

TAKING THE **BM** OUT OF **EBM**: AN EVIDENCE YEAR IN **REVIEW**

MEDS 2021

Jamie Falk, BScPharm, PharmD

Shawn Bugden, BScPharm, MSc, PharmD



University
of Manitoba



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CONFLICTS OF INTEREST

- Presenter's Name: Jamie Falk, Shawn Bugden
- **We have no conflicts to disclose**
- This program has received no financial or in-kind support from any commercial or other organization





“OUTLINE”

- Mask shortage Solved
- CREDENCE Clearwater & Renal Function
- Statins... These are not the tests you are looking for
- Here comes the sun... shedding some light on melanoma rates
- ETHOS... should we believe?
- I think that should work and it does?
- Less with More... BMJ Paper of the Year
- This is Nuts
- I take that back (but not really)
- Subway of Death: on the Moral Determinants of Health
- Pulling Down Statues: Realistic Osler
- Downward Facing Dog and Depression
- Opioids: More is More problems
- The Audacity of Hope... Quick Update on Manitoba's Opioid Atlas
- Bull S – enantiomers



“RESEARCH” NOT IN 2020, BUT COULD’VE BEEN...



terrible bra-mask
technique

Ig® Nobel

2009

PUBLIC HEALTH PRIZE: [Elena N. Bodnar](#), [Raphael C. Lee](#), and [Sandra Marijan](#) of Chicago, Illinois, USA, for inventing a brassiere that, in an emergency, can be quickly converted into a pair of protective face masks, one for the brassiere wearer and one to be given to some needy bystander.

REFERENCE: U.S. patent # 7255627, granted August 14, 2007 for a “[Garment Device Convertible to One or More Facemasks.](#)”

WHO ATTENDED THE CEREMONY: Elena Bodnar.



Last year...

CREDENCE

This year...

DAPA CKD

N Engl J Med Sept 24, 2020 DOI: 10.1056/NEJMoa2024816

	Canagliflozin <i>no./total no.</i>	Placebo	Hazard Ratio (95% CI)	@2.6yrs	@2.4yrs
Efficacy				ARR	ARR
Primary composite outcome	245/2202	340/2199	0.70 (0.59–0.82)	4.4%	5.3%
Doubling of serum creatinine level	118/2202	188/2199	0.60 (0.48–0.76)	3.2%	4.1%
End-stage kidney disease	116/2202	165/2199	0.68 (0.54–0.86)	2.2%	2.4%
Estimated GFR <15 ml/min/1.73 m ²	78/2202	125/2199	0.60 (0.45–0.80)		
Dialysis initiated or kidney transplantation	76/2202	100/2199	0.74 (0.55–1.00)	1.1%	1.7%
Renal death	2/2202	5/2199	NA	NNT=91	NNT=60
Cardiovascular death	110/2202	140/2199	0.78 (0.61–1.00)		
Amputation	3.2% (n=70)	2.9% (n=63)	1.11 (0.79-1.56)		
Fracture	3.0% (n=67)	3.1% (n=68)	0.98 (0.70-1.37)		



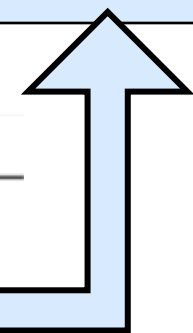
ARR
5.3%

ARR
4.1%

ARR
2.4%

ARR
1.7%

NNT=60



CLASS EFFECT? → **DAPA-CKD**
 → EMPA-KIDNEY (estimated completion 2022)

BACK IN TIME...



PREVENTION AND MANAGEMENT OF
CARDIOVASCULAR DISEASE RISK IN PRIMARY CARE
Clinical Practice Guideline | February 2015



SEPT 2020...

CLINICAL GUIDELINE

Annals of Internal Medicine

Management of Dyslipidemia for Cardiovascular Disease Risk Reduction: Synopsis of the 2020 Updated U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline

Patrick G. O'Malley, MD, MPH; Michael J. Arnold, MD; Cathy Kelley, PharmD; Lance Spacek, MD; Andrew Buel, DO; Sundar Natarajan, MD, MSc; Mark P. Donahue, MD; Elena Vagichev, PharmD; Jennifer Ballard-Hernandez, DNP, FNP-BC; Amanda Logan, MPS, RDN, LD; Lauren Thomas, MS, RDN, LD; Joan Ritter, MD; Brian E. Neubauer, MD, MHPE; and John R. Downs, MD



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SOME KEY TAKE-HOMES...

- For patients not on statins, if ordering lipid levels, order **non-fasting** and not more frequently than **every 10 yrs** (Weak)
- Offer **moderate-dose statins (e.g. atorvastatin 10-20mg)** for patients with 10-yr hard CV risk (e.g. MI, stroke, or CV death) of $\geq 12\%$, LDL of 4.9 mmol/L, or diabetes (Strong)
- Offer moderate-dose statins to those with 10-yr hard CV risk of 6-12% after **discussion of risks, benefits, and preferences** (Weak)
- For **secondary prevention, use moderate-dose statins and, if patient willing...** high-dose statins and/or additional medications (e.g. ezetimibe) (Weak)
- **Do not routinely monitor lipid levels or target LDL** levels in patients receiving statins (Weak)
- Encourage a dietitian-led **Mediterranean diet and regular aerobic physical activity of any intensity & duration** (Weak)
- Implement a structured, **exercise-based cardiac rehab program** for patients with recent coronary heart disease (Strong)



THE CURIOUS CASE OF.....



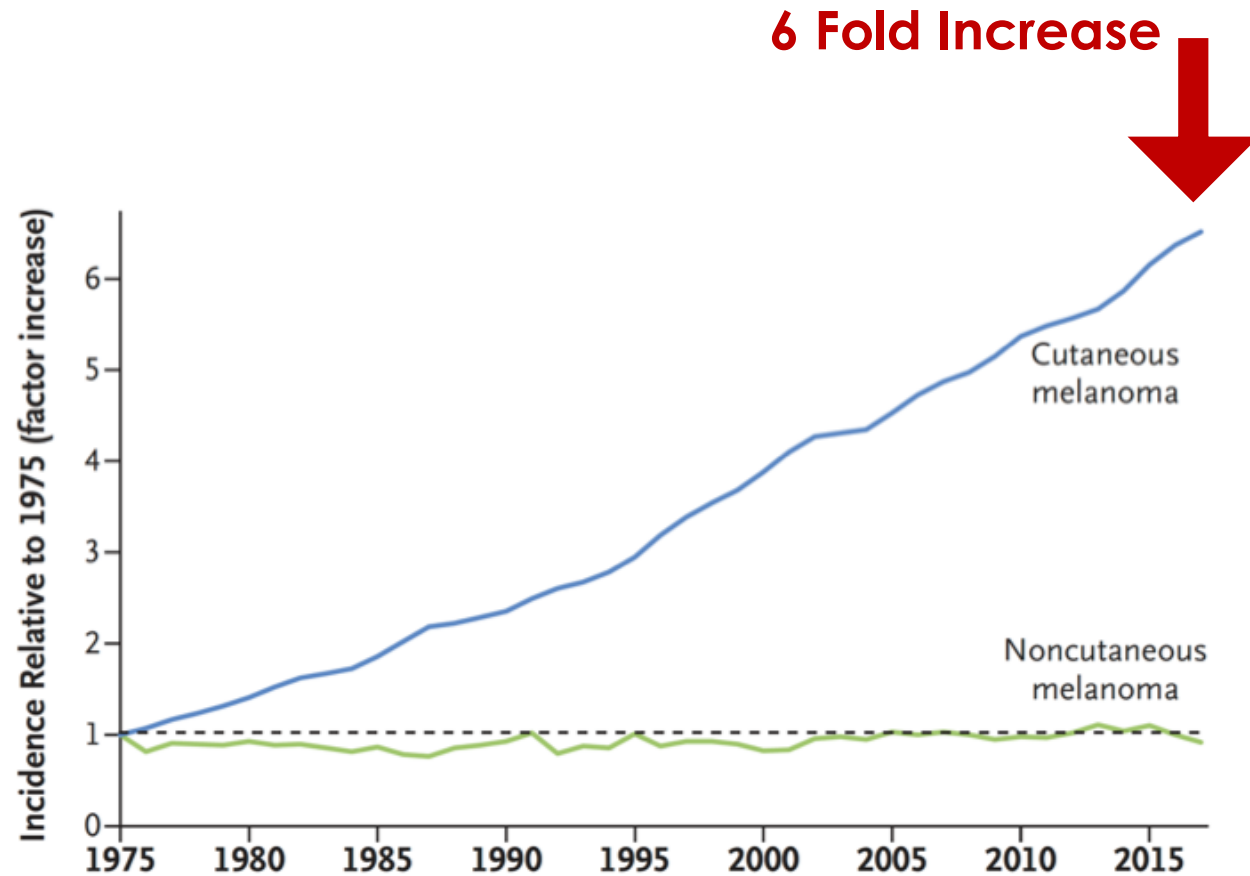
SOUNDING BOARD

The Rapid Rise in Cutaneous Melanoma Diagnoses

H. Gilbert Welch, M.D., M.P.H., Benjamin L. Mazer, M.D., M.B.A.,
and Adewole S. Adamson, M.D., M.P.P.



THE CURIOUS CASE OF THE RAPID RISE IN CUTANEOUS MELANOMA



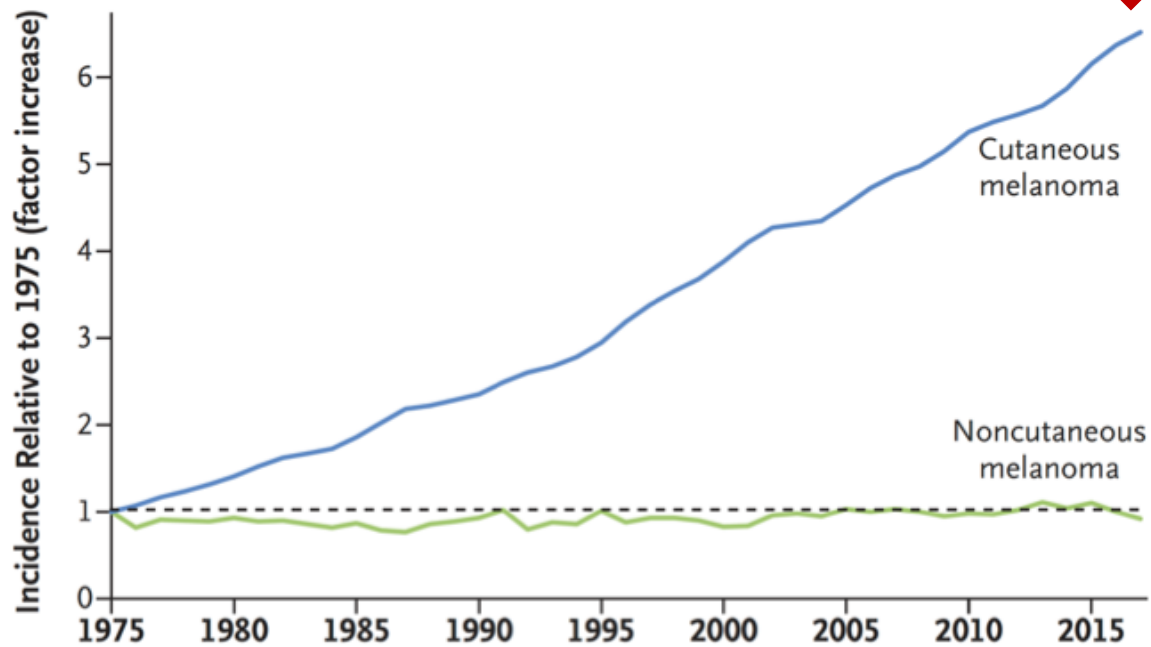
WHY?



HERE COMES THE SUN



6 Fold Increase



Risk

- Sun Exposure RR 1.34 95% CI 1.02 to 1.77
- Sun Burn RR 2.03 95% CI 1.73 to 2.37
- Tanning Beds RR 1.42 95% 1.15 to 1.74

2

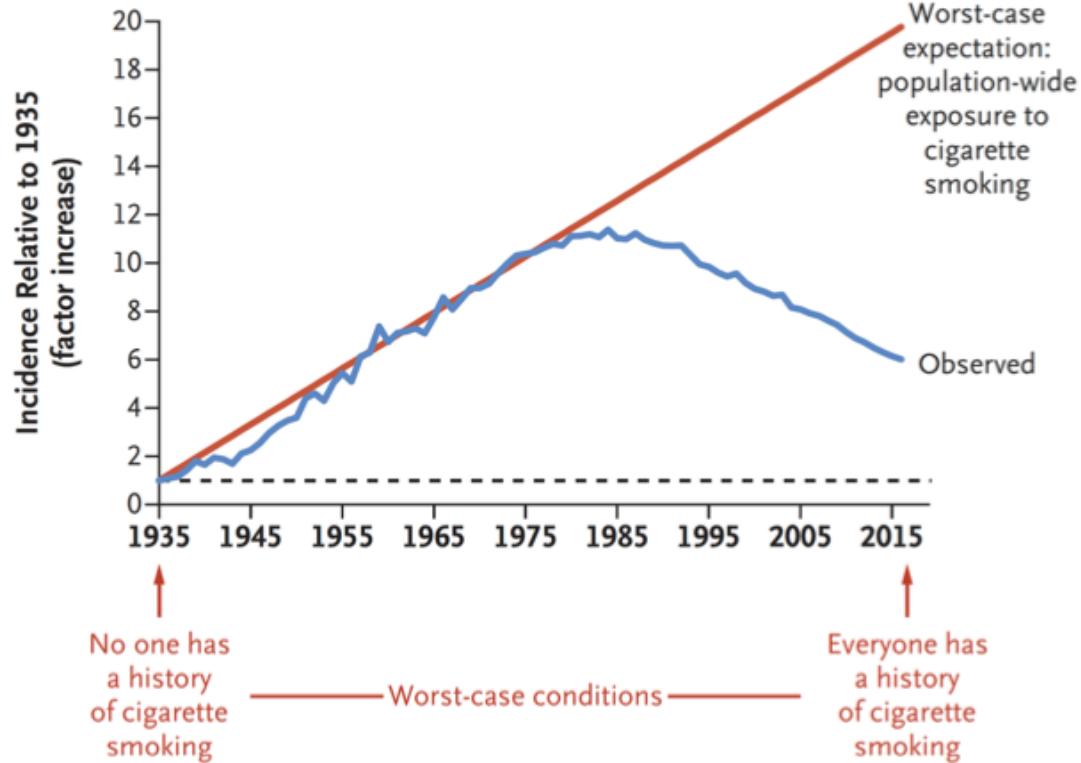
Chen, S.T. et al. *Curr Dermatol Rep* 2013;2:24.
Gandini S. et al. *Eur J Cancer* 2005;41:45.
Boniol M. et al. *BMJ* 2012;347:57.

MAYBE NOT

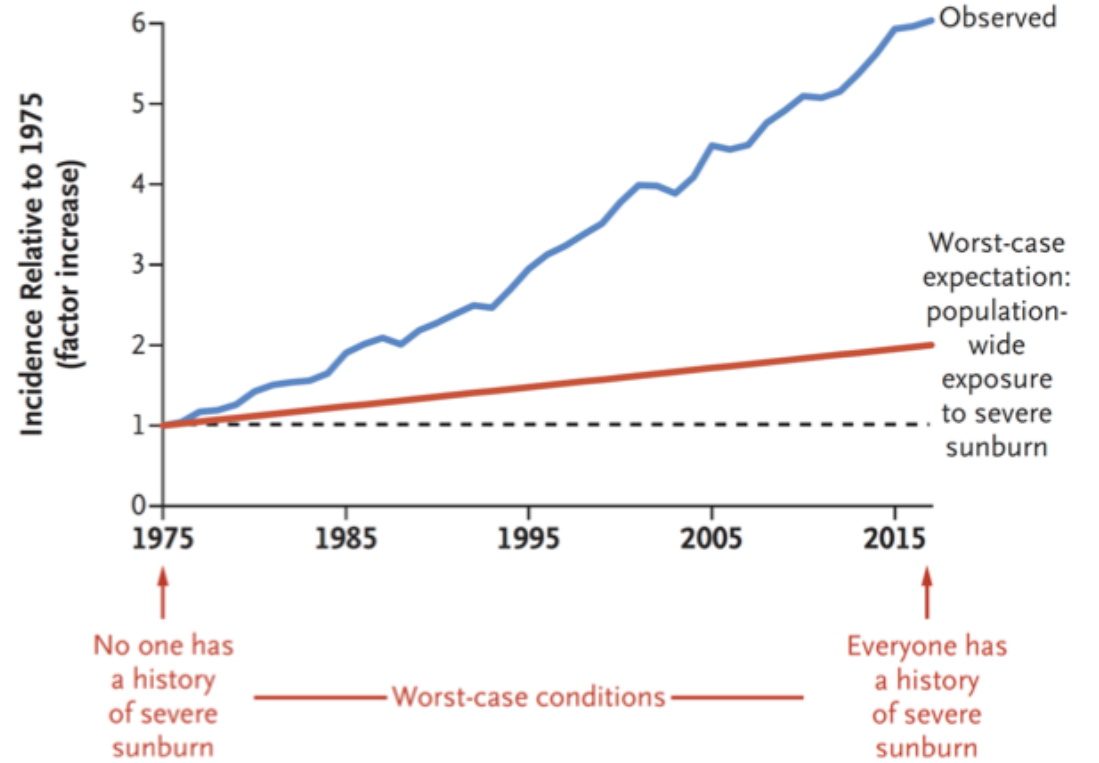
Smoking Risk RR = 20

Sunburn Risk RR = 2

A Lung Cancer among Men

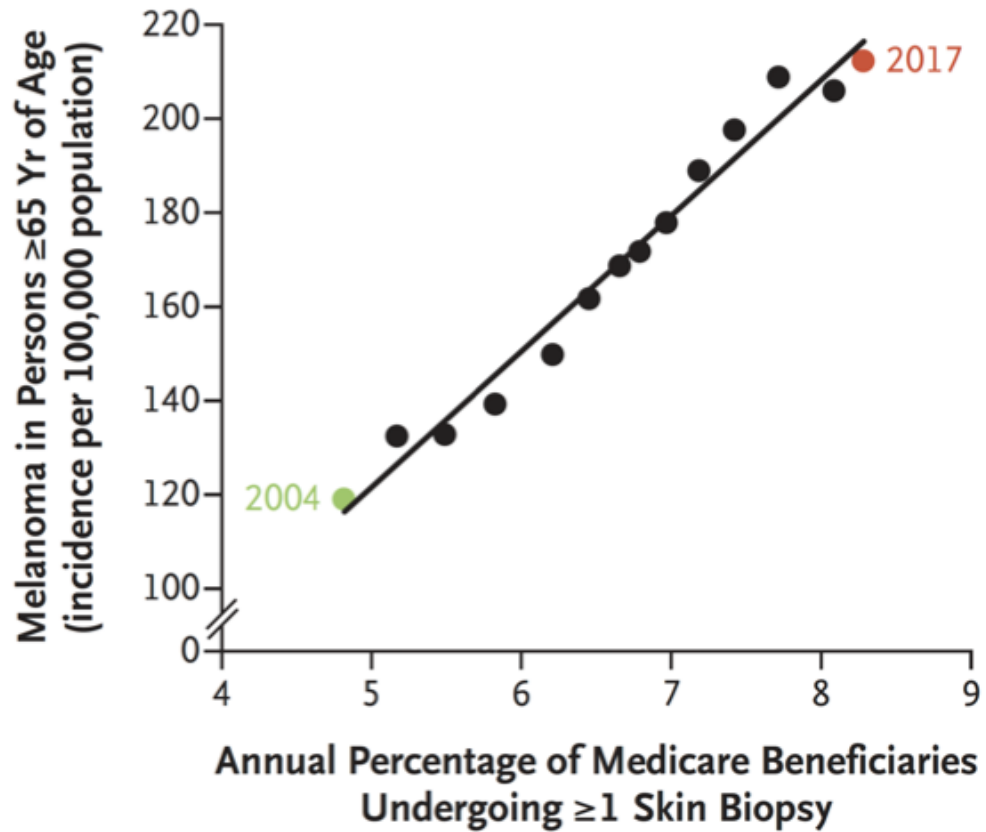


B Cutaneous Melanoma among Men and Women



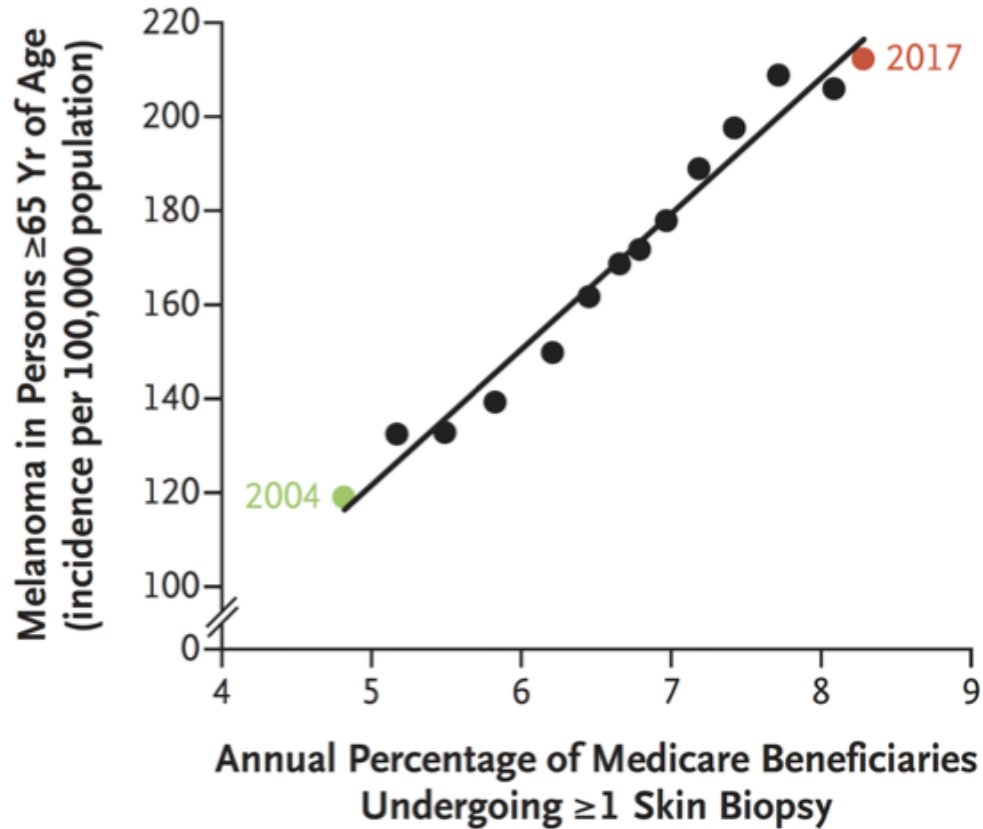
WTF...

A Increasing Use of Skin Biopsies

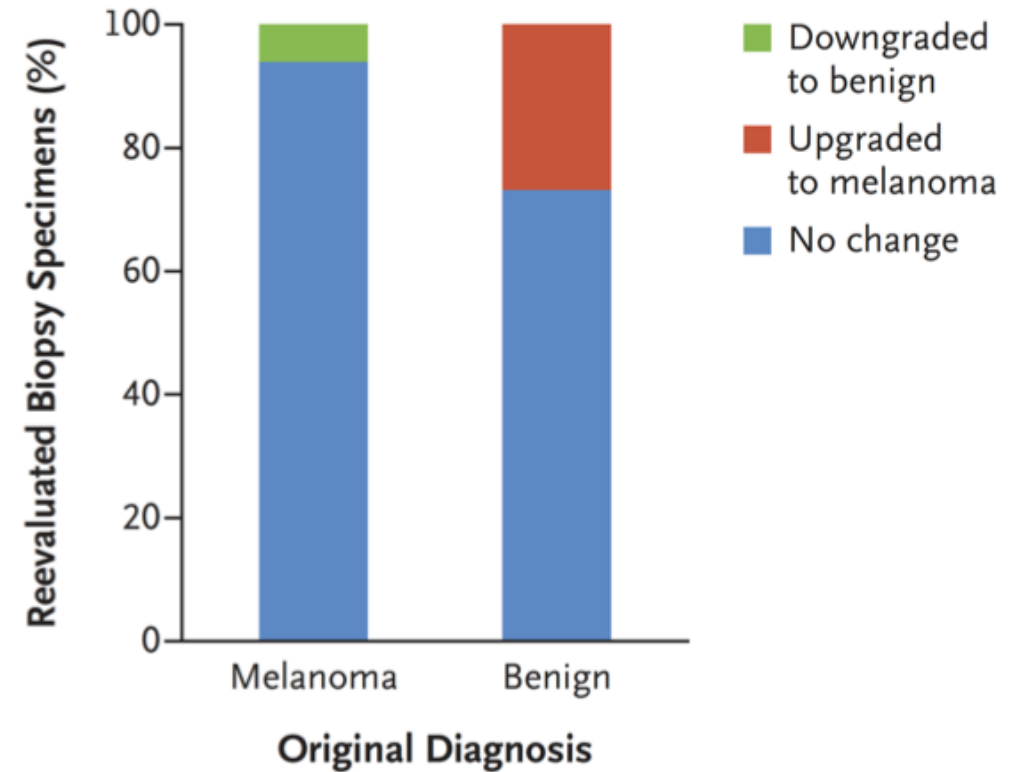


WTF... WHAT THE FRACTION

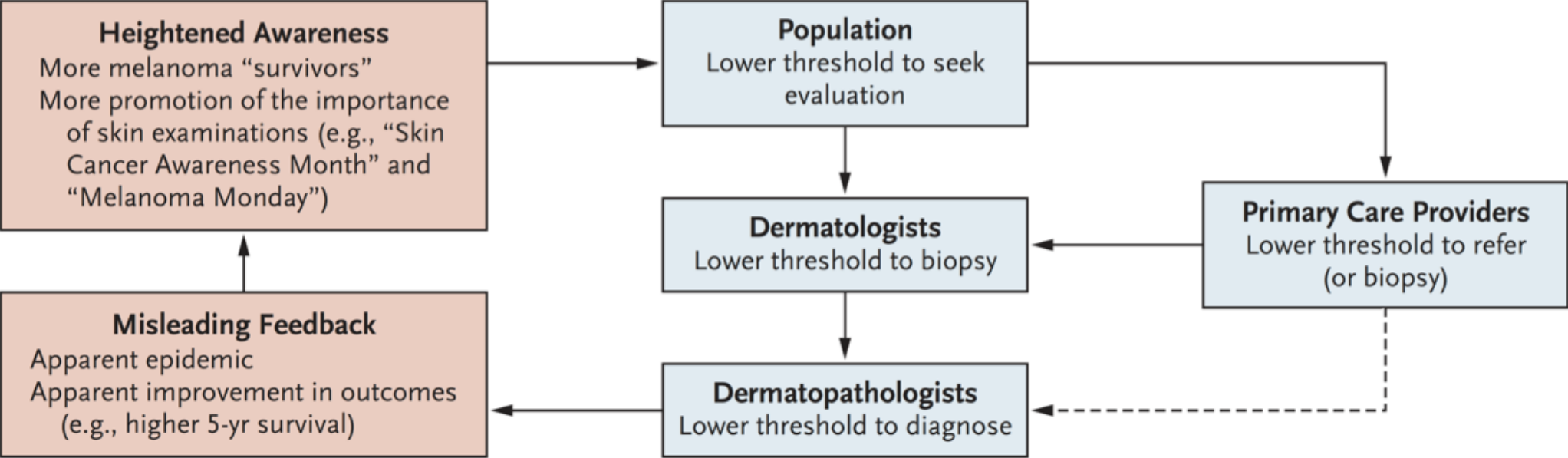
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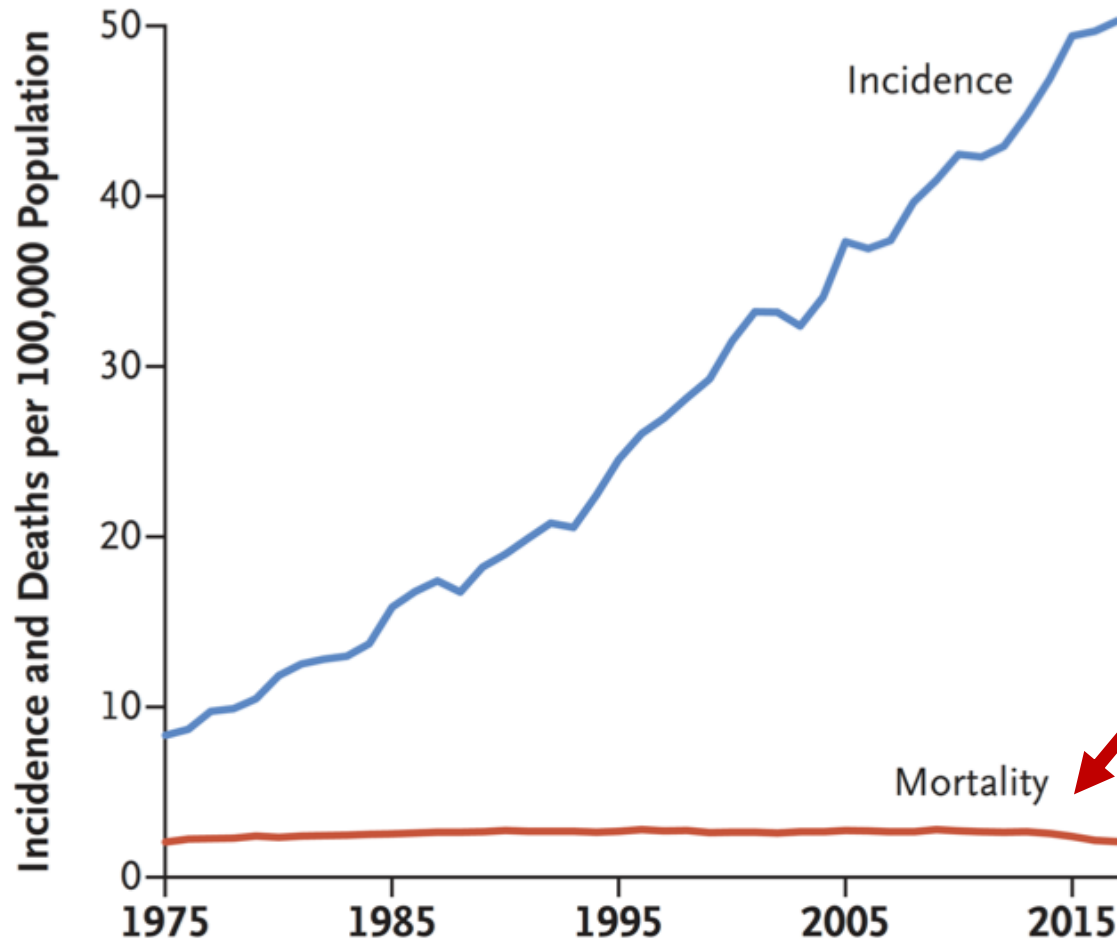
B Falling Pathological Thresholds



FEEDBACK LOOP



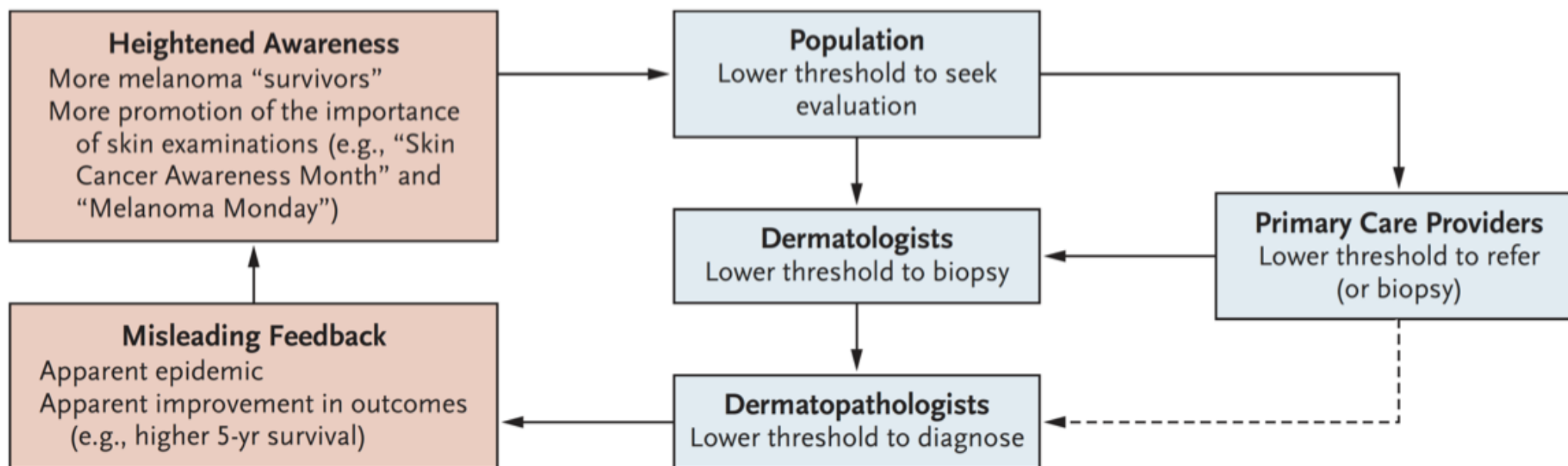
AN INCONVENIENT TRUTH



Checkpoint-blockade immunotherapies – targeted therapy for metastatic melanoma



TIME TO GET OFF THE TRAIN



IMPACT ETHOS

N Engl J Med June 24, 2020;383:35-48

Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD

WHO? FEV1 = 43%, ≥ 1 AECOPD/yr (57% had ≥ 2)

WHAT? LABA+LAMA+ICS (budesonide 320mcg or 160mcg) vs. LABA+LAMA vs. ICS+LABA

What did they find @ 1 yr?

→ ↓ mod-severe AECOPD = **0.35/pt/yr** (or ~1 saved in 3 yrs)

→ ↓ hospitalizations = **NS**

→ ↓ mortality = **1.0% NNT=100** (320mcg), 0.47% (NNT=212) (160mcg)

Did patients **FEEL BETTER?** → **well...**

→ SQRQ change **-1.9 (320mcg)**, **-1.5 (160mcg)** → **NNT MCID = 13-15**

→ TDI change 0.4 (both doses) @24 wks → **MCID NNT not reported**

EFFICACY IN CONTEXT
OF OTHER TRIPLE
TRIALS... **VERY SIMILAR**

What's the
CATCH?

#1

- you could have history of **ASTHMA**
- **80% on ICS** pre-randomization

#2

NNH (pneumonia) = 59

~40% on triple

IMPACT: EFFECT OF ICS USE AT BASELINE ON AECOPD

Am J Respir Crit Care Med;101(12):1508–1516, Jun 15, 2020

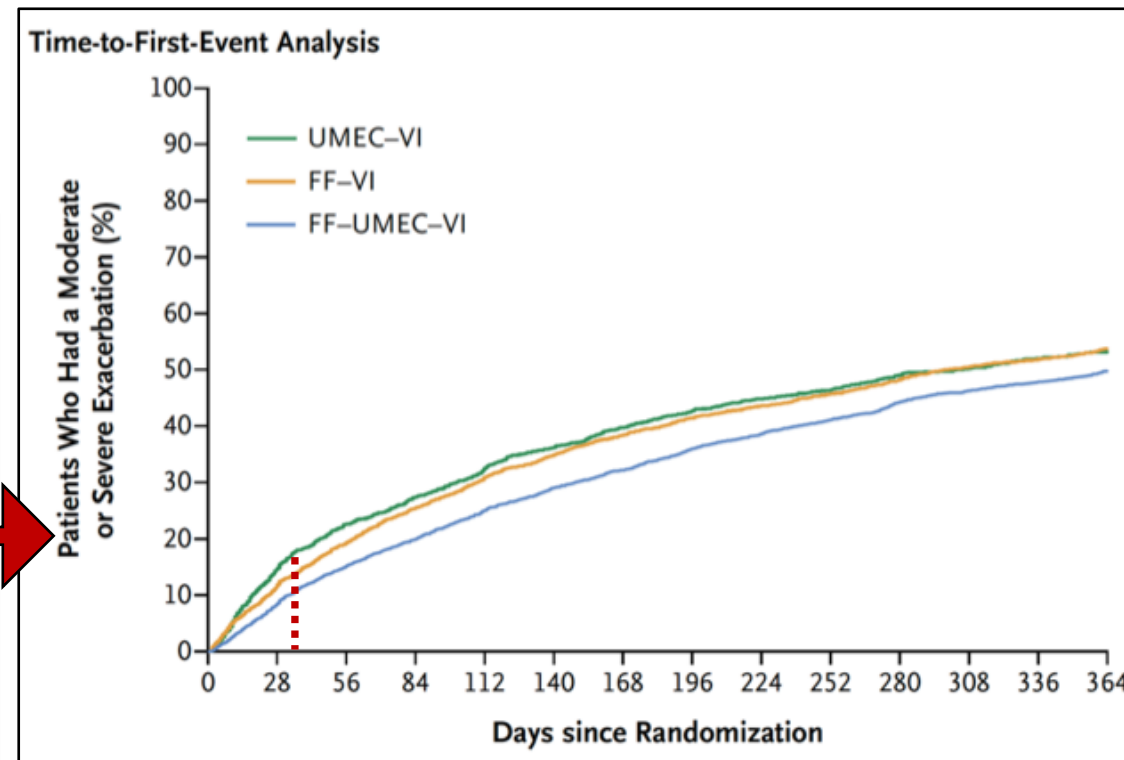
Table 3. Rates of On-Treatment Moderate/Severe Exacerbations in IMPACT by Medication at Study Entry

Baseline Medication*	FF/UMEC/VI (95% CI)	FF/VI (95% CI)	UMEC/VI (95% CI)
Overall	0.91 (0.87–0.95)	1.07 (1.02–1.12)	1.21 (1.14–1.29)
ICS/LAMA/LABA	1.21 (1.13–1.28)	1.43 (1.35–1.53)	1.72 (1.58–1.87)
ICS/LABA	0.70 (0.64–0.77)	0.85 (0.78–0.92)	0.94 (0.83–1.06)
LAMA/LABA	0.84 (0.73–0.98)	1.11 (0.95–1.29)	1.05 (0.86–1.29)
LAMA	0.65 (0.54–0.78)	0.75 (0.64–0.89)	0.61 (0.47–0.80)

IMPACT trial: *N Engl J Med* 2018;378:1671-80

“...more than 70% were receiving an ICS, and patients with a history of asthma were included. Thus, for the patients assigned to the LAMA–LABA group, **many of whom were actually stepping down in their treatment, ICS were abruptly withdrawn at the time of randomization...** This design peculiarity, compounded by the probable inclusion of some patients who **could have met a standard case definition of asthma**, could explain the **rapid surge in exacerbations** observed in the first month after randomization in the LAMA–LABA group; during the subsequent 11 months of follow-up, the incidence of exacerbation with LAMA–LABA was practically identical to that with triple therapy.”

Suissa, Drazen, *NEJM* April 18, 2018 *NEJM*





DEC 18, 2020

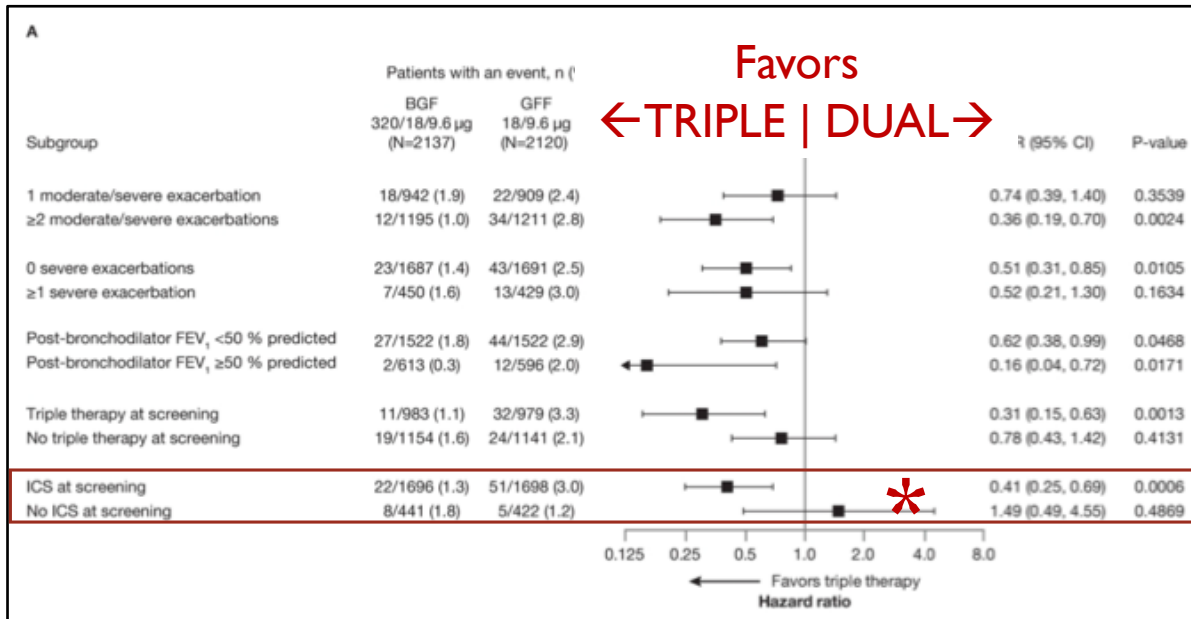
Episode 467: COPD inhalers – the evidence leaves you gasping for breath - PART III

In episode 467, Mike and James finish off talking with Jamie Falk about COPD/inhalers. We go over some of the latest trials for the triple therapies and then wrap up all the evidence into a nice package and put a bow on it. At the end we finally get to the issue of eosinophils and let you know if you need to know this number. Show notes

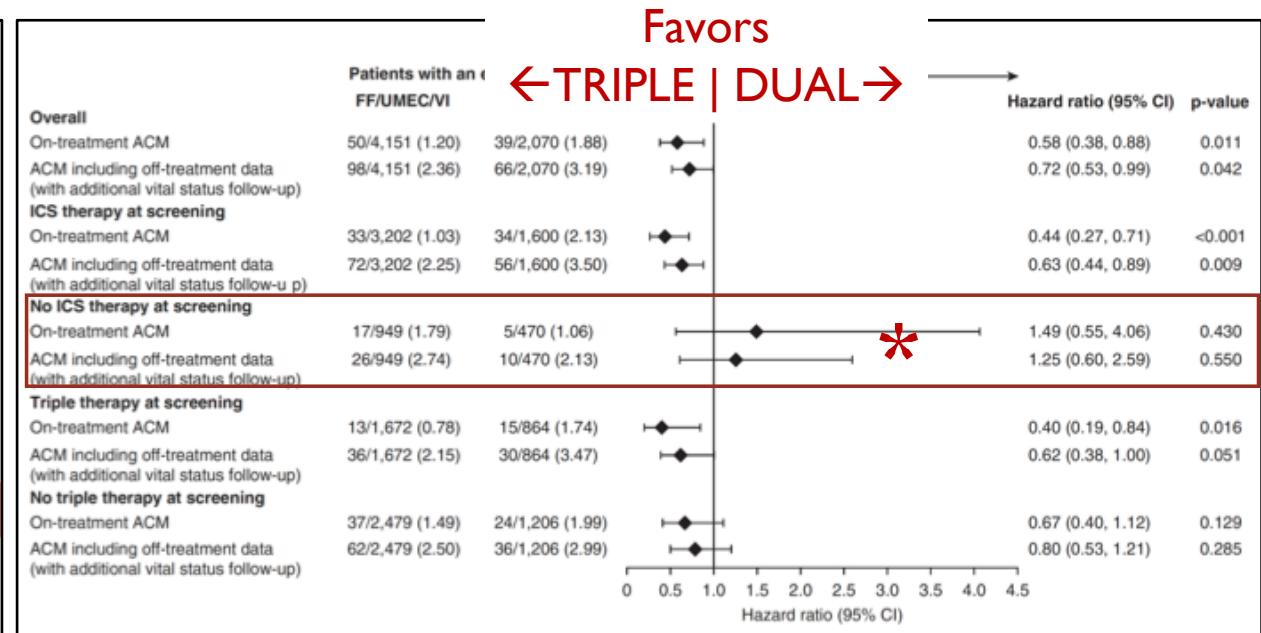
ETHOS & IMPACT:

EFFECT OF ICS USE AT BASELINE ON MORTALITY

ETHOS



IMPACT



FDA, Aug 31, 2020...

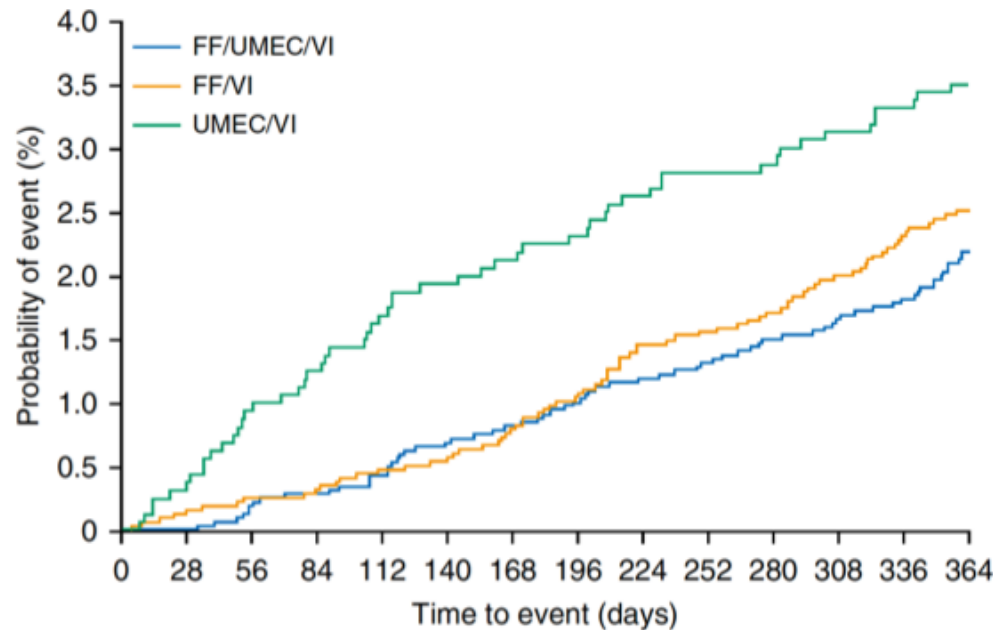
VOTE: Do the data from the IMPACT trial provide substantial evidence of efficacy to support the claim that TRELEGY ELLIPTA improves all-cause mortality in patients with COPD?
Vote Result: Yes: 1 No: 14 Abstain: 0

IMPACT:

EFFECT OF ICS USE AT BASELINE ON **MORTALITY**

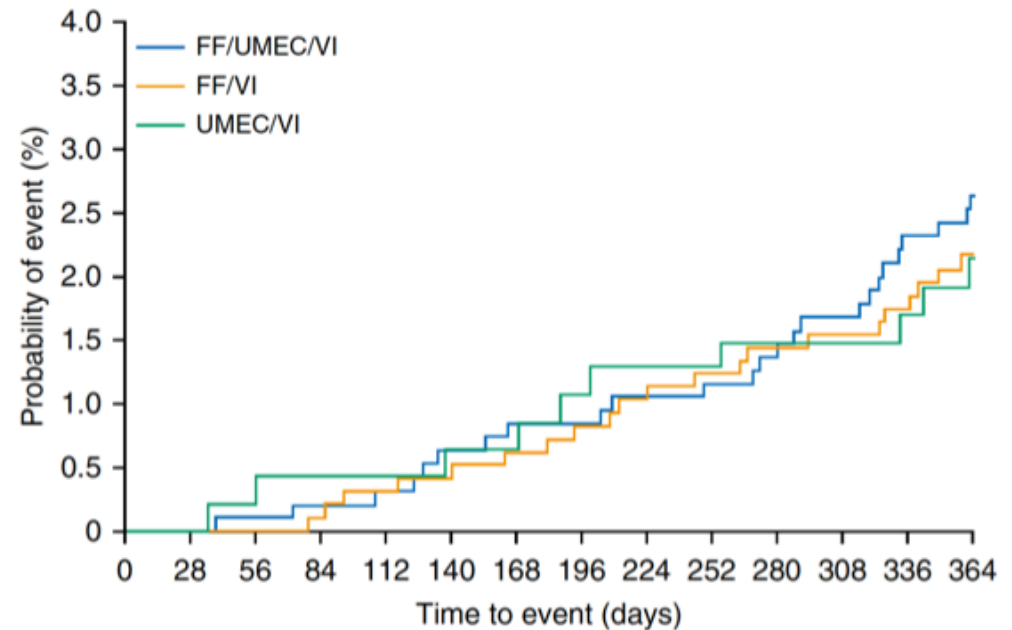
Or look at it this way...

ICS at screening



FF/UMEC/VI	3,202	3,190	3,172	3,154	3,024
FF/VI	3,158	3,147	3,130	3,103	2,941
UMEC/VI	1,600	1,579	1,562	1,546	1,474

No ICS at screening



FF/UMEC/VI	949	947	941	938	895
FF/VI	976	971	965	957	907
UMEC/VI	470	466	465	462	440



And now it's time for...

IT THINK THAT SHOULD WORK...
AND IT DOES!

Intuitive approaches to care that RCTs showed to be true



RCT #1:

N Engl J Med 2020;383:630-9

ORIGINAL ARTICLE

Compression Therapy to Prevent Recurrent Cellulitis of the Leg

Elizabeth Webb, M.P.H., Teresa Neeman, Ph.D., Francis J. Bowden, M.D.,
Jamie Gaida, Ph.D., Virginia Mumford, Ph.D., and Bernie Bissett, Ph.D.

- **WHO:** n=84
 - ≥ 2 episodes of cellulitis in past 2 yrs + edema lasting >3 months in leg(s) with recurrent cellulitis
 - Excluded if regularly wearing stockings prior to trial
 - **INTERVENTION:** compression stockings + cellulitis prevention ed vs. cellulitis prevention ed alone
 - **PRIMARY OUTCOME: recurrent cellulitis**
Stopped early (186 days) \rightarrow **15%** vs. **40% (NNT=4)**
 - **HOSPITALIZATION** for cellulitis \rightarrow **7%** vs. **14% (NSS)**
 - **QoL:** no clinically important differences
- 1) Non-blinded
2) Adherence:
88% ≥ 4 days/wk
73% ≥ 5 days/wk



RCT #2:

The BMJ Awards 2020: Research paper of the year

Prophylactic antibiotics in the prevention of infection after operative vaginal delivery (ANODE): a multicentre randomised controlled trial

Marian Knight, Virginia Chiochia, Christopher Partlett, Oliver Rivero-Arias, Xinyang Hua, Kim Hinshaw, Derek Tuffnell, Louise Linsell, Edmund Juszcak, on behalf of the ANODE collaborative group*

Lancet 2019; 393: 2395–403

NIHR | National Institute
for Health Research

Research
FOCUS

Can a single dose of antibiotics reduce infections after assisted childbirth?

THE PROBLEM



Around 16 percent of women who have forceps or a suction cup to help them give birth develop an infection. For every woman who dies from a pregnancy-related infection, 70 more have a severe infection with long-term health consequences.

THE STUDY

The ANODE study looked at whether a single dose of antibiotics prevented infection after an operative vaginal birth. 1,719 women on the study received an antibiotic and 1,708 were given a placebo (dummy drug), to compare the two.



THE RESULTS

At least 42 percent fewer women who received the antibiotics had an infection than those who had the placebo.



Ask your doctor or nurse about research or find studies seeking volunteers at www.bepartofresearch.uk

The ANODE study was led by the University of Oxford, with funding and support from the National Institute for Health Research (NIHR), which funds life-changing research across England.

ANTIBIOTIC STEWARDSHIP - MORE IS LESS

	Amoxicillin and clavulanic acid (n=1715)	Placebo (n=1705)	RR*	p value
Confirmed or suspected maternal infection	180 (11%)	306 (19%)	0.58 (0.49-0.69)†	<0.0001



- Forceps or Vacuum Delivery
- Single Dose – IV amoxicillin/clavulanic acid 1g/200mg <6 hrs after birth
- 8% ARR in infection (prescription for antibiotics)
- For every 100 prophylactic doses save 168 treatment doses - 17% reduction in antibiotic use
- 1 in 5 have infection - cuts almost in half
- Estimated to prevention 7000 infections a year in UK



PEANUTS

DURING THE HOLIDAYS?

Risk of peanut- and tree-nut–induced anaphylaxis during Halloween, Easter and other cultural holidays in Canadian children

Mélanie Leung, Ann E. Clarke MD MSc, Sofianne Gabrielli MSc, Judy Morris MD MSc, Jocelyn Gravel MD MSc, Rodrick Lim MD, Edmond S. Chan MD, Ran D. Goldman MD, Paul Enarson MD PhD, Andrew O’Keefe MD, Jennifer Gerdts BComm, Derek Chu MD PhD, Julia Upton MD MPH, Xun Zhang PhD, Greg Shand MSc, Moshe Ben-Shoshan MD MSc

CMAJ 2020 September 21;192:E1084-92. doi: 10.1503/cmaj.200034



HOLIDAY

PEANUTS

Box 1: Dates of the holidays studied*

- Halloween: Oct. 31 of every year
- Christmas: Dec. 25 of every year
- Easter: first Sunday of Western Easter
- Diwali: 13th day of the seventh month in the Hindu calendar
- Chinese New Year: first day of the first month in the Chinese calendar
- Eid al-Adha: 10th day of the last month in the Islamic calendar

*Each holiday category was a 5-day period: the day preceding the holiday, the day of the celebration and the following 3 days. We expected the highest risk of exposure and reactions would be during this time interval, given that reactions may occur owing to early consumption and continuous consumption of foods associated with the holiday.



EASTER BUNNY PROOF



Table 2: Crude analysis of mean number of cases of anaphylaxis per day and incidence rate ratios, based on trigger food and holiday

Trigger food	Holiday						
	Rest of year	Halloween	Christmas	Easter	Diwali	Chinese New Year	Eid al-Adha
Peanuts							
No. of cases per day (95% CI)	0.21 (0.20–0.23)	0.39 (0.24–0.65)	0.13 (0.06–0.30)	0.33 (0.20–0.55)	0.24 (0.14–0.44)	0.13 (0.05–0.30)	0.16 (0.07–0.33)
IRR (95% CI)	Reference	1.86 (1.12–3.11)	0.63 (0.28–1.41)	1.57 (0.94–2.63)	1.15 (0.64–2.10)	0.59 (0.24–1.42)	0.73 (0.35–1.55)

Note: CI = confidence interval, IRR = incidence rate ratio.



GETTING TRACTION ON A RETRACTION

Knowledge into practice

CPJ retraction

Risks of maternal codeine intake in breast-fed infants: A Joint Statement of Retraction from the *Canadian Pharmacists Journal* and *Canadian Family Physician*

Ross T. Tsuyuki, BSc(Pharm), PharmD, MSc, FCSHP, FACC, FCAHS, ISHF;
Nicholas Pimlott, MD, CCFP, FCFP

This paper is jointly published in *Canadian Family Physician* and the *Canadian Pharmacists Journal*.

In late 2006 and early 2007, the *Canadian Pharmacists Journal* and *Canadian Family Physician* published columns from the same authors that described a case of infant mortality

toxicity during breast feeding, with no other confirmed cases of neonatal death despite the use of these drugs by millions of nursing mothers over the past two decades.

Around the time of the publication of this paper, Dr. Juurlink



CPJRPC

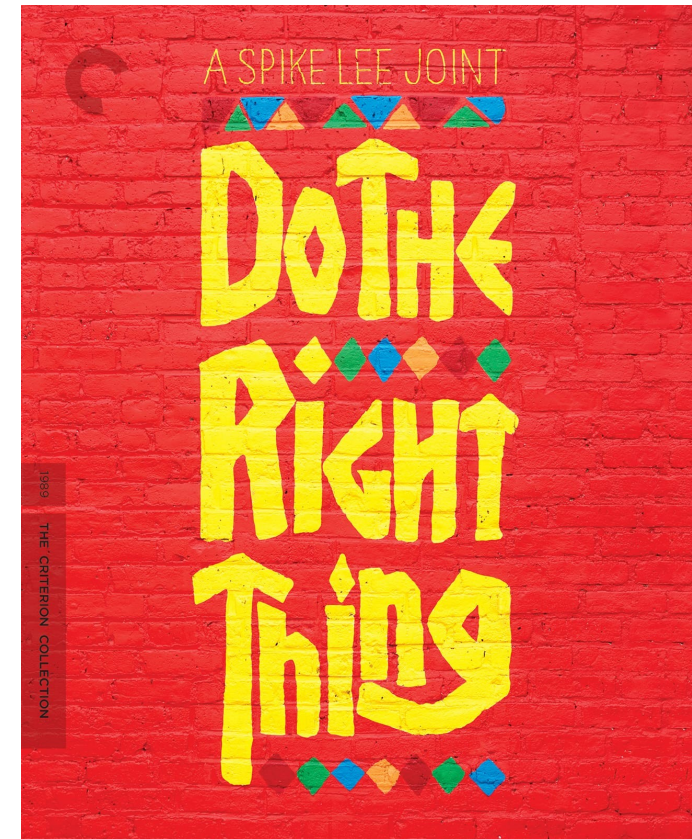


DO THE RIGHT THING

TORONTO STAR

STAR INVESTIGATION

‘We did the right thing:’ Medical journals are retracting columns on a Toronto newborn’s death after reviews conclude the findings were ‘unreliable’



VIEWPOINT

The Moral Determinants of Health

Donald M. Berwick,
MD, MPP
Institute for Healthcare
Improvement, Boston,
Massachusetts.



- 25 year difference
- NYC – 10 year difference – life expectancy goes down by 6 months for every minute on the subway

cmajOPEN

Research

Most medical practices are not parachutes: a citation analysis of practices felt by biomedical authors to be analogous to parachutes

Michael J. Hayes MD, Victoria Kaestner BA, Sham Mailankody MBBS, Vinay Prasad MD MPH

- Eliminate Heart Disease in the entire population - increase life expectancy by 4 years –

The Moral Determinants of Health

Donald M. Berwick,
MD, MPP

Institute for Healthcare
Improvement, Boston,
Massachusetts.



- Repair shops for the damage collectively denoted as “social determinants of health”
- Important and appropriate to expand the role of physicians (and other healthcare providers) and health care organizations into demanding and supporting societal reform

When the fabric of communities upon which health depends is torn, then healers are called to mend it. The moral law within insists so.

- Improving the Social Determinants of Health will be brought at last to boil only by the health of the moral determinants of health

DICLECTIN® CAGE MATCH...



**MEDS
2018:
BM out
of EBM**



Dr. Nav Persaud



Kim Kardashian



SAINT WILLIAM OSLER

The Good

- Canadian – McGill graduate
- Revolutionized medical education
- Founder of Residency programs
- Started 1st Journal Club at McGill
- Founder Johns Hopkins
- Principles and Practice of Medicine
- Medical historian
- “Splendid Profession” committed to public interest



SAINT WILLIAM OSLER (1849-1919)



The Bad

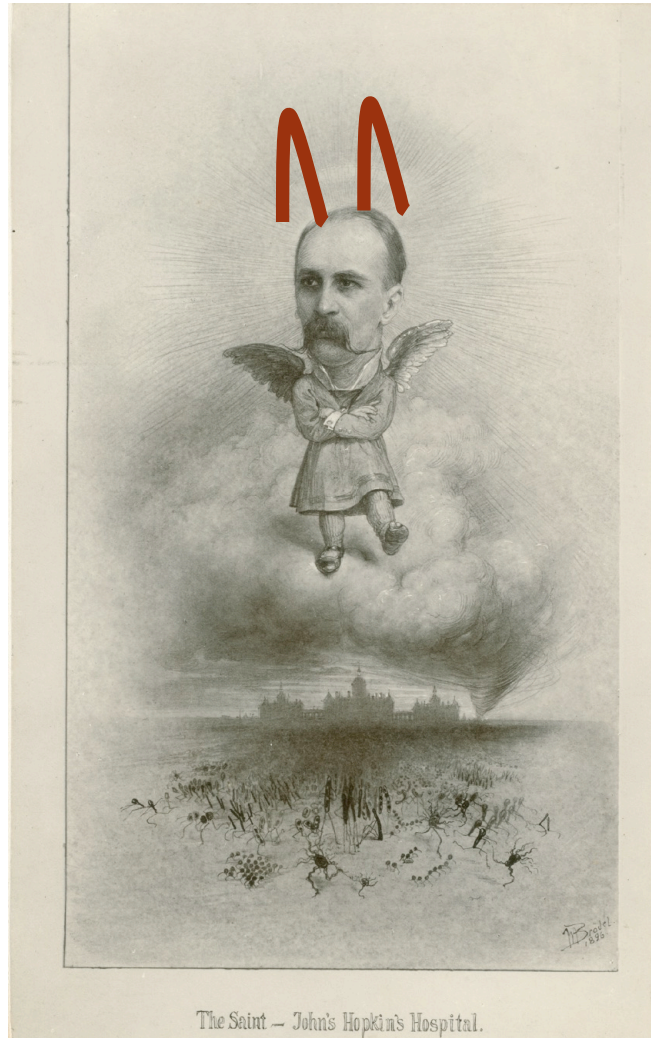
- Naiveté Osler's Construct of profession
- Idealized physician
- Eminence-based Medicine
- Noble Profession – iatrogenic illness, medical research malfeasance, excesses of medical-industrial complex

Bryan, C.S. *NEJM* 2019;381:2194.



~~SAINT~~ WILLIAM OSLER (1849-1919)

The Ugly

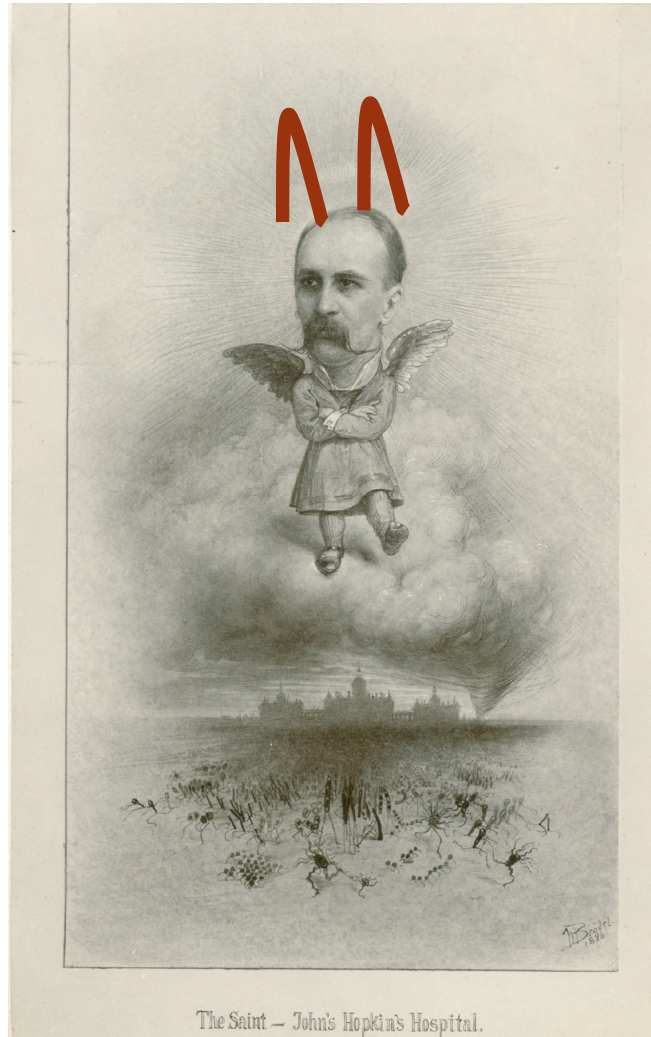


- Pan-American (Medical Congress) “ I hate Latin Americans – but I don’t like to desert my friends”
- Pneumonia deaths on “coloured” ward “the coloured, usually syphilitic and alcoholics were the worst risk in pulmonary disease”
- Immigration “White man’s dominion”
“We are sorry, we would if we could , but cannot come in on equal terms with Europe's”
“We are bound to make our country a White mans country”
- Indigenous People
“every primitive tribe retains some vile animal habit not yet eliminated in the upward march of the race”



~~SAINT~~ WILLIAM OSLER (1849-1919)

The Ugly



- Pan-American (Medical Congress) “ I ~~hate~~ don't care for Latin Americans – but I don't like to desert my friends”
- Pneumonia deaths on “coloured” ward “the coloured, usually syphilitic and alcoholics were the worst risk in pulmonary disease” supporting women
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“We are sorry, we would if we could , but cannot come in on equal terms with Europe's”

“We are bound to make our country a White mans country”

- Indigenous People

“every primitive tribe retains some vile animal habit not yet eliminated in the upward march of the race”

Persaud, N et al. CMAJ 2020;192:E1414



SOLUTION?



The Full Reality

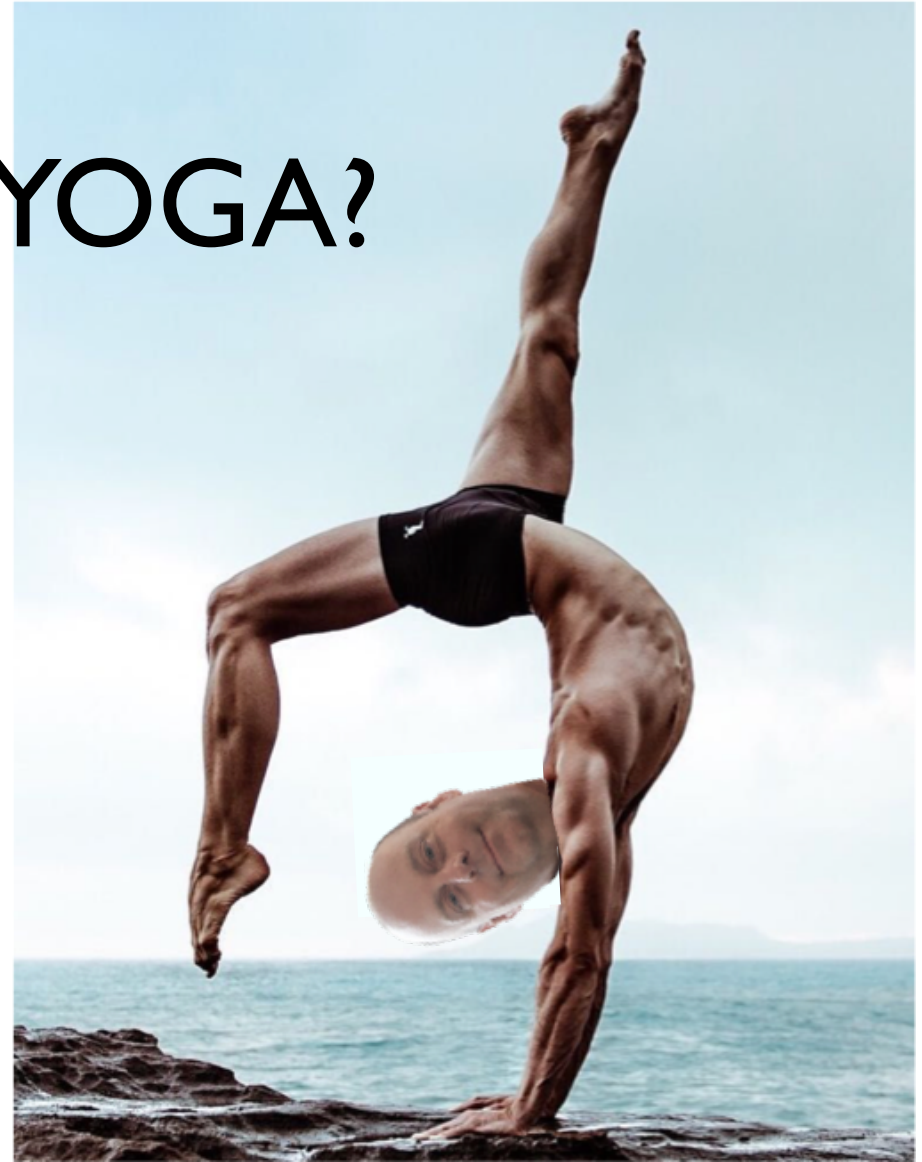
Contemporary of Osler's

- Dr Thomas Augusta
- Dr Anderson Ruffin Abbott
- Dr Oronhyatekha (Burning Sky) and Dr Peter Edmund Jones – Indigenous Physicians

Persaud, N et al. CMAJ 2020;192:E1414



IN THE MOOD FOR YOGA?



IN THE MOOD FOR YOGA?

Effects of yoga on depressive symptoms in people with mental disorders: a systematic review and meta-analysis

Jacinta Brinsley ¹, Felipe Schuch,² Oscar Lederman,³ Danielle Girard,¹ Matthew Smout,⁴ Maarten A Immink,¹ Brendon Stubbs,⁵ Joseph Firth,⁶ Kade Davison,¹ Simon Rosenbaum ^{7,8}

19 RCTs (n=1080)

- **WHO:** 9 depressive disorders, 5 schizophrenia, 3 PTSD, 1 AUD, 1 mixed
- RCTs in meta-analysis = 13 (n=632)

▪ **WHAT:**

- **Yoga**...involving the integration of specific body movements (*asana*) with breathing (*pranayama*) and/or mindfulness (including meditation) where the movement component (**physical activity**) made up **>50% of total intervention**

vs. TAU, waitlist or attention controls

- mean duration = **2.4 months, 1.6 sessions/wk for mean 60 min**
- 17/19 had **yoga practitioner supervision**

▪ **PRIMARY OUTCOME:**

change in depressive symptoms



IN THE MOOD FOR YOGA?

EFFECT SIZE:

Standard Mean Difference (SDM)

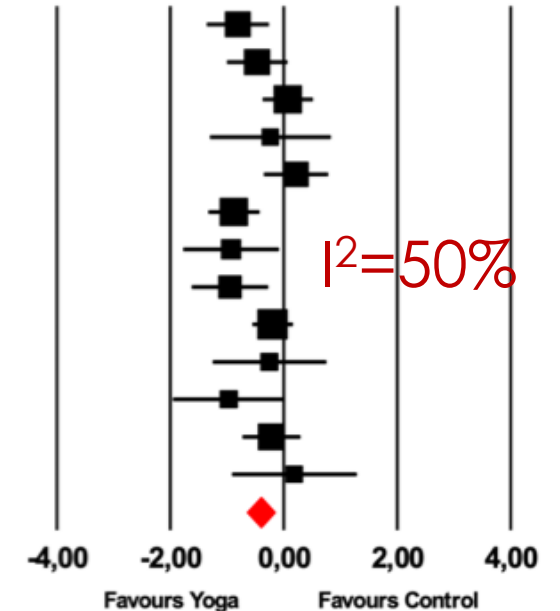
-0.2 = small/modest

-0.5 = moderate

-0.8 = large

Study name	Statistics for each study				
	Std diff in means	Standard error	Lower limit	Upper limit	p-Value
Buttner, 2015	-0,810	0,278	-1,355	-0,265	0,004
Field, 2012	-0,470	0,271	-1,001	0,061	0,083
Field, 2013	0,071	0,225	-0,370	0,512	0,752
Hallgren, 2014	-0,238	0,542	-1,300	0,825	0,661
Jindani, 2015	0,215	0,287	-0,348	0,778	0,454
Lin, 2015	-0,879	0,229	-1,327	-0,430	0,000
Mitchell, 2012	-0,928	0,430	-1,770	-0,086	0,031
Prathikanti, 2017	-0,947	0,343	-1,619	-0,276	0,006
Uebelacker, 2017	-0,197	0,182	-0,553	0,159	0,278
Uebelacker, 2016	-0,251	0,509	-1,250	0,747	0,622
Visceglia, 2011	-0,968	0,501	-1,950	0,014	0,053
van der Kolk, 2014	-0,218	0,259	-0,726	0,290	0,400
Weinstock, 2016	-0,187	0,559	-0,909	1,282	0,738
	-0,406	0,123	-0,647	-0,166	0,001

Std diff in means and 95% CI



DIGGING DEEPER...

1. **higher session frequency** (but not duration)
→ greater symptom improvement
2. **vs. WAITLIST** control (n=4, SMD=-0.58; 95% CI -1.03, -0.12)
vs. ATTENTION controls (n=8, SMD=-0.21; 95% CI -0.54 to 0.12)



DO WE NEED MORE REASONS?

Recall last year...

Ann Emerg Med 2019;74:521-529

Oral Paracetamol Versus Combination Oral Analgesics for Acute Musculoskeletal Injuries

(acetaminophen 1g + ibuprofen 400mg + codeine 60mg X 1 dose vs. acetaminophen 1g X 1 dose)

Table 3. Pain reduction and differences between treatments in change of mean pain scores (out of 10) at 120 minutes.

Reduction in Pain	Combination (n=35)	Paracetamol (n=30)	Mean Difference	P Value*
Pain at rest (95% CI)	-2.9 (-3.7 to -2.2)	-2.4 (-3.2 to -1.6)	-0.5 (-1.6 to 0.5)	.36
Pain with activity (95% CI)	-3.0 (-3.8 to -2.2) [†]	-1.9 (-2.8 to -1.0)	-1.1 (-2.3 to 0.1)	.04

and NNH = 7

Annals of Internal Medicine 2020;173:721-729

Predictors of Prolonged Opioid Use After Initial Prescription for Acute Musculoskeletal Injuries in Adults

A Systematic Review and Meta-analysis of Observational Studies

John J. Riva, DC, MSc; Salmi T. Noor, BHSc, MSc; Li Wang, PhD; Vahid Ashoorion, MD, MSc, PhD; Farid Foroutan, HBS, PhD; Behnam Sadeghirad, PharmD, MPH, PhD; Rachel Couban, MA, MIST; and Jason W. Busse, DC, PhD



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- 13 cohort studies (n=13,263,393)
- Prolonged opioid use:** many definitions
 - median f/u = 12 months (range 3-24 months) after initial rx for **acute** MSK injury (≤ 4 weeks)

PREVALENCE:

10.6% (95% CI, 5.9-16.5%) (**6%** for low risk)

HOW: PRESCRIBING FACTORS

- Rx for >7 days → **4.5% more** (low)
- >1 refill in first month → **2.5% more** (very low)
- >50 MME/day → **13% more** (low)

WHO:

Anticipated Absolute Effect: Risk Difference* (95% CI)

1.1% more (0.7%-1.5%) patients per 10-y increase develop prolonged use

10.5% more (4.2%-19.8%) patients with substance use disorder†† develop prolonged use

0.9% more (0.1%-1.7%) patients with higher numbers of comorbidities§§ develop prolonged use

Overall Certainty of Evidence

Moderate

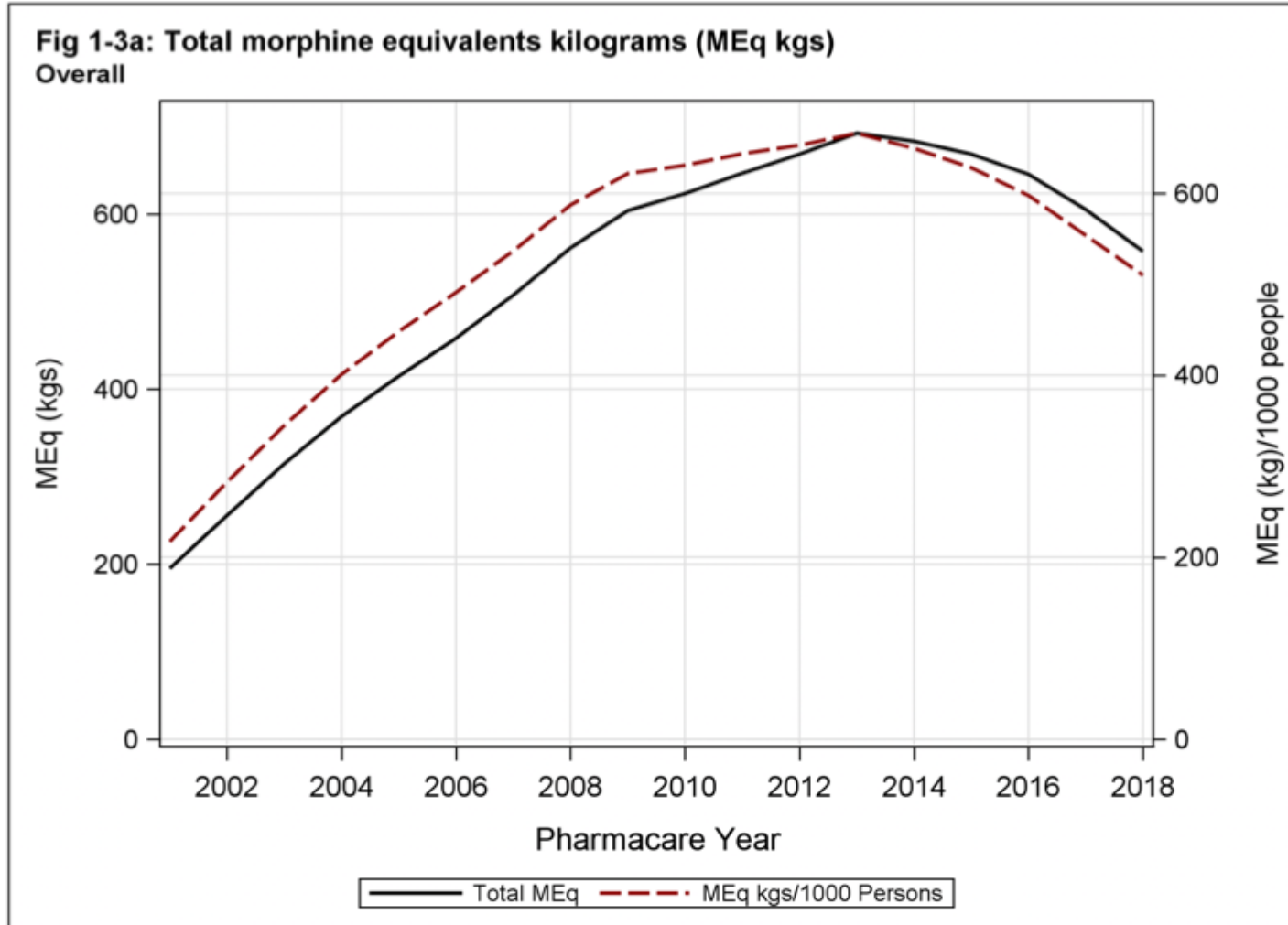
Low

Moderate

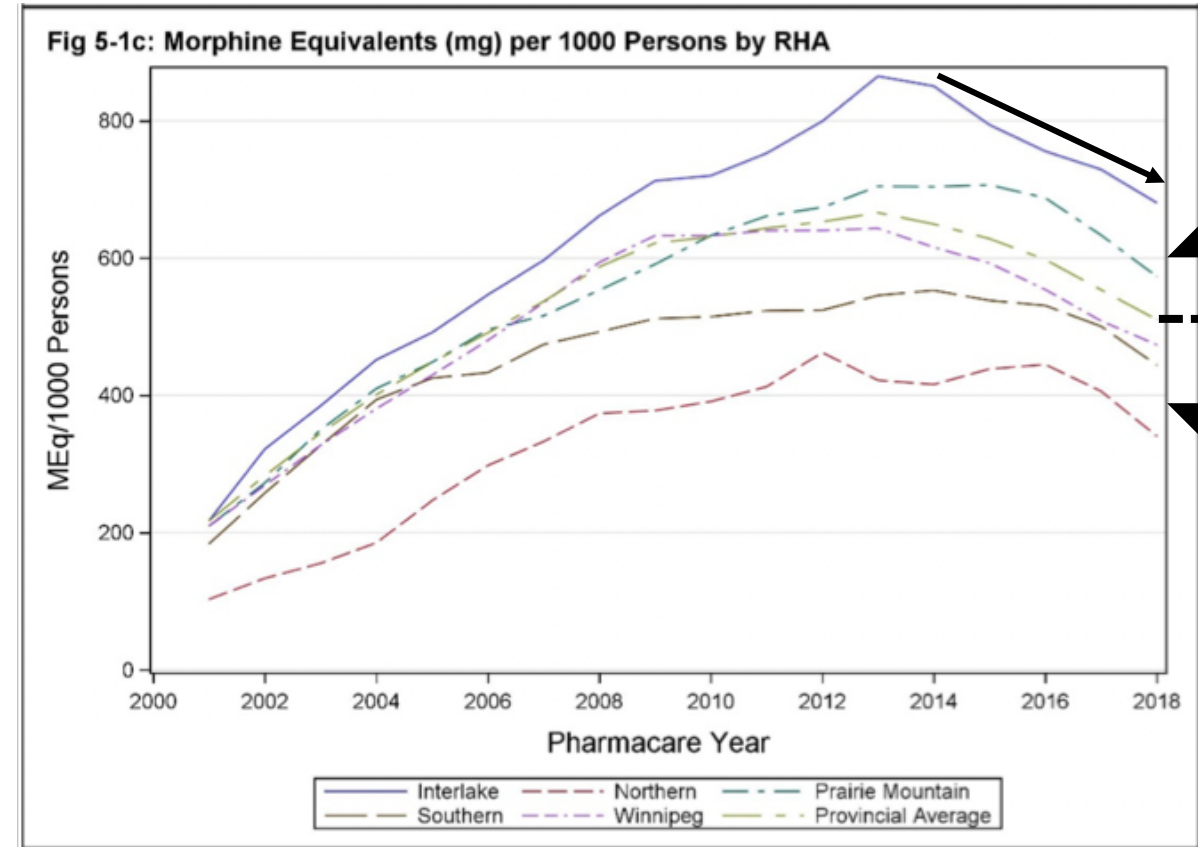
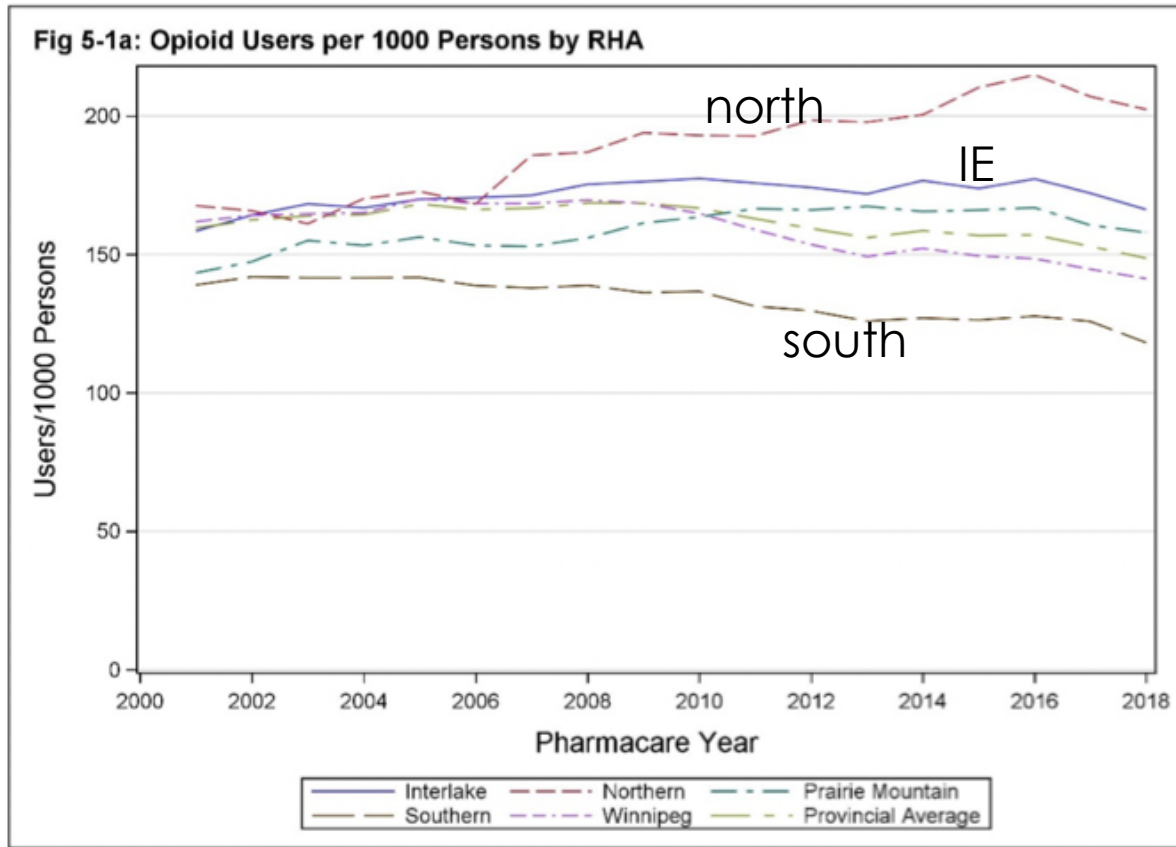


**THE OPIOID CRISIS &
THE AUDACITY OF HOPE**
THE MANITOBA OPIOID ATLAS IN REVIEW

~~POUNDAGE~~ KG-AGE



USE PATTERNS BY GEOGRAPHY



EXEMPTED CODEINE PRODUCTS

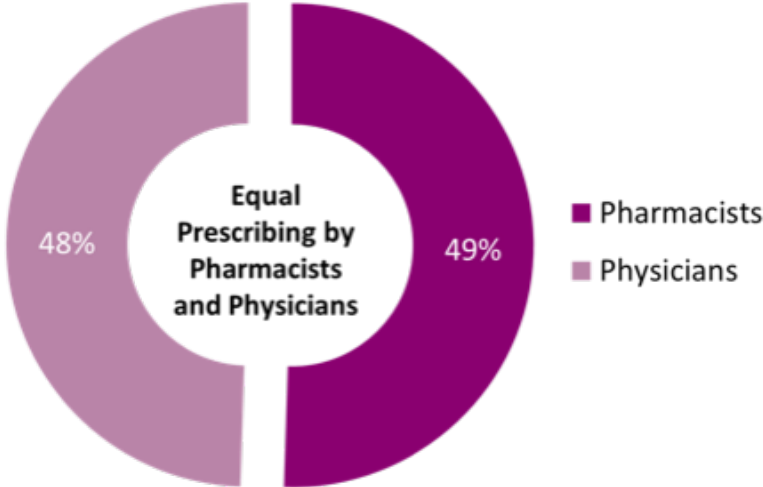


Year Before

Sales data reported

52.5 million

low-dose codeine tablets
sold in Manitoba



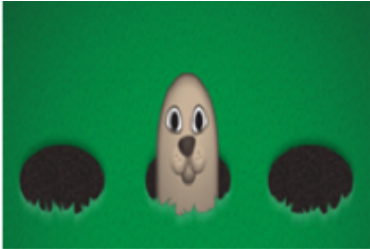
2016

this was a drop **94%**

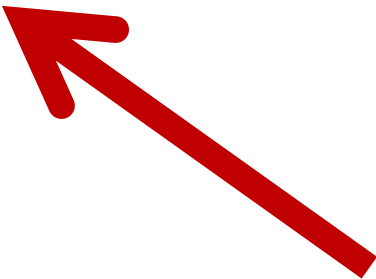
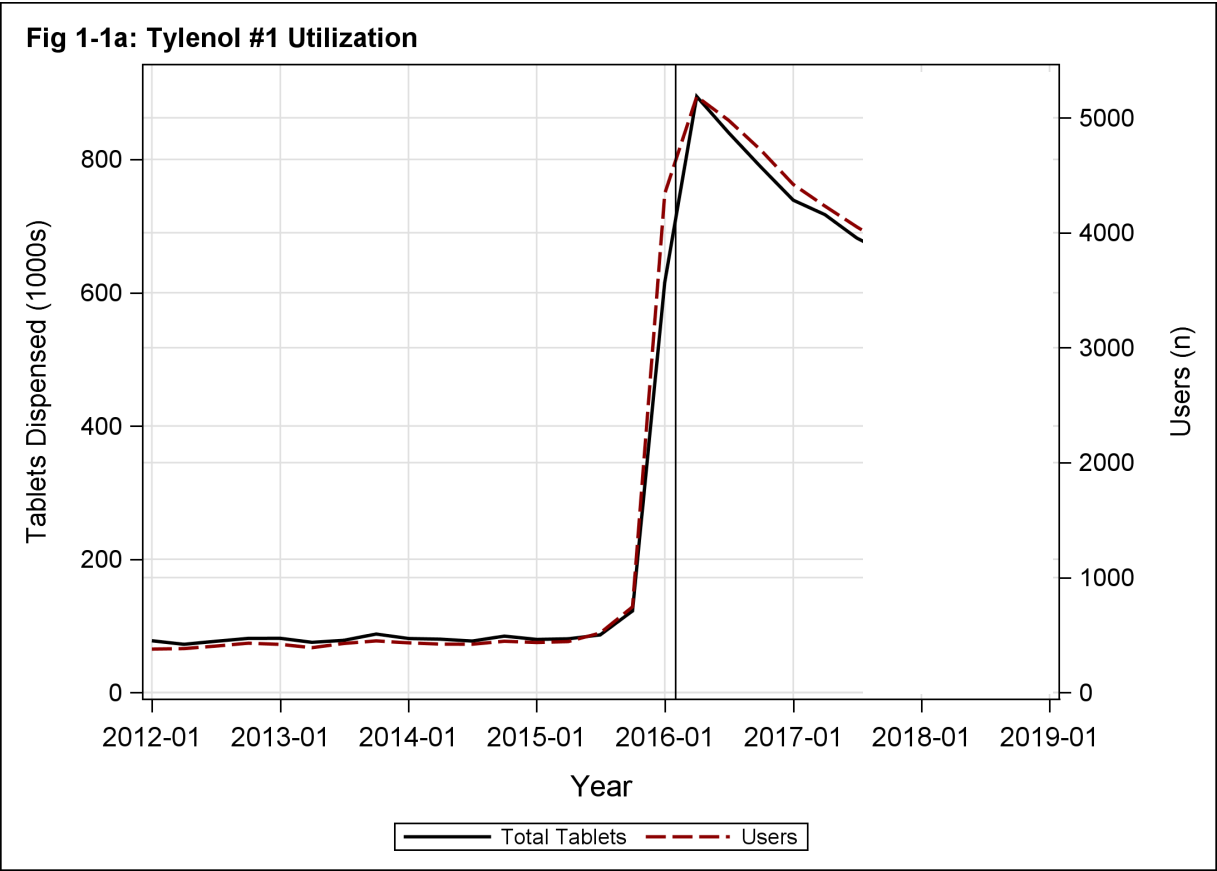
⊘ = 1 million tablets



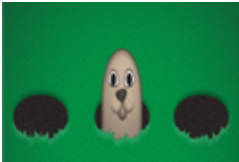
Year After
3.3 million
tablets were sold after
the policy change



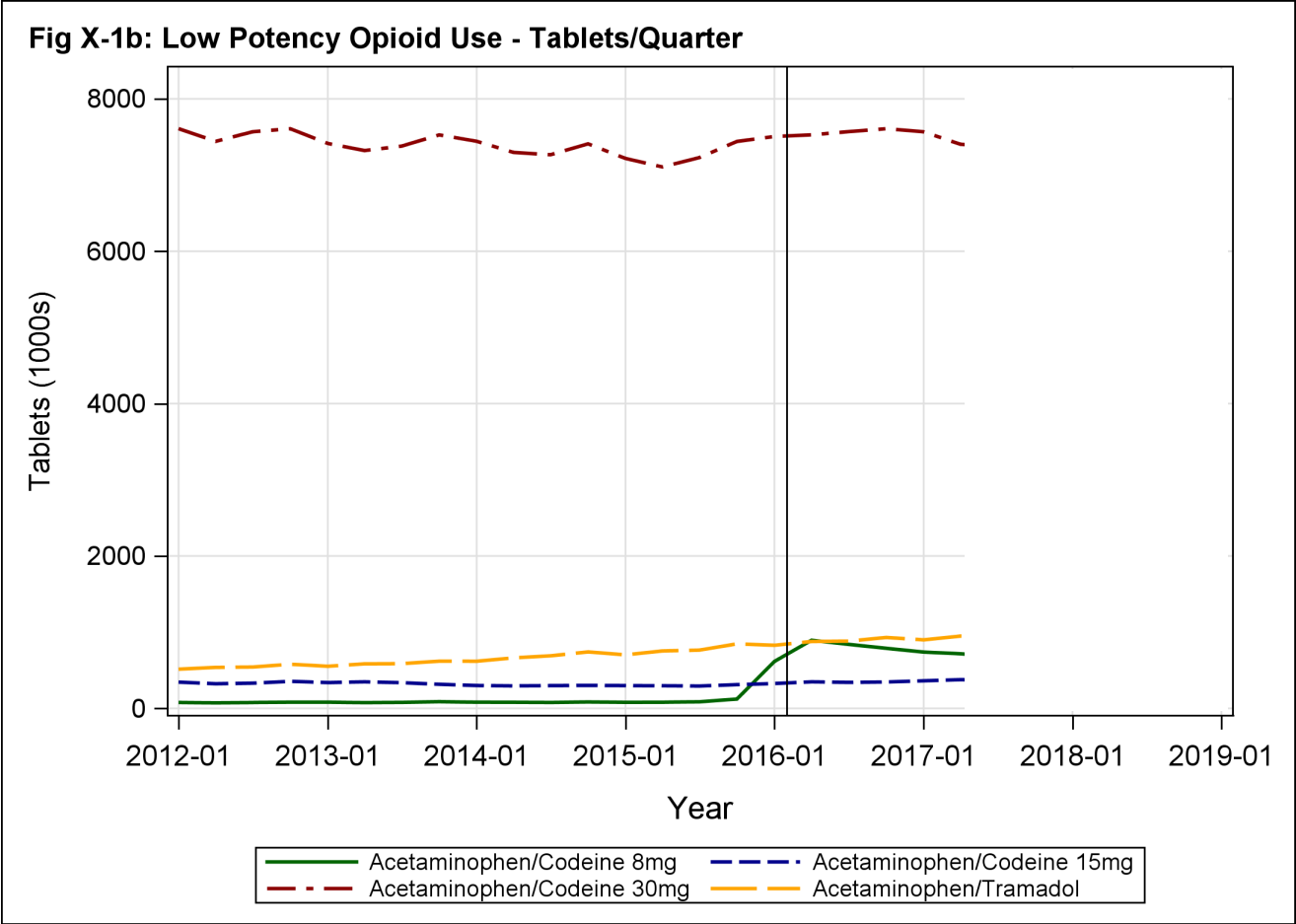
EXEMPTED CODEINE PRODUCTS



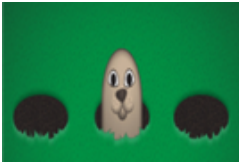
Decline in Low-Dose Prescribing



EXEMPTED CODEINE PRODUCTS



No change in Higher Strength Opioids





here. yer gonna need a slightly bigger scooper for this one.



GET TO KETAMINE & TURN LEFT



- Some indication that ketamine might have a role in treatment-resistant depression
- At a dose of 0.5mg/kg for 100kg person - one IV dose = < \$6



HOLY S - KETAMINE



Clinical Director, Johns Hopkins Psychiatric Esketamine Clinic
Assistant Professor of Psychiatry and Behavioral Sciences

For people who haven't had success with other antidepressants, esketamine gives them the chance to see what it's like to not have depression," says Kaplin. "It gives them hope that they can feel better with the right treatment.

OR...



Joanna Moncrieff
@joannamoncrieff

I am horrified that we can be considering licencing esketamine on such flimsy evidence of benefit and almost no decent medium to longterm safety data - the public will be the guinea pigs @markhoro @CEP_UK @Mad_In_America @HengartnerMP @ReadReadj

Rapid Response:

Re: Esketamine for treatment resistant depression: Putting drug company interests over the public good

We were surprised to see a BMJ editorial endorsing the latest pharmaceutical industry project to profit from

BMJ 2019;366:15572

08 October 2019
Joanna Moncrieff
medical doctor
Dr Mark Horowitz



Allen Frances
@AllenFrancesMD

Smartest people can say dumbest things. NIMH Head all wrong on #ketamine:
1)Patients dont "resist" treatments-meds fail them
2)No really novel antidepressants since first ones 60 yrs ago
3)#FDA rushed approval after 4 small studies
4)Little efficacy vs placebo
5)Safety ignored



Joshua A. Gordon @NIMHDirector

Amazing news from the FDA today: esketamine, the first truly novel antidepressant in decades and first to target treatment-resistant patients, has been approved. @NIMHgov research led the way. nyti.ms/2XEZ9be

8:06 AM · Mar 6, 2019



HOLY S - KETAMINE



- S- enantiomer of ketamine → in a convenient spray bottle
- **\$273**/dose – twice weekly then weekly
- 3 Trials (MADRS 0-60; MCID -2)
 1. -4.0 95% CI (-7.3 to -0.6) → SS
 2. -3.2 95% CI (-6.9 to 0.5) → NSS
-4.1 95% CI (-7.7 to -0.5) → NR
 3. -3.6 95% CI (-7.2 to 0.07) → NSS
- CADTH (Dec 2020) recommends **no**

-20.8 vs. -16.8 =
placebo does 80%



Critical analysis 101:

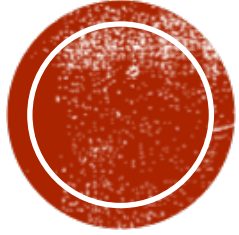
statistically significant difference between the esketamine and placebo groups for the primary outcome; there were **no direct comparisons of esketamine with other known effective antidepressant therapies**; patients in the trials **initiated a new oral antidepressant simultaneously with esketamine**; unresolved bias remained regarding the **potential for unblinding in the trials**; the RCTs were of a **short duration** relative to the duration of MDD; and an **enriched population** was enrolled across the studies. Due



“OUTLINE”

- Mask shortage Solved
- CREDENCE Clearwater & Renal Function
- Statins... These are not the tests you are looking for
- Here comes the sun... shedding some light on melanoma rates
- ETHOS... should we believe?
- I think that should work and it does?
- Less with More... BMJ Paper of the Year
- This is Nuts
- I take that back (but not really)
- Subway of Death: on the Moral Determinants of Health
- Pulling Down Statues: Realistic Osler
- Downward Facing Dog and Depression
- Opioids: More is More problems
- The Audacity of Hope... Quick Update on Manitoba's Opioid Atlas
- Bull S – enantiomers





QUESTIONS?



jamison.falk@umanitoba.ca

 [@JamisonFalk](https://twitter.com/JamisonFalk)

shawnb@mun.ca