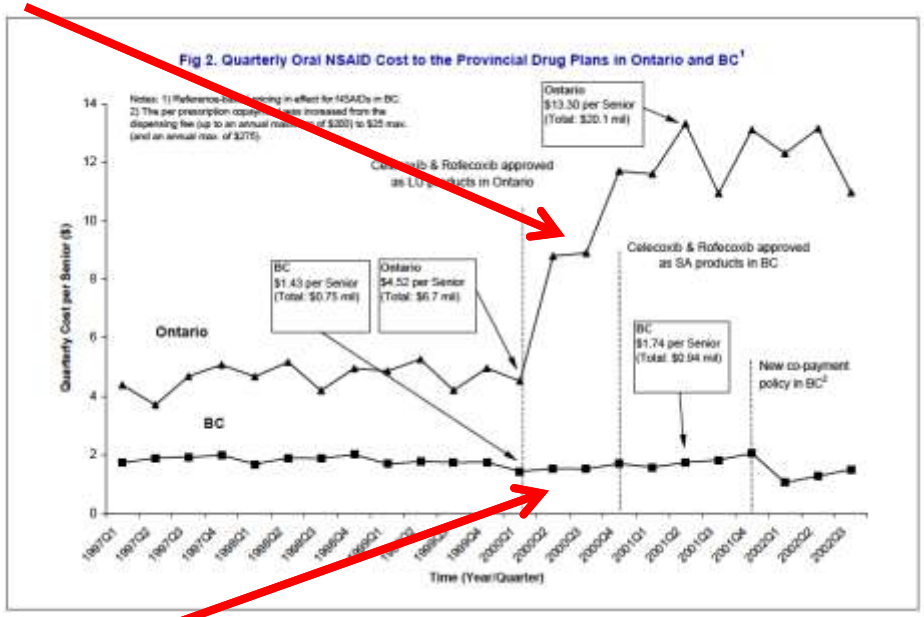
Evidence-informed policy (year 2000)

reimbursed Rx

Cost to province

Ontario





BC

BC's evidence-informed policy

- NSAID use < Ontario
- Unlike Ontario, no large rise in Rx
- Fewer hospitalizations for GI bleeds
- Much lower costs

Q: Why did B.C. win and Ontario lose?

A: Evidence and government backbone

Example 2: drugs for dementia

- donepezil (Aricept), rivastigmine (Exelon), galantamine (Reminyl)
- promoted as beneficial for Alzheimer's
- **Real evidence** showed not usually effective but **dangerous** for some patients
- **Pharmacare did not pay**

Myth

"These days, we've got to look out for ourselves …

… (Doctor) thanks for not forgetting your Alzheimer patients!"

Scientific approach to drug policy

Drugs for Alzheimer's Disease 2005

- No improvement of outcomes important to patients & caregivers
- Significant adverse effects
- Cost (then) $2.5-$5 per day

BC did not pay, until political pressure changed policy

Results

- Dementia drugs used less in B.C., saved $
- No evidence of harm
- Drugs now accepted as of minimal benefit, with many troublesome side effects
- B.C. policy probably saved lives or injuries (e.g. hip fractures from falls)

Reference-based pricing in B.C.

- For calcium channel blockers, 12% cost saving in 1997 without any harms to health

Clin Pharmacol Ther 2003

PHARMACOEPIDEMIOLOGY AND DRUG UTILIZATION

Clinical and economic consequences of reference pricing for dihydropyridine calcium channel blockers

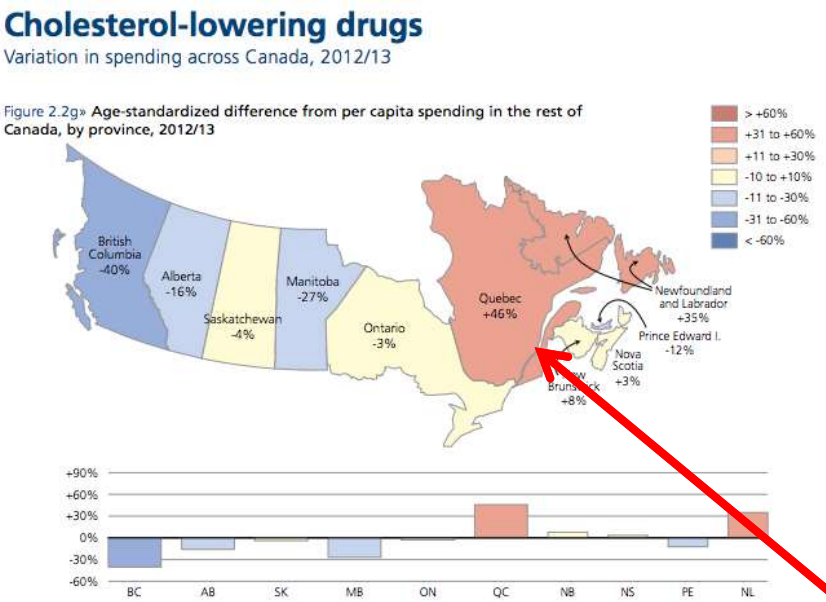
- For ACE-inhibitors, 19% cost saving in 1997 without any harms to health

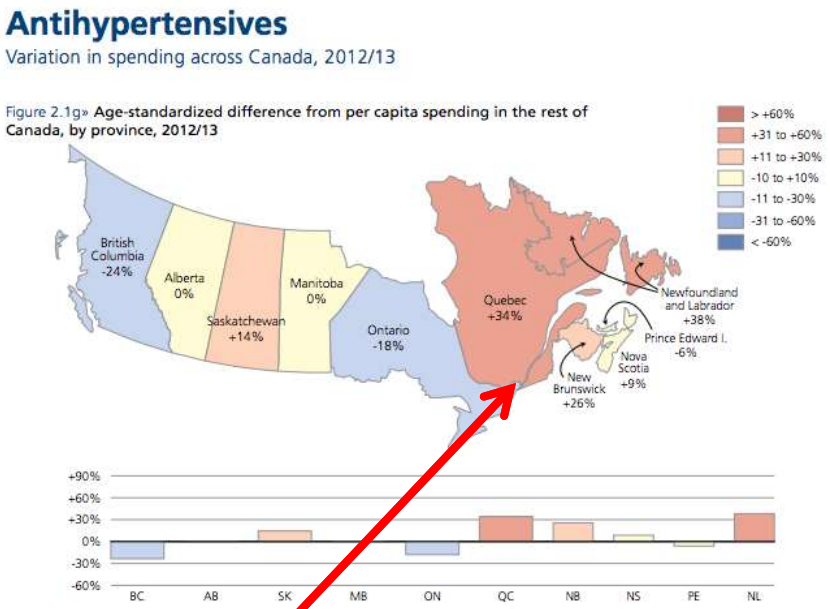
Update: Rx Atlas 2013

Pourquoi le Quebec depense-t'il autant plus?

Drugs to lower cholesterol

Drugs to lower BP





Morgan S et al. Canadian Rx Atlas 2013

Why?

2013: Why is Ontario still >> BC?

Overall

Variation in spending across Canada, 2012/13

Figure 1g» **Age-standardized difference from per capita spending in the rest of Canada, by province, 2012/13**

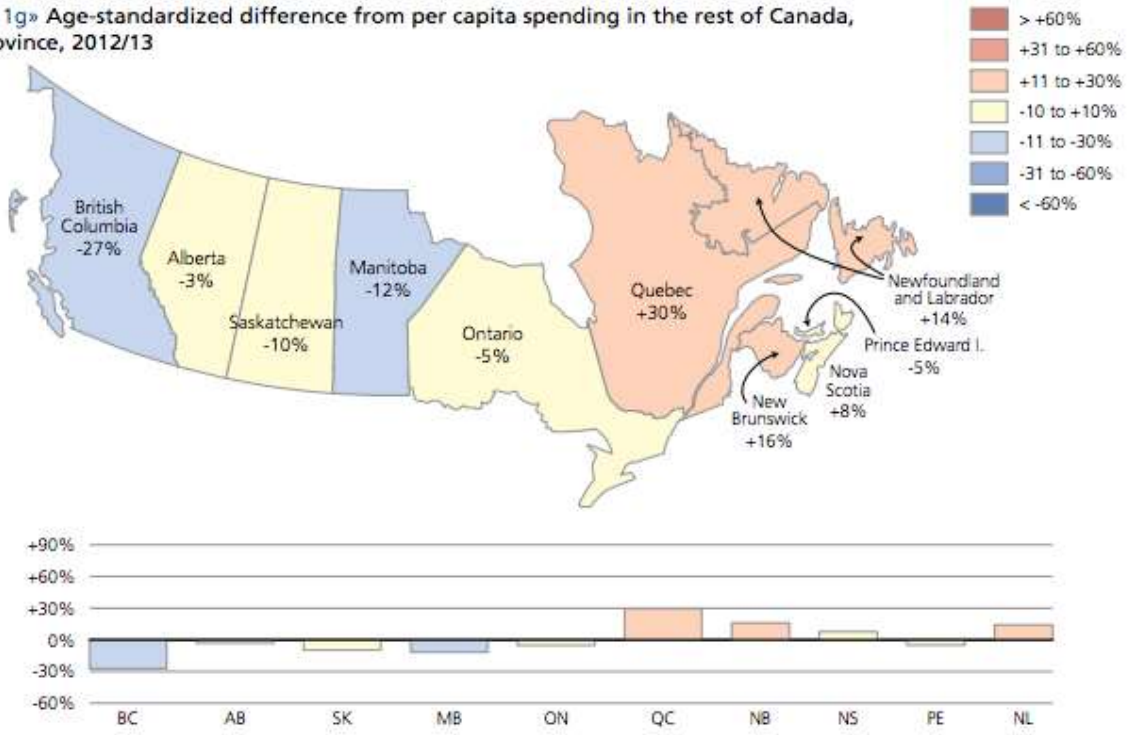


Figure 1h» **Sources of age-standardized difference from per capita spending in the rest of Canada, by province, 2012/13**

Morgan S et al. Canadian Rx Atlas 2013

2013: Pregabalin & gabapentin less in BC – why?

- Canada per-capita spending on pregabalin and gabapentin increased 10.1%/y (62%) from 2007/08 to 2012/13
- **Nfld & Labrador** ↑ **90%**
- **BC** ↑ **5%**


therapeutics letter

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Gabapentin for pain

New evidence from hidden data

Background

therapeutics letter

July - December 2009

Figure: Outpatient costs of gabapentin in B.C. from 1998-2009, based on PharmaNet data

Re-evaluation including unpublished trials

How Neurontin became a blockbuster

Chronic "neuropathic" pain

Benefits: 9 trials (N=1917) assessed mean pain reduction from baseline. Gabapentin reduced weighted mean pain score by -0.78 (-0.99, -0.58) as compared with placebo on a 0-10 point scale. 7 trials (N=1971) assessed patient-reported "moderate or much improvement": gabapentin 37.7%, placebo 20.2%, difference 17.5%, NNT=6. 3 trials (N=1058) assessed percentage of patients achieving at least a 50% reduction in pain score: gabapentin 31.4%, placebo 18.4%, difference 13%, NNT=8. Efficacy was greater in PHN than for other pain conditions.

Harms: In 12 trials (N=2362) gabapentin

Morgan S et al. Canadian Rx Atlas 2013

Conclusions and recommendations

- Misleading promotion pushed gabapentin to blockbuster status; scientific evidence suggests gabapentin has a minor role in pain control.

Do decision-makers respond to evidence like this?

Solifenacin (Vesicare):

anticholinergic that can slightly reduce bladder leakage but causes dry mouth, constipation, blurred vision, impaired thinking, or worse

See: www.ti.ubc.ca for details

Not everyone loves TI

2007 BC > Canadian average

- + 13% for new drugs for chronic pain (gabapentin, pregabalin, topiramate) **policy failure?**
- + 9% for erectile dysfunction drugs (**why?**)

2007 BC << Canadian average

- - 41% cholinesterase inhibitors
- - 38% bisphosphonates
- - 38% NSAIDs (? mainly coxibs)
- - 38% inhaled drugs
- - 37% psychostimulants
- - 34% statins
- - 34% oral diabetes drugs …

Consequences

- 2007: Pharmaceutical Task Force
  conflicted members recommend abolishing TI
- 2008: BC government reduces TI role and budget
- 2012: BC government suspends funding; fires 8 Ministry of Health employees; denies data access for research
- 2014-2017: ½ of original budget - unsustainable

"better to live on our knees than die on our feet"

We're still here (ti.ubc.ca)

- We assess some new drugs for Therapeutics Letters & MOH
- We educate doctors & pharmacists (effect <<< Pharma)
- We assess drug effects at population level by pharmacoepidemiology
- We helped establish Common Drug Review


therapeutics letter

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Is the current 'glucocentric' approach to management of type 2 diabetes misguided?

therapeutics letter
November - December 2016

103

Copies available at Conference and online

Common Drug Review

- 2003: national process to avoid redundant provincial reviews
- Provinces (sans Quebec) contribute $
- Run by CADTH (Ottawa)
- Input from patient groups and manufacturer (+ rebuttal)
- Canadian Drug Expert Committee reviews reports & recomments +/- reimbursement

Summaries are succinct and accessible

Advantages of CDR - example

Advantages

- 6-page summary
- Publicly accessible (cadth.ca/fentanyl-buccal)
- National buy-in (sans Quebec)
- Clear recommendation
- Can protect private payers if they know to look

Fentora (fentanyl) – Feb 21, 2017

COMMON DRUG REVIEW

CADTH CANADIAN DRUG EXPERT COMMITTEE
FINAL RECOMMENDATION

Fentanyl buccal/sublingual effervescent tablet
(Fentora — Teva Canada Innovation)
Indication: Breakthrough cancer pain (adults)

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that Fentora not be reimbursed for the management of breakthrough pain in patients with dysphagia or a lack of adequate pain relief or intolerable opioid-related toxicities or adverse events or contraindication to morphine, oxycodone, or hydromorphone.

Reasons for the Recommendation:
1. There is no evidence available to evaluate the efficacy and safety of Fentora in the population specified in the request for reimbursement; specifically, patients with dysphagia and/or a lack of adequate pain relief and/or intolerable opioid-related toxicities or adverse events or contraindication to morphine, oxycodone, or hydromorphone.
2. There is no evidence that patients who are unable to achieve pain relief with the pain management strategies that are currently available would benefit from treatment with Fentora.

Background:
Fentora has a Health Canada indication for the management of breakthrough pain in cancer patients aged 18 years and older who are already receiving and who are tolerant to continuous opioid therapy for their persistent baseline cancer pain. Fentora is available in multiple doses — 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg — as fentanyl citrate buccal/sublingual effervescent tablets.

Summary of CDEC Considerations
CDEC considered the following evidence: a systematic review of randomized controlled trials (RCTs) of Fentora and a critique of the manufacturer's pharmacoeconomic evaluation.

Patient Input Information:
No patient input was received for this submission.

Disadvantages of CDR model

- Built-in protection for pharmaceutical companies **(confidentiality protects commercial interests but trumps patient interests)**
- Confidentiality limits education about what is learned and training of new people

CADTH Common Drug Review
Clinical Review Report

March 2017

Drug	Fentanyl (FENTORA)
Indication	Management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to continuous opioid therapy for their persistent baseline cancer pain.
Reimbursement request	Management of breakthrough pain in advanced cancer patients 18 years of age or older with the underlying pain adequately managed using a continuous opioid therapy (persistent baseline cancer pain) and one or more of: • Lack of adequate pain relief and/or intolerable opioids related toxicities or adverse events or contraindication to any one of the following short acting/immediate release opioids: morphine, oxycodone, hydromorphone and/or • Difficulty to swallow (dysphagia)
Dosage form (s)	100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg (buccal/sublingual effervescent tablet)
NOC date	21/11/2013
Manufacturer	Teva Canada Innovation

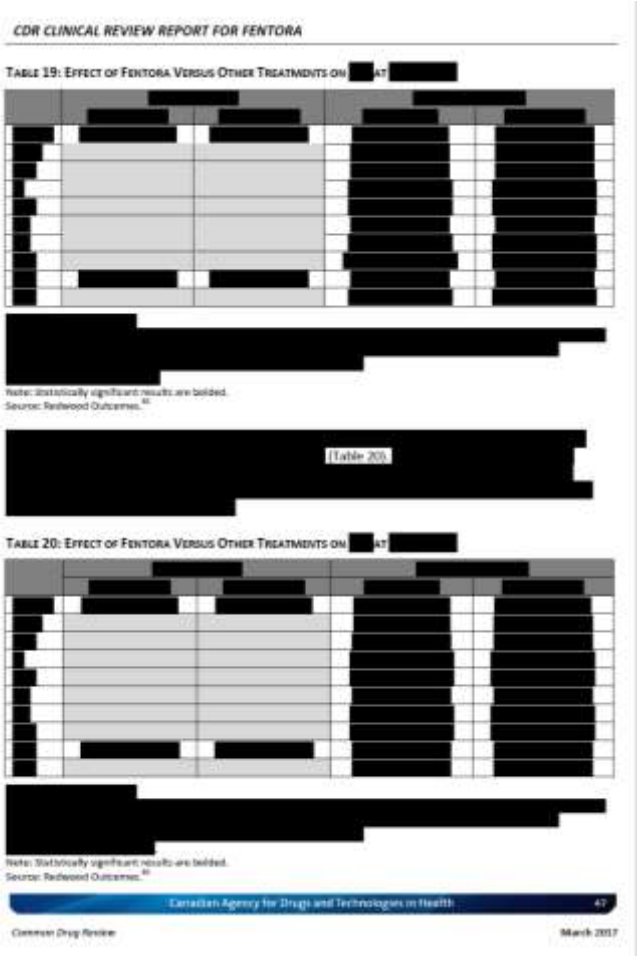
Example: March 2017

fentanyl buccal/sublingual (Fentora)

Disadvantage: example oral fentanyl

We pay for work, but don't get to see results

Summary of comparisons



CDR CLINICAL REVIEW REPORT FOR FENTORA

TABLE 19: EFFECT OF FENTORA VERSUS OTHER TREATMENTS ON [redacted] AT [redacted]

[redacted]

Note: Statistically significant results are bolded.
Source: Redwood Outcomes.[redacted]

[redacted] (Table 20).

TABLE 20: EFFECT OF FENTORA VERSUS OTHER TREATMENTS ON [redacted] AT [redacted]

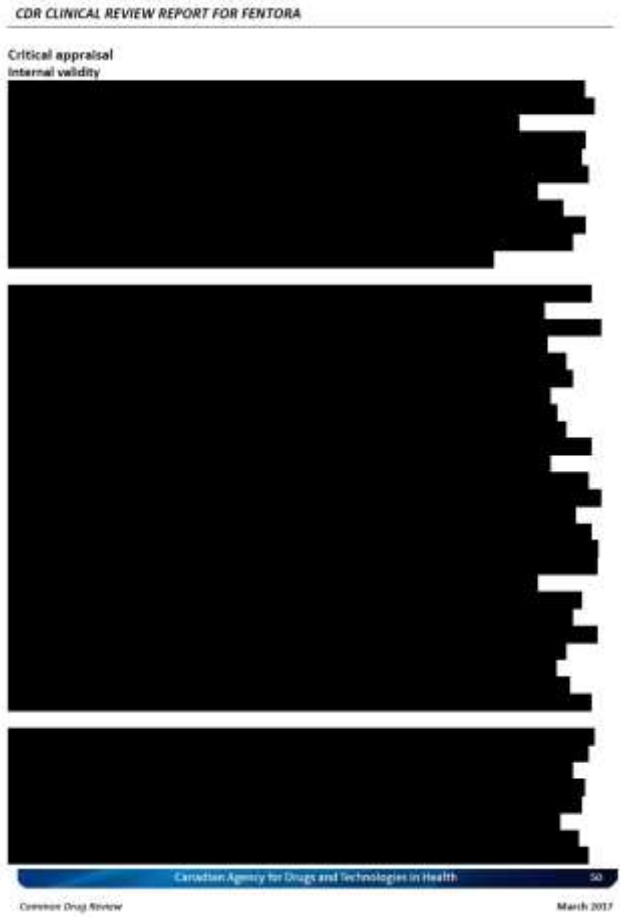
[redacted]

Note: Statistically significant results are bolded.
Source: Redwood Outcomes.[redacted]

Canadian Agency for Drugs and Technologies in Health 47

Common Drug Review March 2017

Critical appraisal of evidence



CDR CLINICAL REVIEW REPORT FOR FENTORA

Critical appraisal
Internal validity

[redacted]

Canadian Agency for Drugs and Technologies in Health 50

Common Drug Review March 2017

Are these the *'sunny ways'* of 2017?

Summary of comparisons

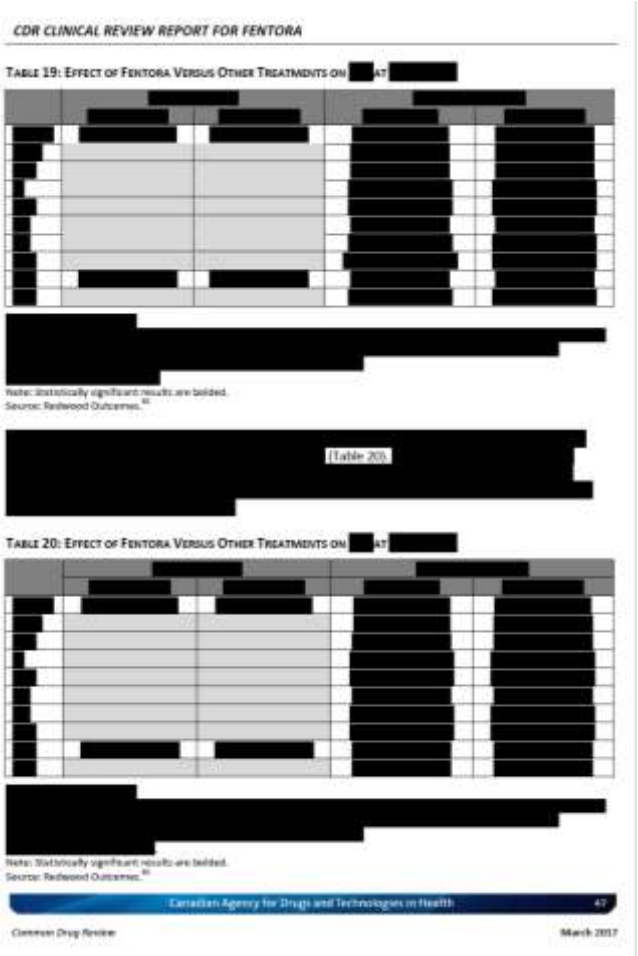

CDR CLINICAL REVIEW REPORT FOR FENTORA

TABLE 19: EFFECT OF FENTORA VERSUS OTHER TREATMENTS ON [redacted] AT [redacted]

[redacted]

Note: Statistically significant results are bolded.
Source: Redwood Outcomes.[redacted]

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TABLE 20: EFFECT OF FENTORA VERSUS OTHER TREATMENTS ON [redacted] AT [redacted]

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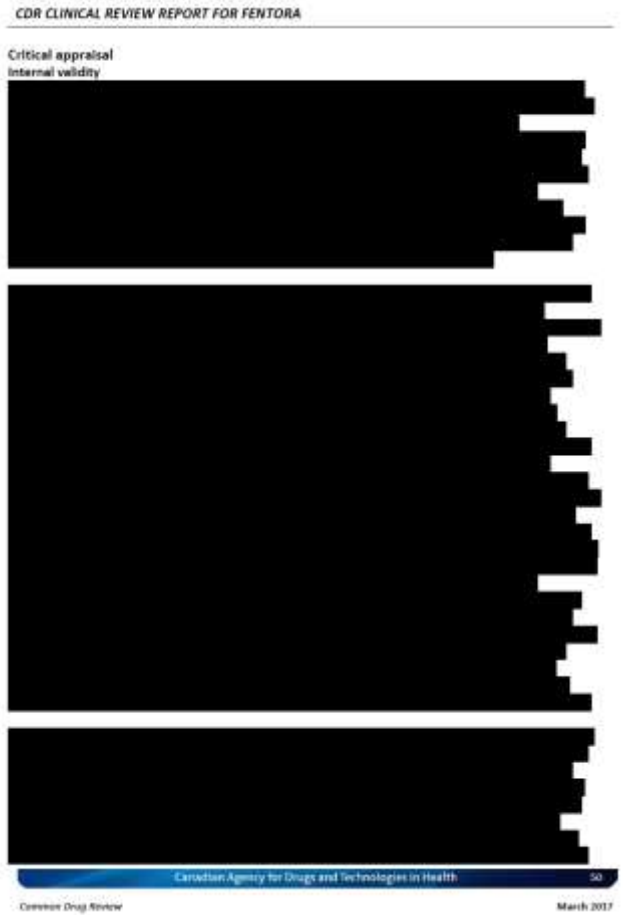
Critical appraisal of evidence


CDR CLINICAL REVIEW REPORT FOR FENTORA

Critical appraisal
Internal validity

[redacted]

Canadian Agency for Drugs and Technologies in Health 50

Common Drug Review March 2017

Reminder: Why are we here today?

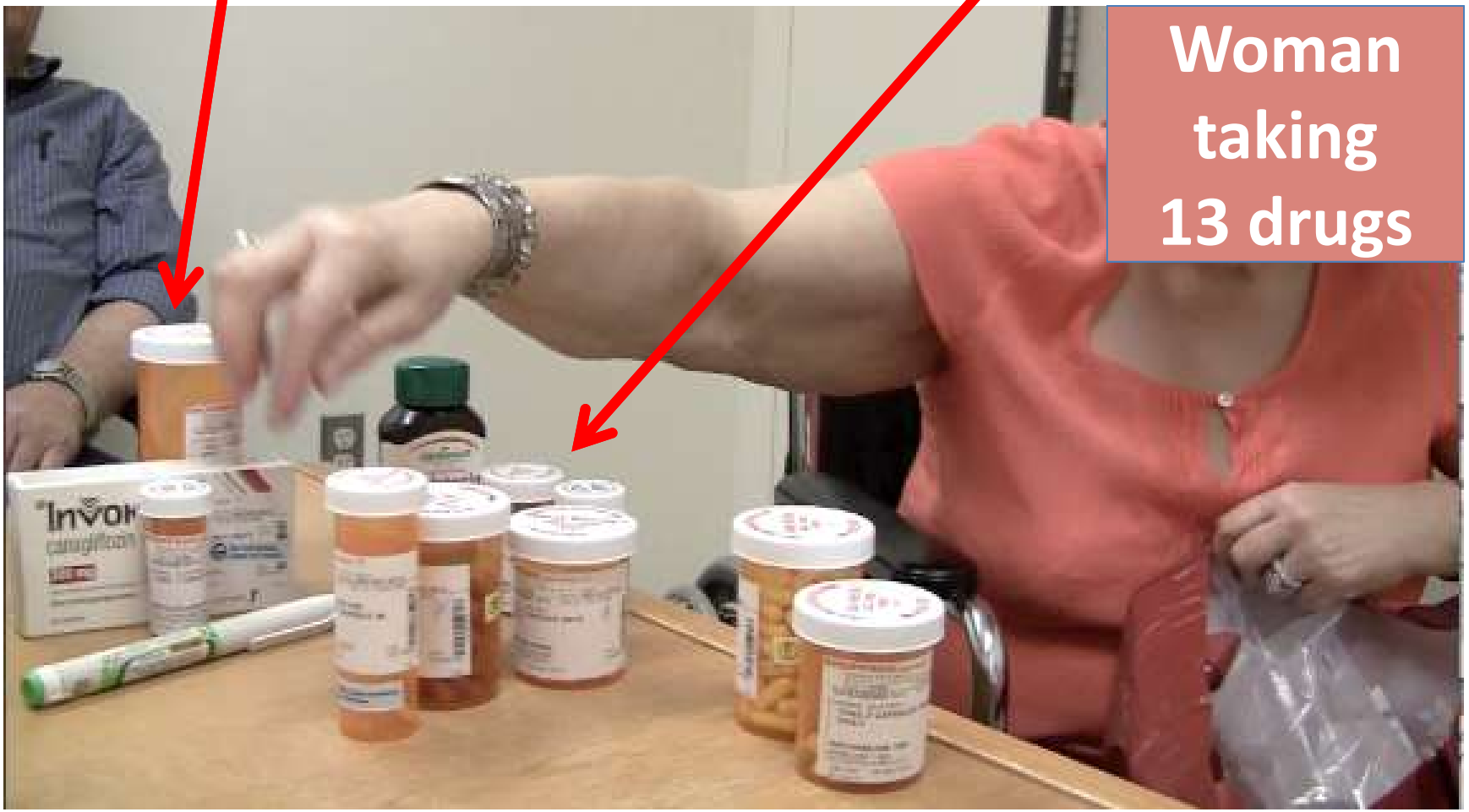
More drugs sans benefits NOT the goal

4 diabetes drugs:

1 new, expensive, ? benefit

1 expensive “me too”

3 sedative/antidepressants



Harms > benefits = bad policy

Wise formularies can help avoid this

(video example in live presentation)

Why we're here today

Dr. Monika Dutt, Canadian Doctors for Medicare
House of Commons Committee - June 6, 2016

- Teenage boy has diabetes requiring insulin
- Parents sometimes cannot afford it
- Mother ends up begging doctor for samples

Dr. Dutt: "That's not the way this teenage boy should have to deal with his health."

Logical expectations of a national pharmacare program

1. **Improve** health of Canadians

2. **Do not increase harms** of inappropriate or excessive use of prescription drugs

3. **Reduce drug costs** to:

a) remain sustainable

b) allow funding of other health determinants: **food & water, education, housing, physical fitness**

Policy and technical requirements:

1. Formulary based on best available evidence evaluated by completely independent group - no conflicts with drug industry

2. Independent group requires expertise in systematic review and critical appraisal as well as practicing clinicians.

Conclusions

- National Pharmacare needs best evidence to get best results
- Evaluation of new drugs must be independent of industry
- B.C. and some countries have shown benefits of this approach
- Harder than it looks, but only way to protect public interest

UBC Therapeutics Initiative
www.ti.ubc.ca

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- and many others including students, grad students, post-docs