29th Annual
Best Science Medicine Course

Formerly the Drug Therapy Decision Making Course – 25 years

May 4th and 5th, 2018

Fairmont Waterfront Hotel
Vancouver, B.C.

FRIDAY Syllabus

COURSE DIRECTORS
Drs. James McCormack, G. Michael Allan and Robert Rangno

COMMITTEE MEMBERS
Drs. Rita McCracken and Tracy Monk

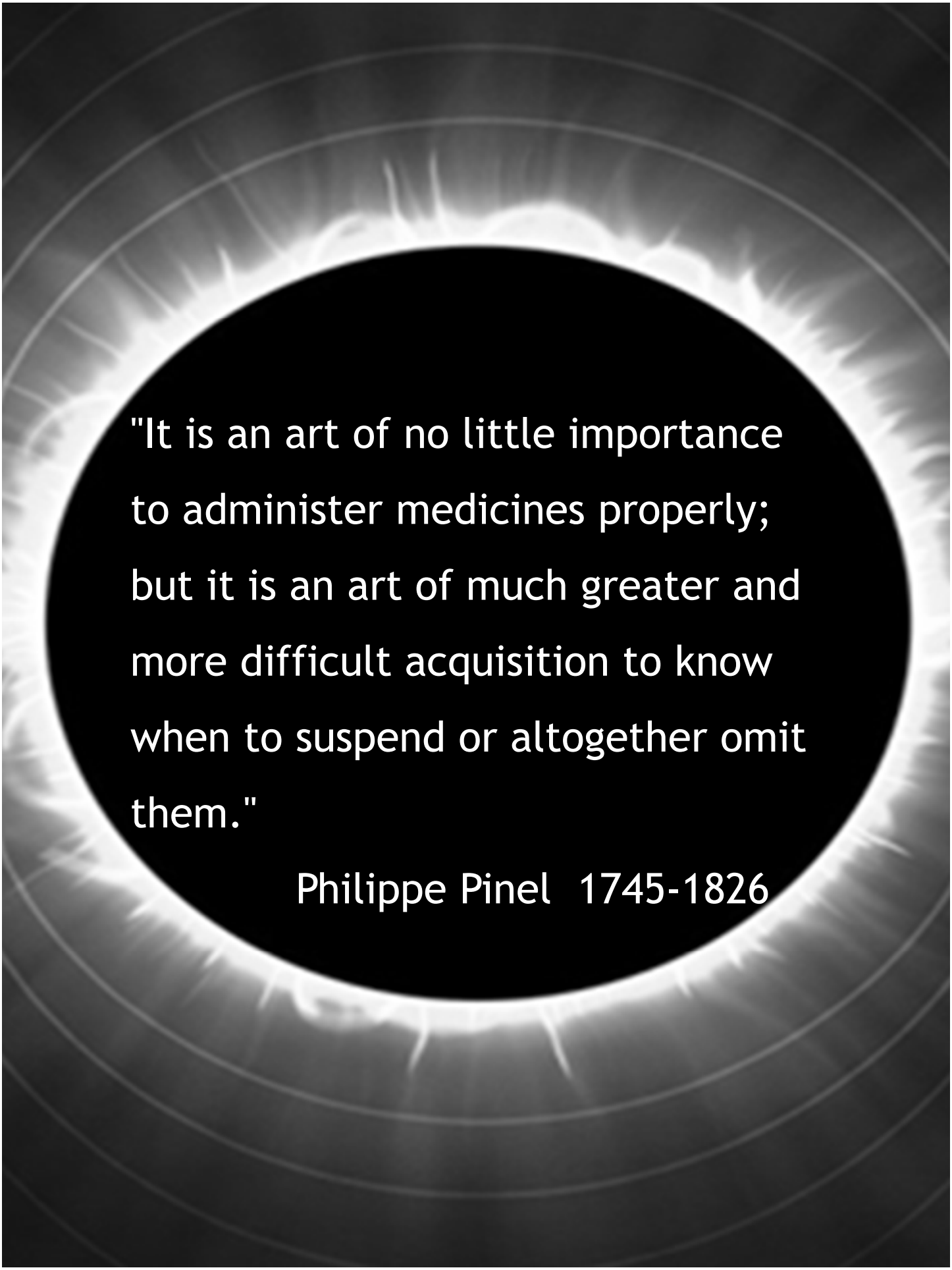
DEPARTMENT OF FAMILY MEDICINE | Leaders in primary care, champions of community health

Providence HEALTH CARE ST PAUL'S HOSPITAL

Evidence Based Therapeutics TEC

A long time ago on a planet far,

far away ….


"It is an art of no little importance to administer medicines properly; but it is an art of much greater and more difficult acquisition to know when to suspend or altogether omit them."
Philippe Pinel 1745-1826

The New Therapeutic Commandments

Thou shalt

1. Have no aim except to help patients according to their goals
2. Always seek knowledge of the benefits, harms, and costs of treatment
3. If all else fails consider watchful waiting
4. Honour balanced sources of knowledge
5. Treat according to level of risk and not to level of risk factor
6. Not bow down to treatment targets
7. Honour thy elderly patient
8. Not pile one treatment upon another
9. Diligently try to find the best treatment for the individual
10. Start with the lowest dose possible

Written by R Lehman, J McCormack, T Perry, A Tejani, J Yudkin

BSMC 29th Annual Best Science Medicine Course

BEST SCIENCE MEDICINE COURSE

Formerly The Drug Therapy Decision Making Course – 25 years

FRIDAY, MAY 4, 2018

07:00 Registration (Muffins & Coffee)
Chairs – Bob Rangno and James McCormack

"You must unlearn what you have learned." – Yoda

08:00 Yoda Expounds — Robert Rangno
08:10 May the evidence be with you - "Power! Unlimited power!" — Mike Allan and James McCormack

"I find your lack of faith disturbing." – Darth Vader

09:00 Personalized medicine and DTC genetic testing – "No. I am your father." — Tim Caulfield
09:20 Agitation in dementia "You will know (the good from the bad) when you are calm, at peace." — Mike Allan
09:40 Questions
09:50 Concussion "Once you start down the dark path, forever will it dominate your destiny, consume you it will." — Tommy Gerschman
10:10 Questions
10:20 Refreshment Break

"Never tell me the odds!" – Han Solo

10:40 Everything to do with stopping clots – "Difficult to see. Always in motion is the future." — Mike Kolber
11:00 Diabetes drugs past to present "Powerful you have become, the dark side I sense in you." — James McCormack
11:20 Questions
11:30 The force of blood pressure "I'm one with the Force. The Force is with me." — Aaron Tejani
12:00 Questions
12:10 Lunch

"Many of the truths that we cling to depend on our point of view." – Obi-Wan Kenobi

13:00 "I have a bad feeling about this" – how to look at trial results that seem to be an anomaly. — Alan Cassels
13:20 Defence of the Sith: are benzos really the bad guys? — Adrienne Lindblad
13:40 Harm reduction for people who use drugs: "No one should be stranded on Planet Hoth." — Christy Sutherland
14:00 Questions
14:20 Refreshment Break

"In my experience there is no such thing as luck." – Obi-Wan Kenobi

14:40 Lab values "Your eyes can deceive you. Don't trust them." — James McCormack
15:10 Thermal detonator vs light sabre. How to order rheumatology tests without hurting civilians. — Kam Shojania
15:30 Opioids for pain "Your focus determines your reality." — Tina Korownyk
15:50 Questions
16:00 Adjourn

Best Science Medicine Course 2018

FACULTY

Course Committee

Co-Chairs:

Bob Rangno, Emeritus Prof., Medicine, Pharmacology, UBC & PHC
James McCormack, Prof., Pharmaceutical Sciences, UBC
G. Michael Allan, Prof., Family Medicine, University of Alberta
& Director, Evidence and CPD Program, Alberta College of Family Physicians

Committee:

Rita McCracken, Clin. Assist. Prof., Medicine and Associate Head, Family Medicine, PHC
Tracy Monk, Clin. Assist. Prof., Medicine, UBC

Guest Faculty

G. Michael Allan, Prof., Family Medicine, University of Alberta
& Director, Evidence and CPD Program, Alberta College of Family Physicians
Alan Cassels, Adj. Prof., Human and Social Development, University of Victoria
Timothy Caulfield, Prof., Faculty of Law, University of Alberta
Canada Research Chair in Health Law and Policy (Tier 1)
Mike Kolber, Assoc. Prof., Family Medicine, University of Alberta
Tina Korownyk, Assoc. Prof., Family Medicine, University of Alberta
Adrienne Lindblad, Assoc, Clin. Prof., Family Medicine, University of Alberta
& Knowledge Translation and Evidence Coordinator, Alberta College of Family Physicians

Local Faculty

Tommy Gerschman, Clin. Instr., Pediatrics, UBC & FHA
Natasha Press, Clin. Assoc. Prof., Inf. Diseases, UBC & PHC
Kam Shojania, Clin. Prof., Medicine, Head, Rheumatology, UBC & PHC
Christy Sutherland, Clin. Asst. Prof., Family Medicine, UBC
Aaron M Tejani, Clin. Asst. Prof., Pharmaceutical Sciences, UBC
Mustafa Toma, Clin. Assoc. Prof., Cardiology, UBC & PHC

FHA – Fraser Health Authority
PHC – Providence Health Care
UBC – University of British Columbia
VCHA – Vancouver Coastal Health Authority
VGH – Vancouver General Hospital

Mike Allan and James McCormack

"The only true wisdom is knowing you know nothing"
Yoda

Welcome!

"You must unlearn what you have learned"
Yoda

29TH ANNUAL

Best Science Medicine Course

Formerly The Drug Therapy Decision Making Course – 25 years

Please let the galaxy, or at least your world, know about the course and what you've learned

#BSMC2018
@BestScienceCME

You can find a pdf of the handouts at http://therapeuticseducation.org/dtc

2018 Best Science Medicine Course

15-20 minute talks – 5 minutes for questions
Conflicts of interest
"As important as asking questions is to question answers"
Coloured slips for questions
Evaluations – computer sheets
The syllabus (pdf) can be found at http://therapeuticseducation.org/dtc
"Challenge" the speakers!
No drug company support
Have fun!!

1) Disclosure of Commercial Support

Neither this program nor the presenter has received financial support from any organization or company.

2) Mitigating Potential Bias

All recommendations and information presented are based on the best-available evidence we could find. Typically this includes meta-analyses, systematic reviews and RCTs. In addition, we don't care what the results are, but rather we care that people know about the results.

3) Objectives

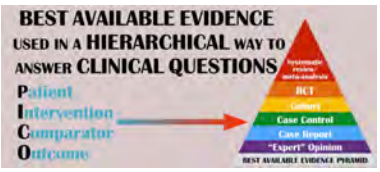
To be able to take the best available evidence for common conditions in primary care and incorporate this information into shared-decision making with patients.

WE ARE ALL KNOWLEDGE BROKERS

OUR BELIEF

All Health Care Providers should have their practice underpinned by the best available evidence

Evidence-Based Practice (EBP)



The foundations of Evidence-Based Practice

Mike Allan and James McCormack

Does *evidence-based hearsay* determine the use of medical treatments?

John P.A. Ioannidis [a, b, c, d, *]

[a] Stanford Prevention Research Center, Department of Medicine, Stanford, CA, USA
[b] Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA
[c] Department of Statistics, Stanford University School of Humanities and Sciences, Stanford, CA, USA
[d] Meta-Research Innovation Center at Stanford (METRICS), Stanford, CA, USA

"the use of many, perhaps most, medical treatments does not depend so much on these evidence-based medicine principles but on what one could call evidence-based hearsay"

Social Science & Medicine 2017;117:256–8

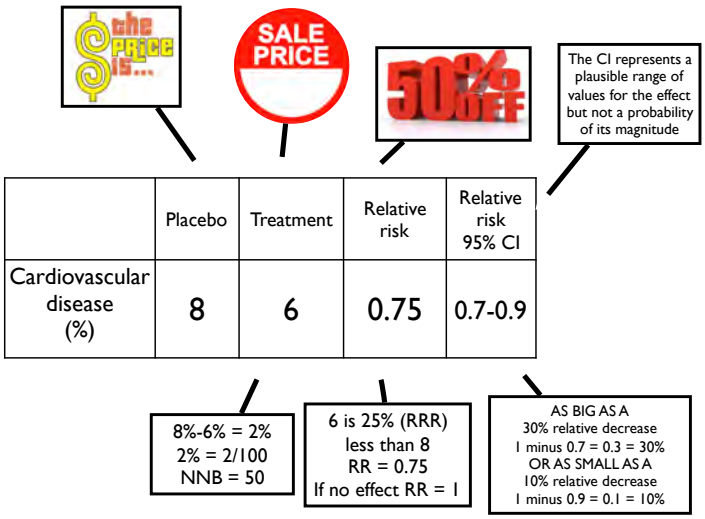
Golden Pill Award

PRESCRIRE AWARDS

	Major therapeutic advance	Clear advantage	Modest improvement
2011	0	0	0
2012	0	0	2 abiraterone (prostate CA) boceprevir (Hep C)
2013	0	0	1 meningococcal conjugate vaccine (infant immunization)
2014	1 cholic acid (hereditary bile acid deficiency)	3 imatinib (ALL) artesunate (malaria) sofosbuvir (HepC conjugate vaccine - infant immunization)	1 sodium phenylbutyrate coated granules (urea cycle disorders)
2015	0	1 propranolol (severe infantile hemangioma)	2 permethrin (scabies) ketoconazole HRA (endogenous Cushing's syndrome)
2016	0	0	2 nivolumab (inoperable melanoma) trametinib (inoperable melanoma)
2017	0	1 asfotase alfa (perinatal and infantile forms of hypophosphatasia)	2 pertuzumab (metastatic breast cancer) emtricitabine/tenofovir (HIV transmission)

Mike Allan and James McCormack

The Numbers



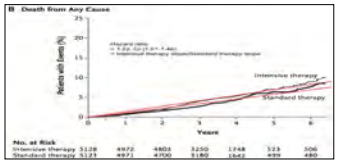
Similar but different relatives

Relative risk/risk ratio (RR) - ratio of two probabilities (%) at one point in time - treatment/control

eg 8% vs 10% - RR = 8/10 = 0.8

most useful in low probability events

Hazards ratio (HR) - ratio of two hazard rates (slopes) over a time period



Odds ratio (OR) - ratio of two odds (25/1) - typically used in case-control studies - typically the incidence is not known

OR is a reasonable estimate of the **RR** if a disease is “rare” <~15% but treating an **OR** as if it were an accurate estimate of the **RR** will typically overestimate both the likely benefits and harms of treatment

Shared-decision making

Mike Allan and James McCormack

Many courts (UK, US, CA)

"The reasonable-patient standard … requires physicians and other health care practitioners to disclose all relevant information about the risks, benefits, and alternatives of a proposed treatment that an **OBJECTIVE PATIENT** would find material in making an intelligent decision as to whether to agree to the proposed procedure"

JAMA 2016;315:2063-4

Conditions requiring risk assessment

The main ones are hypertension, cholesterol, glucose/diabetes, osteoporosis/BMD, atrial fibrillation - also vaccines

Levels of glucose, cholesterol, blood pressure, bone density are almost NEVER markers of disease - they are markers of risk

They all require value-laden decisions

Approximate risk of event over a time period

Approximate benefit

Include harm and costs and inconvenience

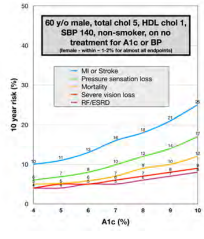
"Fear is the path to the dark side…fear leads to anger…anger leads to hate…hate leads to suffering."

Ballpark Risks (CVD, fractures etc)

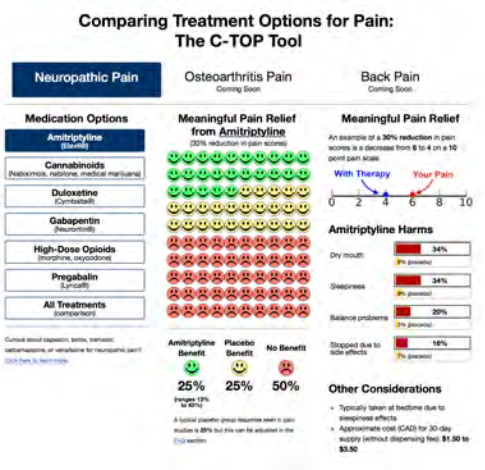
https://therapeuticseducation.org/tools

cvdcalculator.com

sparctool.com



https://sanjaybasu.shinyapps.io/recodesi/



http://pain-calculator.com

Mike Allan and James McCormack

Ballpark Benefits (CVD, fractures etc)

	Time Frame (years)	Approximate RELATIVE RISK REDUCTIONS
Smoking	5	HUGE - JUST !@#$% STOP
Physical activity	5	25% but also other benefits
Mediterranean diet	5	30% and delicious
Statins	5	25-35% + harm
Blood pressure	5	30% and 50% if diabetic? + harm
Other lipid meds	5	0-15%? + harm
Glucose	3-5	15%? + harm
Calcium/Vitamin D	3	10%? + harm
Bisphosphonates etc	3	30% + harm
Zoster vaccine	3	70% - new 90%
Flu vaccine	1	30-80% - varies year to year
Warfarin/NOACs	1	65% + harm
Aspirin	5/1(Afib)	10%?/20% in afib + harm

Categorize to 30% them half as well - work like dynamite warfare zostervaxz - 4 boxes - viagra PPI

Putting it together

Almost everyone - smoking

70-90% - zoster vaccine, flu vaccine (sometimes)

60-70% - warfarin/NOACs

25-35% - physical activity, Mediterranean diet, blood pressure, statins, bisphosphonates, flu vaccine (other times)

20% - aspirin (a fib)

~10-15% - calcium/vitamin D, glucose (some), other lipids meds (some), aspirin

Symptom NNTs

PPIS, sildenafil - NNT ~2

NSAIDs, opioids - pain NNT ~3-5

Antidepressants - severe depression - NNT ~10

Ipratropium - asthma attack - NNT ~11

Cholinesterase inhibitors - ADAS-Cog >4 - NNT ~10

Sleeping pills - improvement in sleep quality - NNT ~13

Steroids - sore throat - NNT ~3, Bell's palsy - NNT ~10

Antibiotics - acute COPD exacerbation - NNT ~5

Topical antibiotics - bacterial conjunctivitis - NNT ~12

Guidelines

Mike Allan and James McCormack

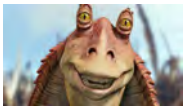
Guidelines would be awesome if they…

Were developed primarily by, and definitely for, the people that ultimately end up using them - different values

Were a credible synopsis of the best available evidence presented in a way that clinicians could easily access and interpret

Allowed patient values and preferences to be taken into account

The Jar Jar Binks of Guidelines



Whelton PK, et al.
2017 High Blood Pressure Clinical Practice Guideline

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

167 pages - 50,000 words
21 authors - 2 had a link to primary care - no FP

Shared decision making - only mentioned so that "adherence to recommendations can be enhanced", or to "drive the ultimate choice of antihypertensive agent"

no information on the magnitude of benefit could be found anywhere in the main treatment section

SPRINT is mentioned numerous times but no mention of the the acute kidney impairment outcomes nor the serious electrolyte abnormalities/serious hypotension

no listing of adverse events or how to prevent them - orthostatic hypotension was mentioned - clinicians were simply advised to be "cautious" and to "monitor carefully".

no mention of cost other than treatment is "cost-effective"

no mention of when to re-evaluate or discontinue treatment

Major Medical Associations Feud Over Diabetes Guidelines npr

CLINICAL GUIDELINES 6 MARCH 2018

Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

"Clinicians should aim to achieve an HbA1c level **between 7% and 8% in most patients** with type 2 diabetes"

Because of harms - primarily internists

CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – *2018 EXECUTIVE SUMMARY*

"**An A1C level of ≤6.5% is considered optimal** if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time."

Because of benefits - primarily endocrinologists

Mike Allan and James McCormack

Other stuff

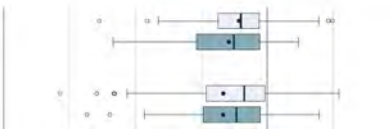
Low Fat vs Low Carb

In your Jeans but not your Genes?

RCT 609 (mean age 40, BMI 33, 57% female).
- 22 dietitian interventions (groups of 17)
- ++ on genetic predisposition/insulin sensitivity

At 1 year (q3 months): range -30 to +10kg
- Low at -5.3kg vs Low Carb -6kg. No stat diff.
- No real difference in any outcomes.

Low-fat genotype	
Healthy low-fat diet	83
Healthy low-carbohydrate diet	70
Low-carbohydrate genotype	
Healthy low-fat diet	63
Healthy low-carbohydrate diet	81



Bottom-Line: Little difference between diets; and "23andme" won't help.

JAMA. 2018;319(7):667-679.

Knee OA & steroid injections

RCT(140): triamcinalone 40mg vs saline q3 mons x2 yrs
- Age 58, 46% male, Pain ~40/100

Outcome: Clinical q3-months, MRI q12-months
- No difference in any clinical endpoints
- Cartilage -0.21mm vs -0.10mm, -0.11 with steroid
  - Cartilage damage in worse area slightly increased
  - But no others: bone marrow edema, effusion, etc.

Bottom-Line: Steroid shots may increase erosion of cartilage slightly but needs confirmation. Pain findings not reliable as most pain effects wears off at 3 months.

JAMA. 2017;317(19):1967-1975.

Subclinical Hypothroidism

RCT, 737 (age ≥ 65, mean 74, 46% male), x18 months,
- TSH 4.6 - <20, mean 6.4, European, 14% CAD

Outcomes: final TSH 3.5 Tx vs 5.3 mIU/L
- Tiredness, Hypothyroid Sx score, Quality of Life, etc: No difference (e.g: hypothyroid score 18 Tx vs 15 placebo)
- CVD, death, etc. No diff.

Earlier Cochrane sys rev also shows no effect.

Bottom-Line: No effect (at all). Don't regularly treat TSH 4.6-10 with normal thyroxine.

Stott, NEJM 2017. 10.1056/NEJMoa1603825. Cochrane Database Syst Rev. 2007;(3):CD003419.

Mike Allan and James McCormack

Got Depression? I can answer that in two questions!

Clinical Question: What is the diagnostic accuracy of the 2-question screen for identifying depression in primary care?

Bottom Line: The 2-question screen is good at ruling out (but not ruling in) depression in primary care. Up to 50% of patients will test positive and should have more thorough evaluation to confirm depression diagnosis. Whether screening alters outcomes is debatable, but the 2-question screen may be reasonable for case-finding or screening higher risk patients.

January 15, 2018

Screening for depression in primary care with two verbally asked questions: cross sectional study

Bruce Arroll, Natalie Khin, Ngaire Kerse

during the past month have you often been bothered by feeling down, depressed, or hopeless?

during the past month have you often been bothered by little interest or pleasure in doing things?

BMJ 2003;327:1144–6

Table 2 Sensitivity, specificity, and likelihood ratios with composite international diagnostic interview as ideal screening tool for major depression

Screening question	Sensitivity % (95% CI)	Specificity % (95% CI)	Likelihood ratio	
			Positive test (95% CI)	Negative test (95% CI)
Both questions	97 (83 to 99)	67 (62 to 72)	2.9 (2.5 to 3.4)	0.05 (0.01 to 0.35)
Depression only question	86 (69 to 95)	72 (67 to 76)	3.0 (2.5 to 3.8)	0.19 (0.08 to 0.48)
Pleasure only question	83 (66 to 92)	79 (74 to 82)	3.9 (3.0 to 5.0)	0.22 (0.1 to 0.49)

Baseline (%)	10	25	50
	POST TEST (%)		
Both questions (-)			
Both questions(+)			

BMJ 2003;327:1144–6

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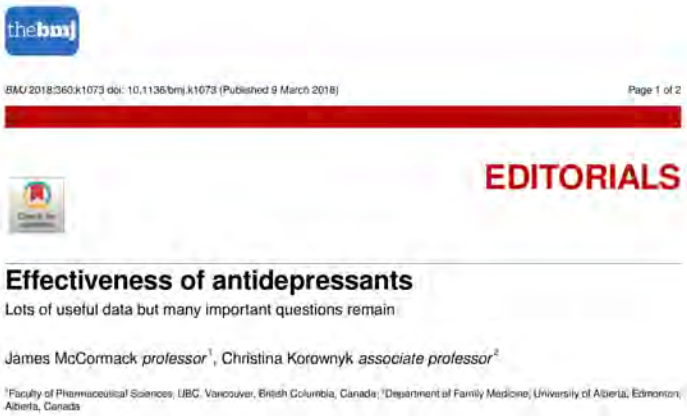
Pleasure only question	83 (66 to 92)	79 (74 to 82)	3.9 (3.0 to 5.0)	0.22 (0.1 to 0.49)

Pre-test probability(%)	**10**	**25**	**50**
	POST TEST (%)		
Both questions (-)	0.6	1.6	4.8
Both questions (+)	25	50	75

BMJ 2003;327:1144–6

Mike Allan and James McCormack



BMJ 2018;360:k1073 doi: 10.1136/bmj.k1073 (Published 9 March 2018) Page 1 of 2

EDITORIALS

Effectiveness of antidepressants

Lots of useful data but many important questions remain

James McCormack *professor*[1], Christina Korownyk *associate professor*[2]

[1]Faculty of Pharmaceutical Sciences, UBC, Vancouver, British Columbia, Canada; [2]Department of Family Medicine, University of Alberta, Edmonton, Alberta, Canada

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

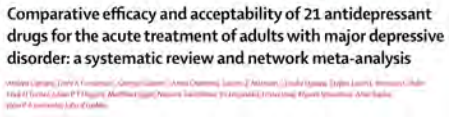
The Lancet
Published online
February 21, 2018

provides as good and balanced a synopsis as we will likely ever have of the results from the 522 trials of 21 antidepressants in 116,477 participants

82% of the included studies - moderate to high risk of bias

78% of studies were funded by drug companies, and many studies failed to report funding at all

the authors report “funding by industry was not associated with substantial differences in terms of response or dropout rates”



Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

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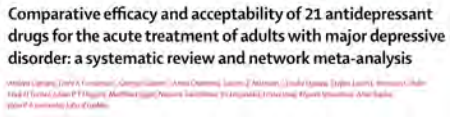
patient population was limited to adults with moderate to severe depression and an average Hamilton depression score of 26.3

primary endpoint - 50% change in Hamilton depression score at 8 weeks

also looked at remission rates at 8 weeks

“all-cause discontinuation” - combines both efficacy and tolerability

looked at drop-outs due to adverse events but didn’t report data on specific adverse effects such as sedation, dry mouth, sexual dysfunction, and weight gain



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all antidepressants “worked”

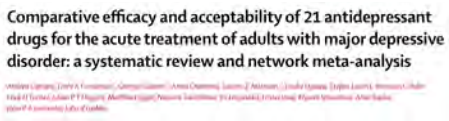
50% change - OR ~ 1.65 for all antidepressants combined

remission - OR ~ 1.55

they found “few differences between antidepressants when all data were considered”

confidence intervals around individual effect sizes were wide

Mike Allan and James McCormack


Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

The Lancet
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February 21, 2018

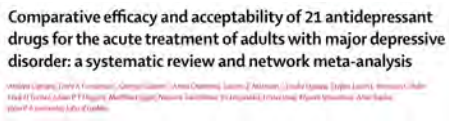
30-40% of placebo group participants report improvement or remission in trials of antidepressants

an OR of ~ 1.6 means about 10-12% more people in the treatment group would benefit compared with the placebo group

absolute response rates placebo ~40% and treatment ~50%

10 patients with moderate to severe depression take an antidepressant for two months

five (50%) will report being “better” but in four of them the response will not be because of the medication


Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

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all-cause discontinuation rates were not statistically different from placebo for most antidepressants in this meta-analysis.

active treatment increased the risk of dropping out because of side effect - OR of ~ 2.3

placebo typically 3-5%

~ 5% more people in treatment groups dropped out because of side effects

What the antidepressant MA doesn't answer

their effect on milder forms of depression

their effects beyond eight weeks of treatment

the harms associated with specific agents and their magnitude

the effectiveness of antidepressants outside the confines of randomised trials

the long-term adverse effects of antidepressants

the likelihood of withdrawal symptoms when treatment stops

comparative benefits and harms of antidepressants relative to non-drug treatments such as cognitive behavioural therapy

which antidepressant should be tried first

which one is likely to work best for an individual patient

Timothy Caulfield

Personalized medicine and DTC genetic testing –

"No. I am your father."

Timothy Caulfield

Faculty/Presenter Disclosure

- **Faculty/Presenter:** Timothy Caulfield
- **Relationships with commercial interests:**
  - **Speakers' Spotlight**
  - **Producer and host, Peacock Alley Entertainment**
  - **Publisher: Penguin Random House Canada**

Disclosure of Commercial Support

- My talks are not associated with any financial support from a commercial entity. The research was supported by grants from entities like the Stem Cell Network, CIHR and Genome Canada.

Mitigating Potential Bias

- Speakers' Spotlight, my publisher and the TV production company have no say or involvement in the content of my presentations.

Learning Outcome Objective Slide

Talk: "Personalized Medicine and DTC Genetic Testing"

Objectives: 1) Review the promise and limitations of personalized medicine, particularly in the context of growing DTC genetic testing industry; and

2) Outline what the evidence says about impact and value of genetic risk information on healthy behaviour change and avoidance of chronic disease.

G. Michael Allan

Agitation/Aggression in Elderly: What works

You will know (the good from the bad) when you are calm, at peace."

G. Michael Allan
Professor, Dept of Family, U of A.
Director, Evidence & CPD Program, ACFP

Faculty/Presenter Disclosure

- **Faculty:** Michael Allan
- **Money:** U of A, CFPC, Alberta Health through ARP
  - **Grants and support from a variety of non-profit sources.**
- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** None

Objectives

1) Understand the risks and benefits of using anti-psychotics in the agitated elderly.
2) Reflect on the application of objective one for when and how to use anti-psychotics
3) Consider the other pharmaceutical options for agitation in the elderly.
4) Learn about the non-pharmaceutical options for management of agitation in the elderly.

What happens when you give placebo?

	Baseline	3 weeks	9 weeks	Improve
Neurobehavioral Rating Scale agitation subscale (NBRS-A)	7.8 (3.0)	5.7 (3.1)	5.4 (3.2)	31%
Cohen-Mansfield Agitation Inventory (CMAI)	28.7 (6.7)	26.9 (6.7)	26.7 (7.4)	7%
Neuropsychiatric Inventory Agitation/Aggression domain (NPI A/A)	8.0 (2.4)	4.9 (3.1)	4.9 (3.8)	39%
Neuropsychiatric Inventory (NPI)-Total	37.3 (17.7)	26.1 (16.1)	28.4 (22.1)	30%
Mental Status Exam (MSE)	14.4	14.9	15.7	9%
Clinical Global Impression of Change (CGI-C)	n/a	29% "improved"	26% "improved"	

- Biggest effect in first weeks.
- Also, more severe scores got greater benefit.

Int Psychogeriatr. 2015; 27(12): 2059–67.

Anti-Psychotics: Benefits

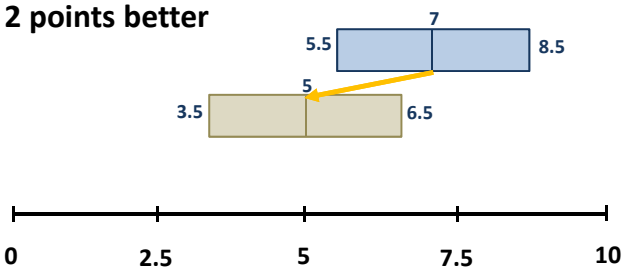
- Systematic review: 16 RCTs (5050 pt)
  - median 10 weeks (range 6-26)
- Score changes (over placebo):
  - CMAI, mean diff= −1.84, (range 29-203)
  - NPI, mean diff= −2.81 (range 0-144)
  - BPRS, mean diff= −1.58 (range 18-126)
  - CGI-C, mean diff= −0.32, (range 1-7)
- All these changes are small.
- Others find similar

J Alzheimers Dis. 2014;42(3):915-37. 2) Cochrane 2006; 1: CD003476. N Z Med J. 2011;124(1336):39-50. Cochrane 2002; 2: CD002852.

How do these numbers work?

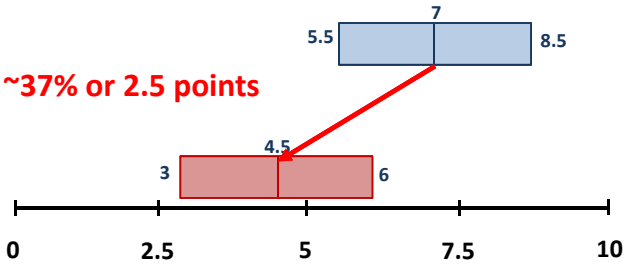
Placebo Effect ~30%:

2 points better

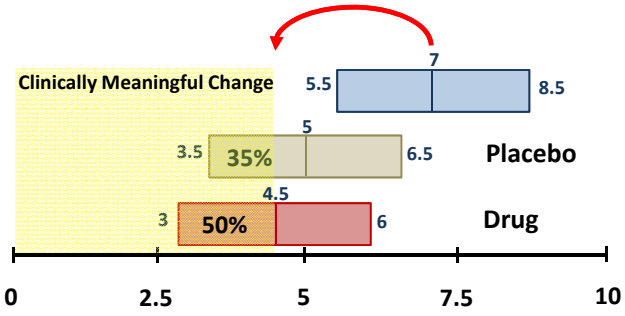


How do these numbers work?

Placebo Effect ~30% +
Drug Effect ~7% more:



How do these numbers work?



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But how many actually get better?

- Systematic Review: 16 RCTs (5110 pts), 8-12 weeks.

Drug	50% improvement in this outcome	Treatment rate	Placebo Rate	NNT
Aripipazole	NPI	49%	38%	10
Risperidone	BEHAVE-AD	46%	33%	8
Risperidone	CGI – C (much /very much improved)	65%	48%	6
Haloperidol*	CGI-C (improved)	67%	59%	ns

- Scales change little but ~50% patients get meaningful change.
- 1 in 6 to 1 in 10 will do meaningfully better than placebo.

Am J Geriatr Psychiatry 2006; 14:191-210. * Cochrane 2002; 2: CD002852.

What are the Adverse Events?

Outcome	Treatment Rate	Placebo Rate	NNH
Mortality	3.6%	2.3%	77
Cerebrovascular	2.1%	0.9%	84
Extrapyramidal	15.2%	8.6%	16
Somnolence	17.0%	7.2%	11
Gait Abnormality	6.9%	1.7%	20
Agitation	**10.6%**	**13.3%**	**38 NNT**
Peripheral Edema[2]	9%	4%	20
UTI[2]	13%	9.4%	28
MSE[2]	Worse by 0.73 (0.38 to 1.09)		

J Alzheimers Dis. 2014;42(3):915-37. 2) Am J Geriatr Psychiatry 2006; 14:191-210.

Adverse Events, Continued

- Withdrawal due to Adverse Events
  - Risperidone 1mg:[1] 11.8% vs 9.2%, NNH 39
  - Olanzapine 5-10mg:[1] 11.5% vs 3.7%, NNH 13
  - Haloperidol:[2] 17% vs 7.2%, NNH 11
- **Bottom-Line**: Lots of harms, and some very concerning ones.

1) Cochrane 2006; 1: CD003476. 2) Cochrane 2002; 2: CD002852.

Stopping Anti-psychotics

- DART-AD:[1] RCT, 165 pts, age 85, 24% male, long-term care
  - Withdraw antipsychotic (placebo) or continue
- Outcomes: Behavior,[2] None stat sign.
  - Mortality: at 2 years, 71% continued vs 46% placebo, (NNT 4)
- Sys Review: 9 trials. No diff behaviour[3] except 1 RCT[4]
  - 110 pts verified good response on Risperidone 1mg, withdrawn after 4-8 months:
    - 30% worsening of NPI: 60% placebo vs 33% risperidone, NNH 4
- **Bottom-Line**: Better to withdrawal soon unless you are sure they have had a good response and likely need it.

1) Lancet Neurol 2009; 8:151–57. 2) PLoS Med 5(4): e76.doi:10.1371/journal.pmed.0050076 3) Cochrane 2013;3: CD007726. 4) N Engl J Med 2012;367:1497-507.

G. Michael Allan

Summing Up

1. Most effect comes from the placebo with anti-psychotics adding little more.
2. A meaningful change occurs in ~50% of patients on anti-psychotic compared to that is ~35-40% with placebo.
3. Antipsychotics have lots of harms, & some are very serious (stroke & mortality), with NNH ~80 (in 3 months)
4. Withdrawal of anti-psychotics will delay one death for every 4 withdrawn, without worsening behaviour in most cases.

Benzodiazepines

- 8 RCTs, benzodiazepine vs anti-psychotics, placebos or other drugs:
  - Benzo vs anti-psychotic: 5 RCTs[1-5]
    - 2 benzo worse, one both worse, one same, one benzo better.
  - Benzo vs placebo: 5 RCTs[3-7]
  - Example (272 pts x1d):[4] Lorazepam 1mg similar to Olanzapine (5mg and 2.5mg), and all better than placebo.
    - 40% improved PANSS-EC (measures agitation) at 2 hours: Lorazepam 72%, Olanzapine 62-67%, placebo 37%. Lorazepam NNT=3.

1) South Med J. 1975;68: 719-724. 2) Am J Psychiatry. 1990;147:1640-5. 3) J Am Geriatr Soc. 1998;46:620-5. 4) Neuropsychopharmacology. 2002;26:494-504. 5) Clin Ther. 1984;6:546-59. 6) Dis Nerv Syst 1965; 26: 591-5. 7) Geriatrics. 1965 ;20:739-46. 8) Int Clin Psychopharmacol 1991; 6:141-6.

Benzodiazepines

- Guidelines for agitation in dementia vary:[9]
  - Some discourage due to adverse events
  - Others consider short-acting prn for infrequent agitation.
- **Bottom-Line:** Many trials are old, most are short and/or small, and the results are inconsistent. Benzodiazepines appear, at best, equivalent to antipsychotics in reducing agitation in the short-term, but superior to placebo. If used, they should be stopped as soon as possible due to potential harms.

McIntosh B, Clark M, Spry C. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2011. Available from: http://www.cadth.ca/media/pdf/M0022_Benzodiazepines_in_the_Elderly_L3_e.pdf

Other Medications

- SSRI:[1] 9 RCTs (692 patients) Vs Haldol:
  - CMAI, Mean Diff, 4.66 [range 29-203], favors Haldol
- Trazodone:[2] 2 RCTs (180 pts but not pooled):
  - Vs Placebo: No effect
- Cholinesterase inhibitors:[3] NPI 1.38 (range 0-144)
- Valproate:[4] 5 RCTs (412 pts) x 6 wks: no effect
- **Bottom-Line**: SSRI, trazodone cholinestase inhibitors, & valproate likely have little to no reliable effect.

1) Cochrane 2011; 2: CD008191. 2) Cochrane: 2004; 3: CD004990. 3) Clin Interv Aging. 2008;3(4):719-28. 4) Cochrane 2009; 3: CD003945

G. Michael Allan

Remember pain

- RCT of assessing for pain
  - 920 Nursing home residents
  - 420 had moderate-severe dementia with behavioural disturbance (352 included)
  - 201 (57%) assessed as having pain (on the mobilisation-observation-behaviour-intensity-dementia-2 pain scale)
- Outcomes
  - 68% needed only acetaminophen, 32% got buprenorphine patch, pregabaline, & rarely morphine).
  - CMAI: −7.0 (−3.7 to −10.3). Others improved as well.
- **Bottom-Line**: Remember agitation may be from pain and as little as acetaminophen may help meaningfully.

BMJ 2011;343:d4065

Summing Up

- None of the other medicines (benzodiazepines, SSRI, trazodone, cholinesterase inhibitors, valproate) work well.
- Maybe benzo's as a back-up, but they may well work less than anti-psychotics and there is no evidence they are safer.
- Remember Pain as a possible cause of agitation.

Non-Pharmaceuticals: Some that May Work

1. Activities (group or individual): e.g. cooking
2. Music Therapy (protocol)
3. Sensory Interventions
4. Working thru paid caregivers for person-centred care & Communication Skills
5. Dementia Care Map
6. Behavioral Management

Most are unclear as inadequate evidence:

- Example: Pet Therapy

Some are Don't Work

- Example Aromatherapy.

Livingston et al. Health Technol Assess 2014;18(39).

Non-Pharmaceutical: Things that likely work

	Effect Size	Studies (patients)
Activities (group or individual): e.g. cooking	-0.8 to -0.6	8 RCT (587) + 2 lower
Music Therapy (protocol)	-0.8 to -0.5	6 RCT (335) + 4 lower
Sensory Interventions	-1.3 to -0.6	7 RCT (508) +6 lower
Working thru paid caregivers for Person-Centred Care & Communication Skills	-1.8 to -0.3	7 RCT (952) + 1 lower
Dementia Care Map	-1.4 to -0.6	2 RCTs (226)
Behavioral Management	Not calculated	1 RCT (31)

- Lots of overlaps.
  - Example activities or sensory might have music as part them.
  - Example DCM and PCC often overlap in same

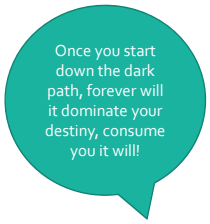
Livingston. Health Technol Assess 2014;18(39).

Summarize Non-drug Measures

- Despite lots of great ideas, little good evidence to support most non-drug measures
- Simple Interventions with possible benefit include activities, music and sensory stimulus. Sadly, there is still real uncertainty if these work reliably.
- Complex Interventions like Dementia Care Maps and trained Patient-Centred Care work but are complex and require broader system level commitment.

Tommy Gerschman

CONCUSSION



29th Annual Best Science Medicine Conference
Friday May 4, 2018 – May the Force Be With You

Dr Tommy Gerschman, MD, FRCPC, MSc
Pediatric Rheumatologist
Special Interest in Pediatric Sport & Exercise Medicine
Clinical Instructor, Department of Pediatrics, UBC
Fortius Sport & Health, Burnaby, BC

Faculty/Presenter Disclosure

- **Faculty/Presenter:** Tommy Gerschman
- **Relationships with commercial interests:**
  - **Grants/Research Support:** *None.*
  - **Speakers Bureau/Honoraria:** *None.*
  - **Consulting Fees:** *None.*
  - **Other:** *None.*
- **Current Practice Setting:**
  - *Pediatrician at Fortius Sport & Health, Burnaby, BC*

Disclosure of Commercial Support

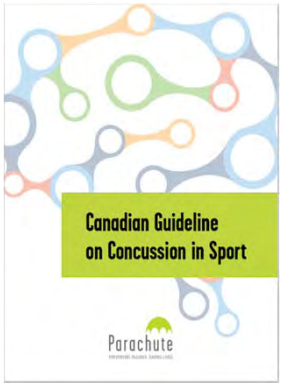
- **No financial support has been received.**
- **No in-kind support has been received.**
- **Potential for conflict(s) of interest:**
  - None.

Learning Objectives

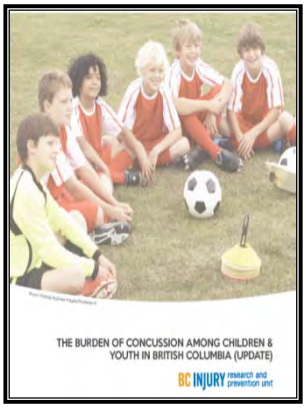
- Be able to understand a working **definition** of concussion.
- Be able to **recognize** a concussion.
- Understand the appropriate role for **rest** in concussion management.
- Understand the concept of **pacing** in a step-wise recovery from concussion.

Tommy Gerschman

Two Key References



Burden of Concussions in BC



- 2001-2014 (0-19y)
  - 2,539 Hospitalizations
- 2012-2015 (10-19y)
  - ~1220 visits @ BCCH ED

Take Home Message #1

- A concussion is a traumatically induced mild brain injury resulting in a functional disturbance of brain function.

I felt a great **disturbance** in the **force**... I fear something terrible has happened.

Traumatic Mild Brain Injury

Tommy Gerschman

Take Home Message #2

- **Remove:**

When in Doubt,
Sit them Out!

Do. Or do not.
There is no try.

ANY ATHLETE WITH A SUSPECTED CONCUSSION SHOULD BE IMMEDIATELY REMOVED FROM PRACTICE OR PLAY AND SHOULD NOT RETURN TO ACTIVITY UNTIL ASSESSED MEDICALLY, EVEN IF THE SYMPTOMS RESOLVE

Take Home Message #3

- Use a multi-modal tool to diagnose a concussion (e.g. SCAT5)

Your eyes can deceive you. Don't trust them.

Multi-Modal Assessment

Tommy Gerschman

Take Home Message #4

- The role for rest is limited.
  - Maximum 24-48 hours before symptom-limited activities

But beware of the dark side. Anger, fear, aggression; the dark side of the Force are they... If once you start down the dark path, forever will it dominate your destiny, consume you it will...

Role of Rest

Take Home Message #5

- **Pacing** is a key concept in recovery.
  - Follow a step-wise and gradual return to activities.
  - Important role for exercise.

Stay on target

- Gold Five

Pacing + Targeted Therapies

Tommy Gerschman

Take Home Messages

- A concussion is a traumatically induced mild brain injury resulting in a functional disturbance of brain function.
- **Remove:** When in Doubt, Sit them Out!
- Use a multi-modal tool to diagnose a concussion (e.g. SCAT5)
- The role for rest is limited.
  - Maximum 24-48 hours before symptom-limited activities
- **Pacing** is a key concept in recovery. Step-wise and gradual return to activities.
  - Important role for exercise.

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Mike Kolber

Everthing to do with stopping clots - "Difficult to see. Always in motion is the future."

Mike Kolber MD, CCFP, MSc

Best Science Medicine 2018

Faculty/Presenter Disclosure

- **Faculty/Presenter:** Mike Kolber
  - Rural Family Physician with interest in GI: Peace River
  - Academic, University of Alberta Department of Family Medicine
- **Where we get Personal $:** U of Alberta Family Medicine
- **Where we get Grant/ Program $:** Alberta College of Family Physicians, Toward Optimized Practice
- **Relationships with commercial interests:**
  - **Grants/Research Support or Speakers Bureau / Honoraria:** None
  - **Consulting Fees:** Not applicable
  - **Other:** emprss: U of A spin off, quality metrics in medical procedures, Alberta Government Expert Drug Committee
- **Insider Information:** Nickname = coupons
  - "Never the first (or last) to prescribe a med"

Objectives

1. What to do with below knee DVTs?
2. VTE treatment: what to use?
   - NOACs vs warfarin
3. How long should I treat?
4. VTE prophylaxis post ortho

Will not cover:

- Diagnosis of DVT / PE, Thrombectomy for VTE
- Intricacies of pro-thrombotic states, General VTE prophylaxis

Mrs OP ~2010

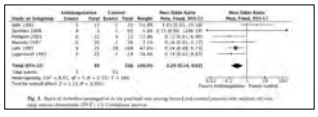
- 65 year old ♀ with ostomy for previous CRC.
- Worried had "stroke" as unilateral swollen leg.
- EMT assesses: "not a stroke"…and leaves
- Kolber: "yup, not a stroke"…and gives LMWH
- Ultrasound confirms below knee DVT

Distal (Below Knee) DVTs

- Proximal DVT Risk: "~33% proximal extension"[1]
  - 2012 MA: 2 RCTs, 6 cohort, 505 pts FU ~3 months[2]
    - Without tx: ~17%, with tx: 3%
  - 2017 MA: Prox. Extension: 12% w/o tx, 6% with[3]

Chest 2016 Recommends:[4]

- **Treat Distal DVTs**
- **Same treatment length as proximal DVT**



[1]Up to Date: April 4, 2018, [2]J Vasc Surg 2012;56:228, [3]Thrombosis Haemostasis, 2017; 15: 1142, [4]Chest 2016; 149(2):315

Kolber's VTE Rules

- **Treat Below Knee VTEs**

Mike Kolber

Treating VTE: NOACs vs Warfarin

- 5 non-inferiority RCTs (~19K patients): DVT or PE
  - ~55-58 yo, ~60% ♂, ~20% previous VTE, ~5% cancer, significant kidney disease excluded
- Industry: but blinded outcome assessors
- Non-inferiority issues:
  - Modified ITT: should be "per protocol" (null = different)
  - Margins: 2-2.75xs: if VTE = 2%, non-inferior if 4 – 5.5%
- TTR warfarin ~60%

EINSTEIN NEJM 2010;363:2499, EINSTEIN–PE NEJM 2012;366:1287
RECOVER: NEJM 2009;361:2342. RECOVER 2 Circulation.2014;129(7):764.
AMPLIFY: NEJM 2013;369:799.

NOACs vs Warfarin: VTE Treatment

	Einstein DVT, PE[1-3] Rivaroxaban (Xarelto)		RECOVER 1-2[4,5] Dabigatran (Pradax)		AMPLIFY[6] Apixaban (Eliquis)	
Patients	DVT: 3449[1] PE: 4832[2] ~60% unprovoked 35% surgery/ immobilization		5107 patients 70% DVT, 30% PE ? provoked		5395 patients 2/3 DVT, 1/3 PE 90% unprovoked	
Important Exclusion	CrCl < 30 ml/min ALT 3X ULN		CrCl < 30 ml/min ALT 3X ULN		Provoked with transient risk factor (ex. post op) CrCl <25 ml/min	
Study Characteristics	Open Label Blinded adjudicators		Triple blinded		Triple blinded	
Dose	Riva 15mg bid x 3 weeks then 20 mg od	LMWH + Warfarin	10 days LMWH or Heparin then Dabi 150mg bid vs Warfarin		Apixa 10 mg bid x 7d then 5 mg bid	LMWH + Warfarin
Follow Up	3,6 or 12 months		6 months		6 months	
Recurrent VTE	Rivaroxaban 2.1%	Warfarin 2.3%	Dabigatran 2.4%	Warfarin 2.2%	Apixaban 2.2%	Warfarin 2.6%
Major* or significant bleed**	9.4%	10%	5.3% NNT=32	8.5%	4.3% NNT=19	9.7%
Death	2.3%	2.4%	1.8%	1.8%	1.5%	1.9%

*Major Bleeding: ↓ Hb ≥ 20 g/l, transfusion ≥2 prbcs, or critical site (retroperitoneal, intracranial)
**Significant bleed: results in medical intervention, unscheduled MD visit, interruption of study med

1. Einstein DVT NEJM 2010;363:2499-510. 2. Einstein- PE NEJM 2012;366:128 3. Einstein combo Thrombosis 2013, 11:21. 4. RECOVER I. NEJM 2009;361:2342 5. RECOVER combo Circulation 2014; 129(7):764. 6. AMPLIFY NEJM 2013;369:799, TFP #111, 2014

NOACs vs Warfarin: VTE Treatment

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Important Exclusion	CrCl < 30 ml/min ALT 3X ULN		CrCl < 30 ml/min ALT 3X ULN		Provoked with transient risk factor (ex. post op) **CrCl <25 ml/min**	
Study Characteristics	**Open Label** Blinded adjudicators		Triple blinded		Triple blinded	
Dose	Riva 15mg bid x 3 weeks then 20 mg od	LMWH + Warfarin	**10 days LMWH or Heparin** then Dabi 150mg bid vs Warfarin		Apixa 10 mg bid x 7d then 5 mg bid	LMWH + Warfarin
Follow Up	3,6 or 12 months		6 months		6 months	
Recurrent VTE	Rivaroxaban 2.1%	Warfarin 2.3%	Dabigatran 2.4%	Warfarin 2.2%	Apixaban 2.2%	Warfarin 2.6%
Major* or significant bleed**	9.4%	10%	**5.3% NNT=32**	8.5%	**4.3% NNT=19**	9.7%
Death	2.3%	2.4%	1.8%	1.8%	1.5%	1.9%

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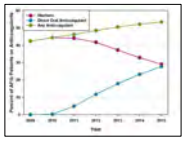
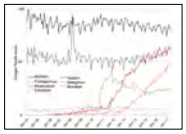
NOACs vs Warfarin: Summary

- Recurrent VTE: similar
- "Easy CCRABs"
  - **Easy**: Apixa, Riva: no preceding LMWH
  - **C**ost: (90 days) ~$300[1] [warfarin $20 ($100 w INRs)]
  - **C**VD: avoid Dabigatran[2]
  - **R**enal impairment: Apixaban (or warfarin)[3]
  - **A**ge: no exclusions in VTE, but AF > 80 → ↑ bleeding[5]
  - **B**leeding concerns: Apixaban or Dabi[6]
    - Unlike AF: VTE studies did not have lower dose NOACs

[1]Price Comparisons - Commonly Prescribed Pharmaceuticals in Alberta 2018
[2]NEJM 2010; 363;19, Arch Intern Med. 2012;172(5):397, [3]Can Journal Cardio 2013; 29: S71
[4]CHEST 2016; 149(2):315, [4b]NEJM 2018;378:615, [6]AMPLIFY NEJM 2013;369:799, [3,5,6]TFP #111, 2014

Trends and Costs
6 months of Treatment





Product	Cost per 6 months	Coverage
Warfarin	40 (210 with labs)	BC / IA covered
Rivaroxaban	590	SA for BC and IA
Apixaban	660	SA for BC and IA
Dabigatran	680	SA for BC and IA
Edoxaban	XXX	SA for BC and IA

Price Comparisons…Prescribed Pharmaceuticals Alberta 2018, available at www.acfp.ca.
Swenson, Health Trends Alberta Apr. 2017, Ann Transl Med 2017;5(16):322, Br J Clin Pharm 2017 83 2096

Kolber's VTE Rules

- Treat Distal (Below Knee VTEs)
- **NOACs / Warfarin have similar outcomes**
  - **"Easy CCCRABs"**

Mike Kolber

Life is Risky
Uprovoked VTE recurs ~ 30% in 10 years

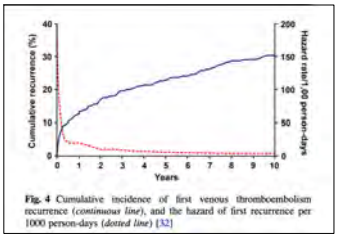


Fig. 4 Cumulative incidence of first venous thromboembolism recurrence (*continuous line*), and the hazard of first recurrence per 1000 person-days (*dotted line*) [32]

J Thromb Thrombolysis 2016: 41:3
Haematologica 2007; 92:199

Risk of Recurrence
Provoked vs Unprovoked

- SR of 15 cohort, RCTs (> 5000 patients)
  - Treated for VTE x ~3/12, FU up to 2 years for recurrent VTE. Best data for 1st year.

VTE type	Recurrence risk (%) 1 year after tx
All Provoked	3.1
Provoked (surgery)	1.0
Provoked (not surgery)*	5.8
Unprovoked	7.9

*Immobilization, casting, pregnancy

Arch Intern Med. 2010;170(19):1710

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Provoked vs Unprovoked

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Provoked (not surgery)*	**5.8**
Unprovoked	**7.9**

*Immobilization, casting, pregnancy

Arch Intern Med. 2010;170(19):1710

Risk of Recurrence
Length of VTE Treatment

- SR: 7 RCTs (~3000 pts) comparing different lengths of tx in 1st time VTE (w/o cancer)
  - 52% ♂, age 60 years
  - 20% distal DVT, 50% proximal DVT, 30% PE
  - 60% provoked*, 40% unprovoked
- Times: 4-6 weeks; 3 months; 6 months; 12+ months

*Provoked Definition: Differed between studies: but all included recent surgery, cast immobilization, or admission to hospital.

BMJ 2011;342:d3036

Treatment Length
Risk of Recurrence

- Overall recurrence = 8% at 2 years
  - 2/3 in 1st 6 months
- ~50% ↓ if distal (c/w proximal) DVT
- ~50% ↓ if temporary RFs (c/w unprovoked)

<u>Length of Treatment and Recurrence:</u>

- All VTEs (provoked, unprovoked): 50%↑ if tx <3 months
- Unprovoked: ↑ if < 3 months (c/w > 3 months)
  - HR 1.4 (0.96-2.01)

BMJ 2011;342:d3036

Kolber's VTE Rules

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  - "Easy CCCRABs"
- **Treat all VTEs for 3 months minimum**
- **Treat unprovoked VTEs for at least 6 months**

Mike Kolber

6 months post unprovoked VTE, now what? Who to consider stopping OAC

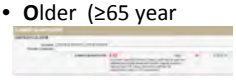
Canadian Cohort: 646 unprovoked VTEs
- 53 yo, 50% ♀, 30% PE
- Treated ~6 months; stopped → ~1.5 year FU

Annual VTE risk (overall): ♂=14%, ♀=6%

HERDO$_2$ Risk Factors (women)

- **H**yperpigment, **E**dema, **R**ed
- **D**-dimer ≥250ug/L
- **O**besity (BMI≥ 30)
- **O**lder (≥65 year

♀<2 RFs =1.6%
♀≥2 RFs =14%



CMAJ 2008;179(5):417

Validating Men Continue +HERDO$_2$ rule

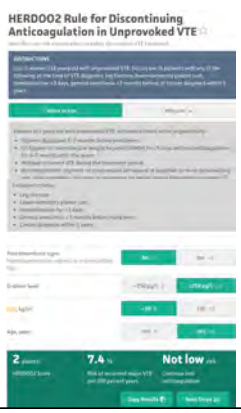
- 3155 unprovoked 1st VTE, tx OAC x 5-12 months
  - Excluded thrombophilics
  - Low risk ♀: HERDO$_2$<2: → stopped treatment
  - High risk: ♂ or ♀HERDO$_2$ ≥2 →MD decided tx
  - 1 year FU

Category	VTE (%, 95% CI)
Low risk ♀ (HERDO$_2$< 2) - stopped	3.0 (1.8-4.8)
High risk ♀or ♂ - stopped	8.1 (5.2-11.9)
High Risk ♀or ♂ - continued	1.6 (1.1-2.3)

For every 16 high risk who continued OAC → 1 less recurrent VTE per year

BMJ 2017;356:j1065

There's an App for That!



https://www.mdcalc.com/herdoo2-rule-discontinuing-anticoagulation-unprovoked-vte

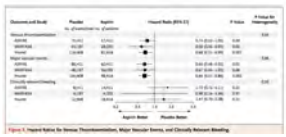
Kolber's VTE Rules

- Treat Distal (Below Knee VTEs)
- NOACs / Warfarin have similar outcomes
  - "Easy CCCRABs"
- Treat all VTEs for 3 months minimum
- Treat unprovoked VTEs for at least 6 months
- **At 6 months: continue ♂ and ♀HERDO$_2$ ≥2**

Extending Beyond 6-12 months

Compared to placebo, Aspirin ↓ recurrent VTE ~30%

- 2 RCTs: uprovoked VTE patients
  - warfarin x 6-12 months → ASA or placebo ~ 2 years.
- ASA: ↓ recurrent VTE ~30% RR (13 vs 18%), NNT = 19, Major Bleeds: no difference



N Engl J Med. 2012; 366:1959, N Engl J Med. 2012; 367:1979, TFP# 93 (2013, updated 2016)

Extending beyond 6 - 12 months

Compared to placebo, NOACs ↓ VTE by 80%

Riva:[1] 1200 pts (75% unprovoked), intial tx x 6-12/12 → Riva 20 mg vs placebo x another 6-12/12
- VTE: 1.3% vs 7.1% RRR ~80%, NNT = 18
  - Major / relevant bleeds: 6% vs 2%, NNH=25

Apixa:[2] 2482 pts (90% unprovoked), initial tx 6-12/12 → Apixa 2.5 or 5mg or placebo x another 1 year
- VTE: 1% vs 7%, RRR~80%, NNT =17
  - Major / relevant bleeding: 4% vs 3%

Dabi:[3] after 3/12 tx (too short)→ placebo, warfarin, Dabi
- VTE: ~1-2% Dabi vs 1% warfarin vs 6% placebo

[1] EINSTEIN NEJM 2010;363:2499. [2]AMPLIFY-EXT NEJM 2013;368:699, [3] NEJM 2013;368:709

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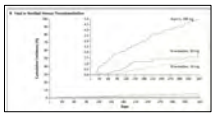
Extending beyond 6 - 12 months
Compared to ASA, Riva ↓VTE by 66%

- 3396 pts post 6-12/12 OAC
  → randomized Riva 20mg or 10mg or ASA x 1 year
  – 58 yo, 55% ♂, uprovoked 40%, 60% had 1 year tx, previous VTE 20%
- VTE: 4.4% ASA, ~1.5% Riva (66% RRR), NNT ~30
- Major / Relevant bleed: 2% ASA, 2-3% Riva (NSS)



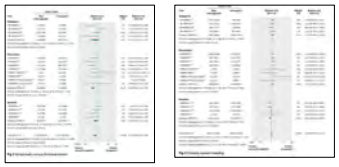
Einstein Choice: NEJM 2017;376:1211

Kolber's VTE Rules

- Treat Distal (Below Knee VTEs)
- NOACs / Warfarin have similar outcomes
  – "Easy CCCRABs"
- Treat all VTEs for 3 months minimum
- Treat unprovoked VTEs for 6 months
- At 6 months: continue ♂ and ♀ HERDO$_2$ ≥2
- **If treating beyond 6-12 months:**
  – **ASA ↓VTE ~30%, NOAC ↓VTE ~80%**

Joint Replacement VTE prevention
NOACs vs Enoxaparin

- 16 RCTs (4 Dabi, 4 Apixa, 8 Riva) ~39,000 pts
  – vs enoxaparin od (11 RCTs) or bid (5 RCTs)* x 9-40d
  – 8 hip, 8 knee, Age~65yo, 60-70% ♀, FU 1-3 months
  – Authors: no conflicts!



Gómez-Outes, BMJ 2012;344:e3675, *CHEST 2013; 144(2):593*

Joint Replacement VTE prevention
NOACs vs Enoxaparin

Direct and indirect comparisons: absolute difference in events per 1000 patients treated*

Comparison	Risk difference (95% CI) Symptomatic venous thromboembolism	Clinically relevant bleeding	Major bleeding	Net clinical endpoint
Direct comparisons:				
Rivaroxaban v enoxaparin	−5 (−9 to −1)	9 (2 to 17)	4 (−0.4 to 8)	−3 (−9 to 3)
Dabigatran v enoxaparin	−2 (−9 to 5)	5 (−4 to 13)	−1 (−6 to 5)	−1 (−9 to 7)
Apixaban v enoxaparin	−1 (−4 to 2)	−8 (−15 to −1)	−1 (−7 to 5)	−1 (−6 to 3)
Indirect comparisons:				
Rivaroxaban v dabigatran	−3 (−11 to 4)	5 (−7 to 16)	4 (−2 to 11)	−2 (−12 to 9)
Rivaroxaban v apixaban	−4 (−9 to 1)	18 (7 to 28)	5 (−2 to 12)	−2 (−9 to 6)
Apixaban v dabigatran	1 (−7 to 8)	−13 (−24 to −2)	0 (−8 to 7)	0 (−9 to 9)

*Random effects model, events while receiving treatment.

Gómez-Outes, BMJ 2012;344:e3675

Joint Replacement VTE prevention
Extended ~6 weeks vs 1-2 weeks

- SR: 16 RCTs, 25,000 pts compared extension with LMWH/UFH, VKA, NOACs to placebo
  – Mostly THR (13 RCTs), TKR (3 RCTs)
- LMWH/UFH:
  – VTE: 3.3% (placebo)→ 2% (NNT = 77)
  – Major Bleeding: 0.4% vs 0.2% (NNH=500)
- NOACs:
  – VTE 1.2% (placebo) → 0.3% (NNT= 100)
  – Major Bleeding: 0.1% both

Cochrane 2016, Issue 3. Art. No.: CD004179

Joint Replacement VTE prophylaxis
Extended Therapy ASA

2 Canadian quality, public funded, non-inferiority RCTs

- Vs LMWH:[1] 736* post hip: daltaparin x 10 days, then daltaparin or ASA for 28+ days. FU 3/12
  – VTE: ASA 0.3%, Dalt 1.3%
  – Major or CR bleed: ASA 0.5%, Dalt 1.3%
- Vs NOAC:[2] 3424 post THR or TKR: 5 days Riva 10mg → RIVA or ASA 81mg (TKR: 9+days, THR: 30+ days)
  – VTE: ASA 0.6%, Riva 0.7%
  – Major or CR bleed: ASA 1.3%, Riva 1%
  – 1 death (PE): ASA arm (TKR): 17 days after ASA stopped

Ann Intern Med. 2013;158:800, NEJM 2018;378:699

Mike Kolber

Kolber's VTE Rules

- Treat Distal (Below Knee VTEs)
- NOACs / Warfarin have similar outcomes
  - "Easy CCRABs"
- Treat all VTEs for 3 months minimum
- Treat unprovoked VTEs for at least 6 months
- At 6 months: continue ♂ and ♀ $HERDO_2 \geq 2$
- If treating beyond 6-12 months:
  - ASA ↓VTE ~30%, NOAC ↓VTE ~80%
- Post THR (TKR): VTE prophylaxis ≥14 days
  - ASA post 5d NOAC or 10d LMWH

Thank you

mkolber@ualberta.ca

Diabetes drugs - past to present
“Powerful you have become, the dark side I sense in you.”

James McCormack
BSc (Pharm), PharmD
Professor
Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, BC, Canada

1) Disclosure of Commercial Support

Neither this program nor the presenter has received financial support from any organization or company.

2) Mitigating Potential Bias

All recommendations and information presented are based on the best-available evidence we could find. Typically this includes meta-analyses, systematic reviews and RCTs. In addition, we don’t care what the results are, but rather we care that people know about the results.

3) Objectives

To be able to take the best available evidence for common conditions in primary care and incorporate this information into shared-decision making with patients.

My Premise

T2DM is not a disease but simply a risk factor

The tests used to diagnose/monitor a person with T2DM are at best tricky to use and are very misleading

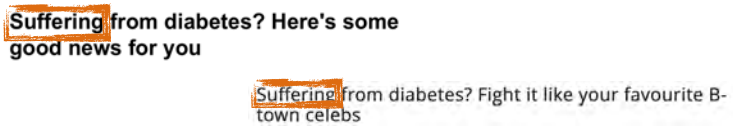
The vast majority of T2DM treatments have been shown to have no benefit and cause harm

A1c is a risk factor so you need to be able to estimate risk

For those that have been shown to have a possible benefit, the benefit is of such a low a magnitude and a high cost that the vast majority of people would likely not take them

Type 2 Diabetes
“The disease who must not be named”

It is NOT a disease
It is a RISK Factor



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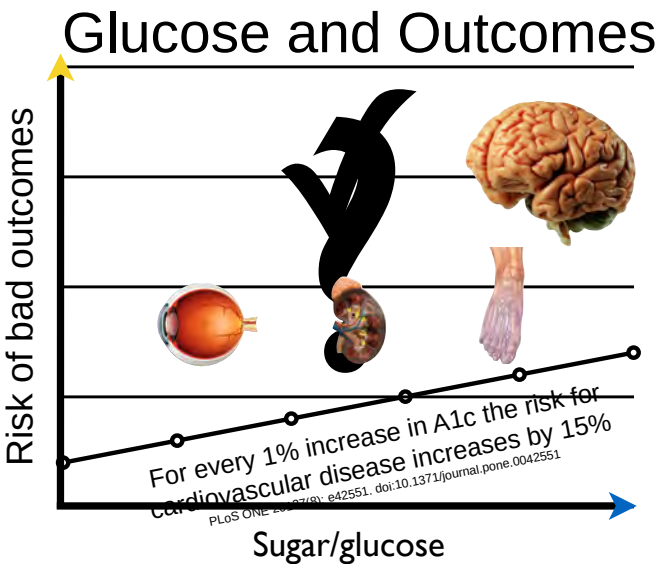
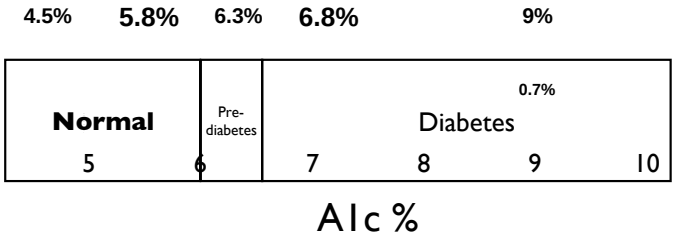


The tests used to diagnose/ monitor a person with T2DM are at best tricky to use

Precisely Imprecise

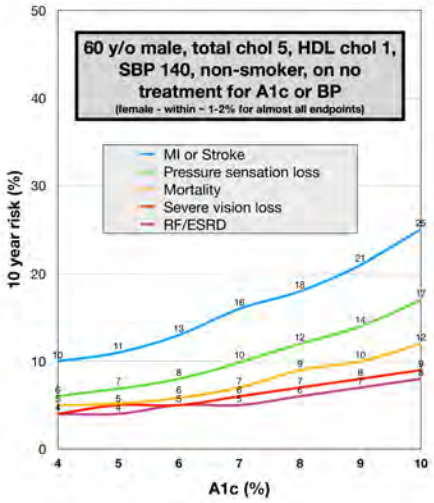
What an A1c result really means



Typical A1c change seen with a medication = 0.7%⬇

Seasonal variation 0.2-0.5%
Higher in the winter
Am J Epi 2004;161:565-74

T2DM risk should not be categorized as YES or NO



https://sanjaybasu.shinyapps.io/recodesi/ - from the ACCORD study

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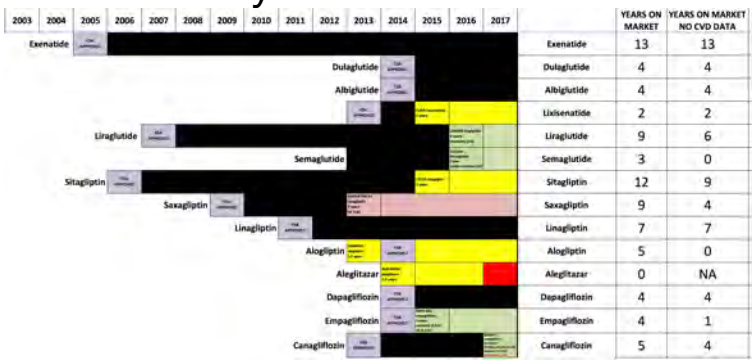
The History of T2DM Treatments



	YEARS ON MARKET	YEARS ON MARKET NO CVD DATA
Exenatide	13	13
Dulaglutide	4	4
Albiglutide	4	4
Lixisenatide	2	2
Liraglutide	9	6
Semaglutide	3	0
Sitagliptin	12	9
Saxagliptin	9	4
Linagliptin	7	7
Alogliptin	5	0
Aleglitazar	0	NA
Dapagliflozin	4	4
Empagliflozin	4	1
Canagliflozin	5	4

the date the drug was brought to market
the date the key clinical outcome trial(s) were published
the outcome - negative, neutral, positive
colour-coded and calculated the years with and without clinically important outcome evidence

The majority of T2DM treatments have been shown to have no benefit and they ALL cause some sort of harm

HARM

1) At a minimum all have cost and inconvenience

2) Most if not all have some adverse effects - weight gain, heart failure, hypoglycemia, genital infections, amputations

An ~100-year History Lesson

(60 years if you don't include insulin)

28 medications

26 have received regulatory approval

19 have been evaluated in at least 1 RCT assessing impact on important outcomes

MY DEFINITION OF IMPORTANT OUTCOMES

1) microvascular (end-stage renal disease/dialysis, renal death, blindness, clinical neuropathy)

and/or

2) macrovascular (all cause mortality, CVD mortality, non-fatal MI, stroke, amputation, heart failure or a composite CVD endpoint)

All the large RCTs evaluating the impact of medications on Clinically Important Outcomes

TABLE 1 - RCTs evaluating the impact of medications on clinical outcomes in T2DM

YEAR	NAME	MEDICATION	RESULT	OUTCOME CHANGED	ABSOLUTE DIFFERENCE/ TIME
1970	UGDP	tolbutamide (Orinase)	NEGATIVE	CVD mortality	↑8%/5 years
1971		phenformin (DBI)	NEGATIVE	Mortality	↑ 6%/5-8 years
1976		tolbutamide (Orinase)	NEGATIVE	Fatal MI	↑ 5%/5 years
1982		insulin	NEUTRAL		
1998	UKPDS 33/34	insulin, chlorpropamide, glyburide/ glibenclamide, glipizide	NEUTRAL		
1998		metformin, insulin, chlorpropamide, glyburide/ glibenclamide, glipizide	NEUTRAL except POSITIVE for metformin	Mortality MI	↓7%/11 years ↓ 6%/11 years
2003	STOP-NIDDM	acarbose (Precose)	POSITIVE	MI	↓ 1.5%/3 years
2005	PROACTIVE	pioglitazone (Actos)	POSITIVE	MI	↓ 1.5%/3 years
2007	RECORD	rosiglitazone (Avandia)	NEGATIVE	Heart failure	↑ 1%/4 years
2012	ORIGIN	insulin	NEUTRAL		
2013	EXAMINE	alogliptin (Nesina)	NEUTRAL		
2014	SAVOR-TIMI 53	saxagliptin (Onglyza)	NEGATIVE	Heart failure	↑ 1%/2 years
2014	ALECARDIO	aleglitizar	NEUTRAL		
2015	ELIXA	lixisenatide (Adlyxin)	NEUTRAL		
2015	TECOS	sitagliptin (Januvia)	NEUTRAL		
2015	EMPA-REG	empagliflozin (Jardiance)	POSITIVE	Mortality Heart failure	↓ 2.5%/3 years ↓ 1.5%/3 years
2016	SUSTAIN 6	semaglutide	POSITIVE	Combined outcome	↓ 2%/2 years
2016	LEADER	liraglutide (Victoza)	POSITIVE	Mortality	↓ 1%/4 years
2017	CANVAS	canagliflozin (Invokana)	POSITIVE	Combined outcome Heart failure Amputations	↓ 2%/3.5years ↓ 1%/3.5 years
2017	EXSCEL	exenatide (Byetta)	NEUTRAL		
2017	ACE	acarbose (Procose)	NEUTRAL		

mystudies.org

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Studies Overall

17 RCTs have evaluated 20 of the 28 medications

47% (9/19) of the medications evaluated showed NO OVERALL BENEFIT

32% (6/19) SHOWED SOME BENEFIT (on at least one, and TYPICALLY ONLY ONE, clinically important outcome)

21% (4/19) SHOWED OVERALL HARM (no benefit and harm for at least one clinically important outcome)

Study Outcome Synopsis

16 studies

MICROVASCULAR OUTCOMES - positive impact **= NONE**

MACROVASCULAR OUTCOMES

MORTALITY: 3 a decrease (metformin/empagliflozin/liraglutide) and 1 an increase (tolbutamide)

MI: 3 a decrease (metformin/acarbose/pioglitazone) and 1 an increase (tolbutamide)

HF: 2 a decrease (empagliflozin/canagliflozin) and 2 an increase (rosaglitazone/saxagliptin)

COMBINED CVD ENDPOINT: 2 a decrease but not on individual endpoints (semaglutide/canagliflozin)

AMPUTATIONS: 1 an increase (canagliflozin)

Original Article

Circ Cardiovasc Qual Outcomes. 2016;9:00-00.August 2016

Glycemic Control for Patients With Type 2 Diabetes Mellitus
Our Evolving Faith in the Face of Evidence

René Rodríguez-Gutiérrez, MD, MSc; Victor M. Montori, MD, MSc

"no significant impact of tight glycemic control"

Review

Diabetes Metab 2014 Feb 3. pii: S1262-3636

Effects of pharmacological treatments on micro- and macrovascular complications of type 2 diabetes: What is the level of evidence?

R. Boussageon[a,*], F. Gueyffier[b,c], C. Cornu[b,c,d]

"In 2013, the level of evidence for the clinical efficacy of antidiabetic drugs is disappointing and does not support the millions of prescriptions being written for them"

EMPA-REG - non-inferiority (safety) was the primary outcome

A1c 8.1%, age 63, 71% male, SBP 135, on glucose agents, previous CVD 100%, total chol 163, HDL 44 - 3.1 years

Pooled dose data	Empagliflozin (%)	Placebo (%)	Absolute #s
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	10.5	12.1	**~1.5%**
Hospitalization for heart failure	2.7	4.1	**~1.5%**
Mortality	5.7	8.3	**~2.5%**
Genital infections	6.4	1.8	**~5%**
Doesn't increase risk of HF or hypoglycaemia 👍			

Primary outcome = 0.86 RR; 95.02% confidence interval, 0.74 to 0.99
P=0.04 for superiority
Endpoints not looked at - ESRD, blindness, amputation

N Engl J Med 2015;373:2117-28

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Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events

Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)

Nov 13, 2017

"Canagliflozin reduced cardiovascular outcomes with no statistical evidence of heterogeneity of the treatment effect across the primary and secondary prevention groups"

Secondary

"Canagliflozin reduced cardiovascular outcomes with no statistical evidence of heterogeneity of the treatment effect across the primary and secondary prevention groups"

NEJM Journal Watch

Canagliflozin Works as Both Primary and Secondary Prevention in Patients with Diabetes Type 2

P&T Community

THE ONLINE RESOURCE FOR P&T DECISION MAKERS

CURRENT ISSUE OF P&T

Invokana Demonstrates Cardiovascular Benefit for Type-2 Diabetes Patients

Outcomes Improve for Those With and Without a History of Prior CV Events

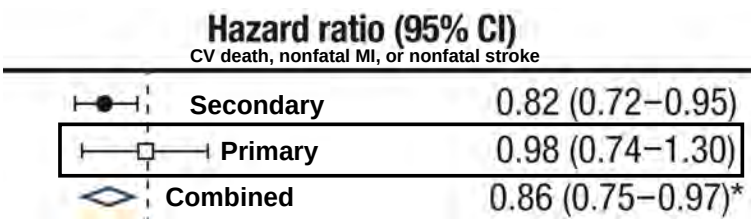
DIABETES IN CONTROL

News and information for Medical Professionals.

AJMC Managed Markets Network

premise. The results showed that the SGLT-2 inhibitor was effective in reducing the risk of CV outcomes in patients with and without a prior history of cardiovascular disease. Patients in the

	Number of participants	Patients per 1000 patient-years: Canagliflozin	Patients per 1000 patient-years: Placebo	Hazard ratio (95% CI)		Interaction *P* value
CV death, nonfatal MI, or nonfatal stroke	796	34.1	41.3	Secondary	0.82 (0.72–0.95)	0.16
	215	15.8	15.5	Primary	0.98 (0.74–1.30)	
	1011	26.9	31.5	Combined	0.86 (0.75–0.97)*	



Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

N Engl J Med 2017; 377:2097-2099 | November 23, 2017 | DOI: 10.1056/NEJMc1712572

CANVAS - absolute difference over 5 years

Primary outcome

2.3% (95% CI, 0.4 to 4.2) - NNT 43

Hospitalized for HF

1.6% (95% CI, 0.7 to 2.5) - NNT 63

Serious decline in kidney function

1.8% patients (95% CI, 0.8 to 2.8) - NNT 57

Amputation

1.5% (95% CI, 0.8 to 2.2) - NNH 68

James McCormack

The Gliflozins - overall

	Empagliflozin EMPA-REG 3.1 y **% = placebo rate**	Canagliflozin CANVAS 3.6 y **% = placebo rate**	Dapagliflozin DECLARE-TIMI 58 (APRIL 2019)
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	0.86 (0.74–0.99) 12.1%	0.86 (0.75–0.97) **9.8%**	?
Mortality	0.68 (0.57-0.82) 8.3%	0.87 (0.74–1.01) **6.5%**	?
Serious adverse events	0.90 (0.84-0.96) 42.3%	0.93 (0.87-1.00) ?	?
Composite renal events increased creatinine or BUN levels, decreased eGFR, renal impairment and renal failure	*0.63 (0.54-0.72) ?	*1.29 (0.78-2.15) ? 0.60 (0.47-0.77) ? CANVAS different renal groupings	*1.64 (1.26-2.13)
Acute renal impairment/ failure events	*0.72 (0.60-0.86) 3.1%?	*0.67 (0.25-1.80) ?	*0.75 (0.33-1.74)
Amputations (primarily toe)	?	1.97 (1.41-2.75) **1.2%**	?
Fractures	No difference	1.26 (1.04–1.52) **4.3%**	?

*from Diabetes Obes Metab 2017;19:1106–15

Effect of Sodium-Glucose Cotransport-2 Inhibitors on Blood Pressure in People With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of 43 Randomized Control Trials With 22 528 Patients

Mohsen Mazidi, PhD; Peyman Rezaie, MSc; Hong-Kai Gao, MD, PhD; Andre Pascal Kengne, MD, PhD

J Am Heart Assoc. 2017;6:e004007. DOI: 10.1161/JAHA.116.004007

Effect on systolic blood pressure

⬇ 2.46 mmHg

Weight

⬇1.88 kg

The gliflozins DO NOT make ANYONE feel better

THE NUMBERS	***Secondary (EMPA-REG)**	**Primary ??**
BENEFIT - Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	4%/yr	2%/yr
~15% relative benefit	0.6%/yr	0.3%/yr
Over 5 years - EMPA-REG was only 3 years	3%	1.5%
	NNT 33	NNT 67
HARM - Genital infections	5%	5%
COSTS - just drug cost to prevent one event Yearly Cost = $3 x 365 ~$1,100 Cost for 5 years ~$5,500	$180,000	$360,000

*Only ~15% of T2DM patients have a risk similar to that seen in EMPA-REG

Diabetes Ther 2017;8:365–76

So if most medications have been shown to lower glucose but not change outcomes what the !@#$% should you do?

Emphasize, EMphasize, EMPhasize physical activity and eating "healthy" food

Don't emphasize targets - an A1c of 7-8 is quite reasonable

The medications with the best of the weakest evidence are metformin, and then just in secondary prevention empagliflozin/canagliflozin, maybe liraglutide

They all cause side effects

We don't really know about long-term adverse effects

The new agents are not inexpensive

Aaron Tejani

Title:
The Force of Blood Pressure: "I'm one with the Force. The Force is with me."

Presented by:
Aaron M Tejani, BSc(Pharm), PharmD
Researcher, Therapeutics Initiative (UBC)
Email: aaron.tejani@ti.ubc.ca
Website: www.ti.ubc.ca
Twitter: @amtejani @Drug_Evidence

Link to Slides (Active on Thursday 3 May 2018):
http://prezi.com/ctnevbud48uh/?utm_campaign=share&utm_medium=copy&rc=ex0share

Learning Objectives:

1. Why should we be concerned with elevated blood pressure?

- **Be able to state the type and magnitude of risk associated with different levels of elevated blood pressure in adults**

2. What do know about the variability in blood pressure measurements?

- **Be able to quantify the amount of variability with single and multiple blood pressure measurements in a patient with hypertension.**
- **Be able to identify the implications of variability when determining how much a particular medication lowers BP.**

3. What do we know about a dose response for common BP lowering medications?

- **Describe if there is "value" in increasing the dose of common BP lowering medications.**

4. Should we be aiming for particular BP targets for adults with hypertension?

- **Describe how the SPRINT trial adds to what we know about blood pressure targets.**
- **Describe if lower BP targets are justified for diabetic patients.**

5. Should we choose medications based on BP lowering ability or by class of medication?

- **Explain why BP lowering as an outcome is not a reliable surrogate for morbidity and mortality.**
- **List which BP medication classes have evidence for reducing the risk of important health outcomes (for first-line or second-line choices).**

Alan Cassels

What happens when trial results look like an anomaly?

The case of Zoledronic acid.

CFPC CoI Templates: Slide 1

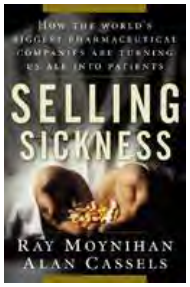
Faculty/Presenter Disclosure

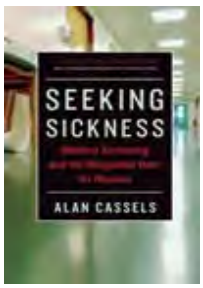
- **Faculty/Presenter: Alan Cassels with help from Dr. Teppo Jarvinen,** MD, PhD. Professor, Orthopedics and Traumatology. University of **Helsinki** and **Helsinki** University Hospital, Finland.
- **Relationships with commercial interests:**
  - **Grants/Research Support:** *None*
  - **Speakers Bureau/Honoraria:** *None*
  - **Consulting Fees:** *None*
  - **Admiration for Wookies:** *Nada*
  - **Other:**
    - *Salary at UBC at the Therapeutics Initiative*
    - *Book royalties (Greystone Books, Agio books)*
    - *Honoraria for reviewing for HealthNewsReview.org*

CFPC CoI Templates: Slide 3

Mitigating Potential Bias

- I wrote a chapter on osteoporosis in Selling Sickness, and on osteoporosis screening in Seeking Sickness. Neither book mentions zoledronic acid.





29th Annual Best Science Medicine Course: Slide 4

Learning Outcome Objective Slide

Attendees at my talk would learn about the key research around a widely used bisphosphonate (zoledronic acid) and be able to consider for themselves whether certain claims are “true” in the sense that they know what “truth” is.

Alan Cassels

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 24, Number 7, 2009
Published online on February 16, 2009; doi: 10.1359/JBMR.090209

Antifracture Efficacy and Reduction of Mortality in Relation to Timing of the First Dose of Zoledronic Acid After Hip Fracture

Erik Fink Eriksen,[1] Kenneth W. Lyles,[2] Cathleen S. Colón-Emeric,[3] Carl F. Pieper,[3] Jay S. Magaziner,[3] Jonathan D. Adachi,[4] Lars Hyldstrup,[5] Chris Recknor,[6] Lars Nordsletten,[7] Catherine Lavecchia,[8] Huilin Hu,[8] Steven Boonen,[9] and Peter Mesenbrink[8]

ABSTRACT: Annual infusions of zoledronic acid (5 mg) significantly reduced the risk of vertebral, hip, and nonvertebral fractures in a study of postmenopausal women with osteoporosis and significantly reduced clinical fractures and all-cause mortality in another study of women and men who had recently undergone surgical repair of hip fracture. In this analysis, we examined whether timing of the first infusion of zoledronic acid study drug after hip fracture repair influenced the antifracture efficacy and mortality benefit observed in the study. A total of 2127 patients (1065 on active treatment and 1062 on placebo; mean age, 75 yr; 76% women and 24% men) were administered zoledronic acid or placebo within 90 days after surgical repair of an osteoporotic hip fracture and annually thereafter, with a median follow-up time of 1.9 yr. Median time to first dose after the incident hip fracture surgery was ~6 wk. Posthoc analyses were performed by dividing the study population into 2-wk intervals (calculated from time of first infusion in relation to surgical repair) to examine effects on BMD, fracture, and mortality. Analysis by 2-wk intervals showed a significant total hip BMD response and a consistent reduction of overall clinical fractures and mortality in patients receiving the first dose 2-wk or later after surgical repair. Clinical fracture subgroups (vertebral, nonvertebral, and hip) were also reduced, albeit with more variation and 95% CIs crossing 1 at most time points. We concluded that administration of zoledronic acid to patients suffering a low-trauma hip fracture 2 wk or later after surgical repair increases hip BMD, induces significant reductions in the risk of subsequent clinical vertebral, nonvertebral, and hip fractures, and reduces mortality.
J Bone Miner Res 2009;24:1308–1313. Published online on February 16, 2009; doi: 10.1359/JBMR.090209

Key words: hip fracture, bisphosphonate, osteoporosis, infusion, zoledronic acid

Address correspondence to: *Erik Fink Eriksen, MD, DMSc, Department of Endocrinology, Aker University Hospital, N-0154 Oslo, Norway, E-mail: efinkeriksen@live.com*

Antifracture Efficacy and Reduction of Mortality in Relation to Timing of the First Dose of Zoledronic Acid After Hip Fracture**

"We concluded that administration of zoledronic acid to patients suffering a low-trauma hip fracture 2 wk or later after surgical repair increases hip BMD, induces significant reductions in the risk of subsequent clinical vertebral, nonvertebral, and hip fractures, and reduces mortality."

ORIGINAL ARTICLE
Endocrine Care

Effect of Osteoporosis Treatment on Mortality: A Meta-Analysis

Mark J. Bolland, Andrew B. Grey, Greg D. Gamble, and Ian R. Reid

Does drug treatment of osteoporosis reduce mortality?

Details:
- **10 studies**
- **5 different treatments**
- **Total of almost 40,000 patients**
- **10% reduction in mortality**

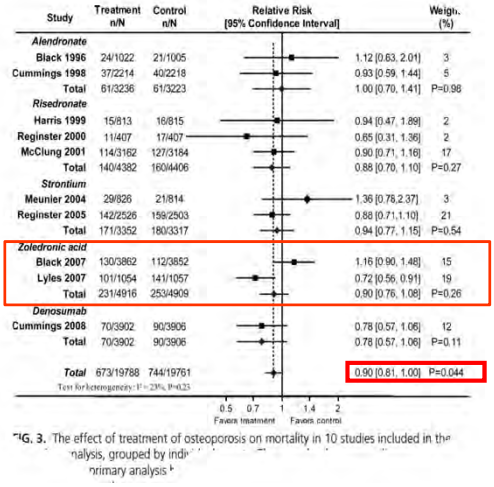
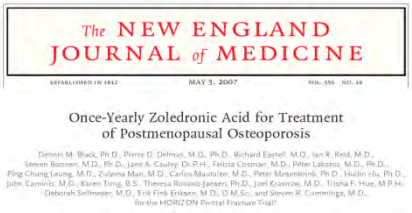


FIG. 3. The effect of treatment of osteoporosis on mortality in 10 studies included in the nalysis, grouped by indi primary analysis

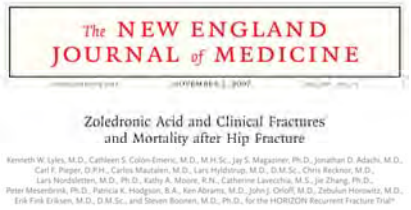
Alan Cassels


The NEW ENGLAND JOURNAL of MEDICINE

MAY 3, 2007

Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis

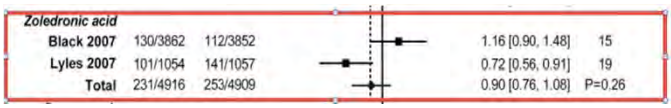
THE BLACK STUDY
(Horizon PFT)


The NEW ENGLAND JOURNAL of MEDICINE

Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture

THE LYLES STUDY
(Horizon RFT)

What were the rates of deaths on zoledronic acid?



Black zoledronic acid 130/3862= 0.034
placebo 112/3862=0.029

Difference: 0.005 or
0.5% Increased risk of death

Lyles: zoledronic acid 101/1054=0.096
placebo 141/1057=0.133

Difference: 0.037 or
3.7% Reduced risk of death

Why doesn't this make sense?

- Loss to follow up
- Early trial termination
- The "house of cards" phenomenon. Withdraw one card and the whole house collapses.

Loss to follow up

- Loss to follow up was a minor problem in the primary prevention trial (Black), in the secondary prevention trial (Lyles) , 155/ 295 participants withdrew consent or were lost to follow-up in the zoledronate arm and 137/316 in the placebo arm.
- This corresponds to a relative risk of consent withdrawal or loss to follow-up in zoledronic acid users of 1.21 (95% CI 1.03-1-43; p=0.02) compared with those on placebo.
- Consent withdrawal or loss to follow-up have been shown to be related to higher rate of disability and death.

Alan Cassels

I have got a "Bad Feeling" about: "Early trial termination"

- The Lyles trial was stopped early, following an additional unplanned interim analysis.
- Early termination of trials has been shown to overestimate reported benefits, with a ratio of relative risks versus non-truncated trials of 0.71 (95% CI 0.65-0.77), regardless of whether statistical stopping rules are used.

ORIGINAL ARTICLE

Endocrine Care

Effect of Osteoporosis Treatment on Mortality: A Meta-Analysis

Mark J. Bolland, Andrew B. Grey, Greg D. Gamble, and Ian R. Reid

Authors state:

"Finally, we performed a series of sensitivity analyses. Only one study was carried out after hip fracture (4, i.e., HORIZON/Lyles et al. NEJM 2007). When we excluded this trial from the primary analysis, the overall result was not significant (RR, 0.94; 95% CI, 0.84 –1.06; P 0.31)."

2010 Clinical Practice Guidelines Osteoporosis

good health except for the presence of increased fracture risk. The only clinical trial providing evidence that fracture prevention can reduce mortality was in participants receiving zoledronic acid within 90 days of hip fracture; mortality was analyzed as a secondary outcome and biases may have limited the validity of the results (e.g., not all participants were followed for the entire 36 months).[172] However, a recent meta-analysis also reported a 10% reduction in mortality in older individuals at high risk of fractures treated with osteoporosis therapies.[150] Prescribing information for osteoporosis pharmacologic agents is summarized in Table 6.

"Highly significant mortality-benefit!"

Professor Erik Eriksen

***Dr. Eriksen has been an employee of and owns stock in Novartis.**
as per disclosure found here:
http://onlinelibrary.wiley.com/doi/10.1359/jbmr.090209/full

Alan Cassels

Is it plausible there is a mortality benefit of bisphosphonates?

- One study is one study.
- It lost a significant number of patients to follow up, and was terminated early. The science is unconvincing.
- It is highly unlikely there is a “mortality benefit” from bisphosphonates

YET we see:

- The “mortality prevention” case for bisphosphonates persists and is found in guidelines.

Revenge of the Sith: Are Benzo's Really the Bad Guys?

Adrienne Lindblad

Knowledge Translation and Evidence Coordinator, Alberta College of Family Physicians

Associate Clinical Professor, Family Med, UofA

Faculty/Presenter Disclosure

- **Faculty/Presenter:** Adrienne Lindblad
- **Relationships with commercial interests:**
  - **Grants/Research Support:** *None*
  - **Speakers Bureau/Honoraria:** *None*
  - **Consulting Fees:** *None*
  - **Other:** *Employee of Alberta College of Family Physicians*

Learning Objectives

At the end of this presentation, participants will be able to:

1) Discuss the potential risks of benzodiazepines, including dementia, falls/fractures and mortality, including limitations in the literature, and any differences between short and long-term use
2) Compare the above risks of benzodiazepines with other commonly used medications

Is it the drug or confounding?

- "Benzodiazepines are Prescribed More Frequently to Patients Already at Risk for Benzodiazepine-Related Adverse Events in Primary Care" [1]
  - BZD users more likely to be smokers, have depression, osteoporosis, COPD, EtOH abuse, sleep apnea and asthma
    - High-dose users even higher risk
- BZD users have (per 100 patients): more primary care visits (408 vs 203), specialist visits (815 vs 578), ED visits (47 vs 29), hospitalizations (26 vs 15).[1]
- Half of French users have comorbidities or other medications that increase risk of BZD ADRs.[2]

[1]J Gen Intern Med. 2016;31(9):1027-34. [2]Eur J Clin Pharmacol. 2016;72(7):869-76.

Adrienne Lindblad

Dementia

Don't forget the evidence

- 3 systematic reviews, mainly case-control studies
  - 10 studies, n=101,659[1]
    - Dementia with BZD OR=1.78, I^2=99%
  - 6 studies, n=45,391[2]
    - Dementia with BZD aRR~1.5
    - Same regardless if recent or past use
      - IF REAL: Assume risk of dementia in community-dwelling elderly aged 65-79: 1.3%:[3]
        - Risk increased by 50% new risk=1.95%, NNH=153 over 7.3 years
      - Over age 80: Baseline risk 5%, new risk=7.5%, NNH=40
  - 9 studies, results not meta-analyzed[4]
    - Several studies do not account for EtOH, education, depression, anxiety, etc.
- 3 big issues: consistency, other causes, prodrome effects

[1]Neuroepidemiol. 2016;47:181-91. [2]PLoS ONE. 2015;10(5):e1027836. [3] https://www.statcan.gc.ca/pub/82-003-x/2016005/article/14613/tbl/tbl01-eng.htm. [4]Expert Opin Drug Saf. 2015;14(5):733-47.

Problem #1: Consistency

- Prospective US cohort of 3434 patients, mean follow-up 7.3 yrs
- No association between dementia and BZD use in the highest users (HR 1.07, 0.71-1.27)
  - Moderate use: 1.25 (1.03-1.51)
  - Low use: 1.31 (1.00-1.71)
- No association in mean cognitive score or rates of decline in score

BMJ 2016;352:i90.

Problem #2: Other Causes and Confounders

- Canadian case-control study of 1796 AD cases and 7184 controls
- Use within 5-10 years of dx date: aOR=1.43 (1.28-1.60)
- No effect for exposures <3 months
  - 3-6 months: aOR=1.28 (0.97-1.69)
  - >6 months: aOR=1.74 (1.53-1.98)
- Risk higher with long-acting: 1.59 vs short-acting: 1.37
- Only ~30% of patients on BZD had dx of insomnia, depression or anxiety
  - *So why there they using them???*

BMJ. 2014;349:g5205.

Do other drugs cause dementia?

- SSRIs faster rate of cognitive decline over 5 years in community dwelling elderly women based on cognitive scores
- Risk of dementia compared to non-users: OR 2.17 (1.49-3.15)

J Gerontol A Biol Sci Med Sci. 2017 Dec 12; epub ahead of print

Problem #3: Dementia Prodrome?

- Sleep problems, mood disorders, anxiety can precede dementia up to 10 years
- Confounding by indication and "reverse causation"??

PLoS ONE. 2015;10(5):e0127836.

Mortality: Do BZD kill people?

Mortality

- Systematic Review, 25 studies of "hypnotics-anxiolytics"[1]
  - Overall mortality: HR=1.43 (1.12-1.84). I^2=99%
    - Just BZD: HR=1.60 (1.03-2.69). I^2=99%
    - Just Z-drugs: HR=1.73 (0.95-3.16). I^2=97%
  - From 1-19 different adjustments: Age, $Pa0_2$, cancer, sleep duration, smoking in males only, habitual snoring, TB, etc. Rarely adjusted for mental health conditions

[1]Aust NZ J Psych. 2016;50:520-33.

Adrienne Lindblad

Examples

- Cohort newly admitted nursing home patients:[1]
  - "BZD" had higher rate of mortality than atypical antipsychotic users RR=1.37, adjusted RR=1.20 (0.96-1.50)
    - Not just BZD…
  - Conventional antipsychotics RR=1.37, adjusted RR=1.52 (1.14-2.02)
  - Antidepressants RR=1.25, adjusted RR=1.20 (0.95-1.51)
- Other cohorts:
  - Azithromycin compared to amoxicillin: HR 2.02 (1.24-3.30).[2]
    - Levofloxacin similar
- In real-life:
  - ADR-related deaths most common with anticoagulants, antiplatelets, opioids, digoxin, RAS inhibitors. [3,4]

[1]CMAJ. 2011; 183:E411-9. [2]NEJM. 2012;366:1881-90. [3]Eur J Clin Pharmacol. 2018 Mar 19 epub ahead of print. [4]Ann Pharmacother. 2012;46:169-75.

Falls and Fractures

Falls and Fractures

- Any fracture with BZD RR=1.25 (hip fracture similar).[1]
- Are short-acting better than long-acting?
  - Short-Acting RR=1.29 (1.56-1.44). I2=53%
  - Long-acting RR=1.21 (0.95-1.54). I2=79%
- Is long-term use still a risk?
  - Systematic review 18 studies on BZD and hip fracture:[2]
  - BZD RR=1.52 (1.37-1.68). I2=67% (due to lengths of tx)
    - Short-term RR=2.40 (1.88-1.92).
    - Medium-term RR=1.53 (1.22-1.92).
    - Long-term RR=1.20 (1.08-1.34).
  - 6 studies on z-drugs: RR=1.90 (1.68-2.13). I2=26%
    - Short-term RR=2.39 (1.74-3.29).

[1]Osteoporosis Int. 2014;25:105-20. [2]PLoS One. 2017;12(4):e0174730

Falls and Fractures

- Systematic Review of 22 studies of meds and falls in elderly (n=79,081). Risk of falls in "good studies":[1]
  - BZD: OR=1.65 (1.39-1.98)
  - Antidepressants: OR=1.68 (1.39-2.06)
  - Others with fall risk: NSAIDs, antihypertensives, diuretics
- Antidepressants consistently associated with fractures.[2,3]

[1]Arch Intern Med. 2009;169:1952-60. [2]Osteoporos Int. 2013 Jan;24(1):121-37. [3]Ann Pharmacother. 2012 Jul-Aug;46(7-8):917-28

Adrienne Lindblad

So what is the risk of broken bones?

- Assume risk of hip fracture 1.6%.[1]
- Assume BZD increase risk by 25%[2]: Risk increases to 2%, NNH=250.

[1]Arch Intern Med. 2004;164(14):1567-72. [2]Osteoporosis Int. 2014;25:105-20

Do patients feel better when we stop BZD?

- Not by much.
- Pseudo-RCT motivated quitters in 138 primary care patients (14 yrs of use):[1]
  - 6 outcomes different, most uninterpretable (example some decreased and some increased)
  - 21 outcomes no difference
- DB, RCT in 55 patients (1/3 dropped out):[2]
  - Change in daily functioning score at 1 year: 6 points on ~140 point scale
- Non-randomized study: No change in reaction times or cognitive errors between withdrawal and users.[3]
  - Reaction times slower compared to non-study, non-insomniac cohort (325 ms vs 268 ms)

[1]Psych Med. 2003;33:1233-37. [2]Eur J Clin Pharmacol. 1997;51:355-8. [3]Eur J Clin Pharmacol. 2014;70:319-29.

Does stopping BZD prevent falls or help balance?

- Withdrawal study of 92 people in Finland of temazepam & z-drugs.[1]
  - Not randomized, mainly on z-drugs, problems with categorization
  - Handgrip strength: NSS in men between withdrawers and users
    - Women: significantly better ~2 kg
  - No difference in balance scores
- RCT of 93 elderly randomized to withdrawal or not (19% of those approached to participate).[2]
  - By 38 weeks, almost half dropped out
  - 17 falls recorded in withdrawal, 40 in those who stayed on medication
  - ?regression to the mean?
    - Baseline # who had fallen in last year: ~50% withdrawal groups cf 20%
  - Number of fallers unknown
  - 47% restarted meds 1 month after study
- Bottom Line: unknown if stopping BZD reduces fall risk

[1] BMC Geriatrics. 2014;14:121. [2]JAGS. 1999;47:850-3.

Power Hungry

- Stopping BZD at all costs?
- Recent systematic review of 38 RCTs, n=2543
- Used “safer” drugs to help get people off BZD
  - Carbamazepine, valproic acid, TCAs, pregabalin, SSRIs…

Cochrane Database System Rev. 2018;3:CD011481

So what do we do?

- Any psychotropic appears to have risks of falling, fractures, mortality and dementia.
  - Avoid “delusions of grandeur”
- Press for better data/information
  - Shared, informed, decision-making
- “Be mindful of the future, but not at the expense of the moment.”

The End…and may the Force be with you

Christy Sutherland

Harm Reduction for people who use drugs: "No one should be stranded on Planet Hoth"

Christy Sutherland MD CCFP dABAM
Medical Director PHS Community Services Society
Physician Education Lead BC Center on Substance Use

Faculty/Presenter Disclosure

- **Faculty/Presenter: Christy Sutherland**
- **Relationships with commercial interests:**
  - **Grants/Research Support: none**
  - **Speakers Bureau/Honoraria:** *none*
  - **Consulting Fees:** *none*
  - **Other: Providence Health, Vancouver Coastal Health, Medical Director PHS Community Services Society, Physician Education Lead BC Center on Substance Use**

Learning Objectives

- Define Harm Reduction
- Evaluate the research analyzing Harm Reduction

- 4 people in BC die each day from overdose
- All of these are preventable deaths – no one should die of opioid overdose

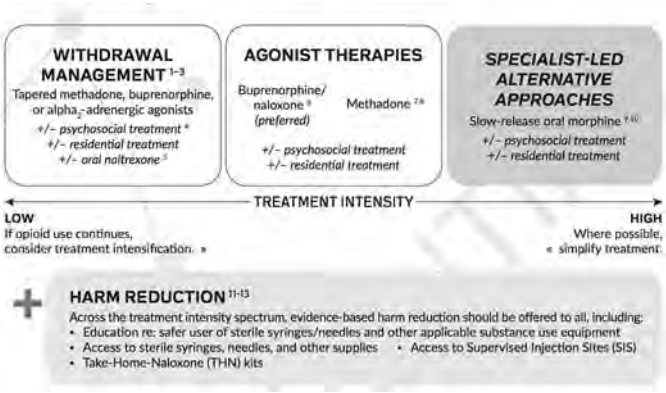
Christy Sutherland

- Total deaths for 2016 - 967
- Projected deaths for 2017 – over 1500

Addiction involves the Brain:

The Old Chart – we don't use this framework anymore

- Prevention
- Harm Reduction
- Withdrawal Management
- Outpatient Counseling
- 12 step and other group therapies
- Intensive Day Treatment
- Short-Term Residential Transitional Treatment
- Intensive Residential Treatment
- Long-Term Residential Treatment
- Supportive Housing
- Maintenance of abstinence



Principles of Harm Reduction

- Pragmatism
- Human Rights
- Focus on Harms
- Maximize Intervention Options
- Priority of immediate goals
- Drug user involvement

Harm Reduction: A British Columbia Community Guide. British Columbia Ministry of Health, 2005.

Christy Sutherland

PRAGMATISM

Harm reduction accepts that the non-medical use of psychoactive or mood altering substances is a near-universal human cultural phenomenon.

It acknowledges that, while carrying risks, drug use also provides the user and society with benefits that must be taken into account.

Harm reduction recognizes that drug use is a complex and multifaceted phenomenon that encompasses a continuum of behaviours from abstinence to chronic dependence, and produces varying degrees of personal and social harm.

HUMAN RIGHTS

- Harm reduction respects the basic human dignity and rights of people who use drugs. It accepts the drug user's decision to use drugs as fact and no judgment is made either to condemn or support the use of drugs.
- Harm reduction acknowledges the individual drug user's right to self determination and supports informed decision making in the context of active drug use.
- Emphasis is placed on personal choice, responsibility and self-management

FOCUS ON HARMS

- The priority is to decrease the negative consequences of drug use to the user and others, rather than decrease drug use itself.
- While harm reduction emphasizes a change to safer practices and patterns of drug use, it does not rule out the longerterm goal of abstinence.
- Harm reduction is complementary to the abstinence model of addiction treatment.

MAXIMIZE INTERVENTION OPTIONS

- Harm reduction recognizes that people with drug use problems benefit from a variety of different approaches.
- There is no one prevention or treatment approach that works reliably for everyone.
- It is choice and prompt access to a broad range of interventions that helps keep people alive and safe.

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PRIORITY OF IMMEDIATE GOALS

- Harm reduction establishes a hierarchy of achievable steps that taken one at a time can lead to a fuller, healthier life for drug users and a safer, healthier community.
- It starts with “where the person is” in their drug use, with the immediate focus on the most pressing needs.
- Harm reduction is based on the importance of incremental gains that can be built on over time

DRUG USER INVOLVEMENT

- The active participation of drug users is at the heart of harm reduction.
- Drug users are seen as the best source of information about their own drug use, and are empowered to join with service providers to determine the best interventions to reduce harm from drug use.
- Harm reduction recognizes the competency of drug users to make choices and change their lives.

Harm Reduction & Engagement

- Creating opportunities for engagement are critical
- Target marginalized populations who are not engaged with the health care system and for whom treatment is not an immediate realistic option
- Engage → link to health services → foster the trust and potential for accessing treatment

Common Myths about Harm Reduction

- Harm reduction enables drug use and entrenches addictive behaviour
- Harm reduction encourages drug use among non-drug users.
- Harm reduction drains resources from treatment services.
- Harm reduction is a Trojan Horse for decriminalization & legalization
- Harm reduction increases disorder & threatens public safety & health.

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Drug policies must be pragmatic. They must be assessed on their actual consequences, not on whether they send the right, the wrong or mixed messages.

Public Health Perspectives for Regulating Psychoactive Substances
The Health Officers Council of British Columbia

Harm Reduction

- Needle exchange
- Supervised Injection
- Condoms
- Seat belts
- Managed Alcohol
- Crack pipe distribution
- Injection supplies
- Low Barrier Housing
- Safe indoor space
- Take Home Naloxone

Harm Reduction

Making people uncomfortable does not decrease drug use

Non toxic drug consumption in a safe space

Known substance, known dose, clean supplies

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Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.sciencedirect.com/journal/drug-and-alcohol-dependence

Review

Supervised injection services: What has been demonstrated? A systematic literature review

Chloé Potier, Vincent Laprévote, Françoise Dubois-Arber, Olivier Cottencin, Benjamin Rolland

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Supervised injecting centres
Drug consumption room
Drug consumption facility
Injection drug user

ABSTRACT

Background: Supervised injection services (SISs) have been developed to promote safer drug injection practices, enhance health-related behaviors among people who inject drugs (PWID), and connect PWID with external health and social services. Nevertheless, SISs have also been accused of fostering drug use and drug trafficking.

Aims: To systematically collect and synthesize the currently available evidence regarding SIS-induced benefits and harm.

Methods: A systematic review was performed via the PubMed, Web of Science, and ScienceDirect databases using the keyword algorithm [("SUPERVISED" OR "SAFE(R)") AND ("INJECTION" OR "INJECTING" OR "SHOOTING" OR "CONSUMPTION") AND ("FACILITY" OR "FACILITIES" OR "ROOM" OR "GALLERY" OR "CENTRE" OR "SITE")].

Results: Seventy five relevant articles were found. All studies converged to find that SISs were efficacious in attracting the most marginalized PWID, promoting safer injection conditions, enhancing access to primary health care, and reducing the overdose frequency. SISs were not found to increase drug injecting, drug trafficking or crime in the surrounding environments. SISs were found to be associated with reduced levels of public drug injections and dropped syringes. Of the articles, 85% originated from Vancouver in Sydney.

Conclusion: SISs have largely fulfilled their initial objectives without enhancing drug use or drug trafficking. Almost all of the studies found in this review were performed in Canada or Australia, whereas the majority of SISs are located in Europe. The implementation of new SISs in places with high rates of injection drug use and associated harm appears to be supported by evidence.

Supervised Injection

- Well studied – 75 articles in this meta-analysis (85% are from Vancouver)
- Demonstrated to
  - Promote safer injection conditions
  - Enhance access to primary care
  - Reduce overdose frequency
  - Do not increase injection
  - Do not increase drug trafficking
  - Do not increase crime
  - Reduce levels of public drug injections
  - Reduce dropped syringes

Services at a Supervised Injection Site

- Wound care
- Condoms
- Referrals to detox – Onsite
- Referrals for housing
- Methadone and buprenorphine/naloxone starts

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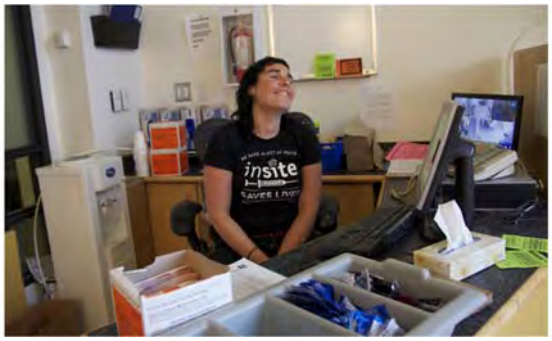
Injection Supplies

Welcoming and Safe



Worldwide, there has never been an overdose death in a supervised injection site since they have start started being studied

"For every complex problem there is an answer that is clear, simple, and wrong."

H. L. Mencken

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a 'risk environment' framework envisages drug harms as a product of the social situations and environments in which individuals participate. It shifts the responsibility for drug harm, and the focus of harm reducing actions, from individuals alone to include the social and political institutions, which have a role in harm production.

T. Rhodes
Risk environments and drug harms: A social science for harm reduction approach
International Journal of Drug Policy, 20 (2009), pp. 193–201

The creation of safer environments goes beyond safer use by individuals to a focus on determinants of the harms of drug use including drug policy, policing, income and housing policies.

Housing and harm reduction: What is the role of harm reduction in addressing homelessness?
Bernadette (Bernie) Pauly

History of Naloxone Distribution

- First programs:
  - Jersey 1998
  - Berlin 1999
- Now >180 programs in 17 US states
- Between 1996-2010:
  - 53,032 kits distributed
  - 10, 171 kits used

BMJ 2001;322:895
Centre for Disease Control and Prevention, 2010

A Systematic Review of Community Opioid Overdose Prevention and Naloxone Distribution Programs

Angela K. Clark, MSN, RN, Christine M. Wilder, MD, and Erin L. Winstanley, PhD

- **19 studies**
- **Outcomes:**
  - ↓ in fatal & non-fatal overdoses
  - ↑ in knowledge
  - Appropriate response to opioid overdose

Community-based opioid overdose prevention programs (OOPPs) that includ... to alarming... view descri... ticular focu... atic search... and assigne... OOPPs me... findings in... one admini... ceiving nal... OOPP char... responses,... responses.... gests that b... to reverse o... ing can be done successfully through OOPPs.

Key Words: naloxone, opioid overdose, overdose prevention, substance abuse services

(*J Addict Med* 2014;8: 153–163)

and prevents fatalities (Buajordet et al., 2004; Clarke et al., 2005; Dahan et al., 2010; Boyer, 2012). In 1996, community-... e preven... n directly ...al, 2007; ...tration of ... off-label ...tion pro... ...nistrators ...al, 2007; ...mmunity... ...n various ...s, deten... ... facilities ...programs ...o identify ... respond, including administration of naloxone (Enteen et al., 2010).

Because of the novelty of OOPPs, published information on them is limited. There are no published systematic literature reviews describing OOPPs or assessing their outcomes. This article reviews characteristics and outcomes of OOPPs as described in the current peer-reviewed literature. The review ...

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Conclusions

- Harm reduction is part of the continuum of care for people who use drugs
- It is a human rights approach that incorporates drug users into planning and delivery
- It decreases morbidity and mortality, and decreases costs
- People who use drugs are a key component to innovating and practicing harm reduction

BC Center on Substance Use OAT Course

http://www.bccsu.ca/provincial-opioid-addiction-treatment-support-program/

dr.christy.sutherland@gmail.com
www.phs.ca
@PHS_PrimaryCare

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1) Disclosure of Commercial Support

Neither this program nor the presenter has received financial support from any organization or company.

2) Mitigating Potential Bias

All recommendations and information presented are based on the best-available evidence we could find. Typically this includes meta-analyses, systematic reviews and RCTs. In addition, we don't care what the results are, but rather we care that people know about the results.

3) Objectives

To be able to take the best available evidence for common conditions in primary care and incorporate this information into shared-decision making with patients.

Just a few of the diagnoses that are solely or partially lab-based dependent

Acid-Base Disorders
Acidosis and Alkalosis
Acidosis/Alkalosis
aCL Syndrome
ACS
Acute DIC
Acute Idiopathic Polyneuritis
Acute Inflammatory Demyelinating Polyneuropathy
Acute Kidney Injury
Acute Myocardial Infarct
Acute Renal Failure
AD
Addison Disease
Adrenal Insufficiency
Adrenal Insufficiency and Addison Disease
AKI
Albuminuria
Alcohol dependence
Alcoholism
Allergies
Alzheimer Dementia
Alzheimer Disease
AMI
Anemia
Anemopathy
Angiitis
Angina
Angina pectoris
Ankylosing Spondylitis
Anthrax
Anticardiolipin Antibody Syndrome
Antiphospholipid Antibody Syndrome
Antiphospholipid Syndrome
aPL Syndrome
APLS
APS
ARF
Arteritis
Arthritis
AS
Asthma
Atypical Mycobacteria
Atypical Pneumonia
Autoimmune Diseases
Autoimmune Thyroiditis
Avian Flu
Bacillus anthracis infection
Bacterial Arthritis
Bacterial Vaginosis
Benign Prostatic Hyperplasia
Benign Prostatic Hypertrophy
Biological Warfare
Bioterrorism Agents
Bleeding Disorders
Blood in the urine
Bone Marrow Disorders
Borrelia burgdorferi Infection
Borrelia mayonii Infection
BPH
Breast Cancer
CAH
Cancer
Candidiasis
Carbohydrate Intolerance
Cardiovascular Disease
Celiac Disease
Celiac Sprue
Cervical Cancer
CF
CFIDS
CFS
CHF
Chlamydia
Chronic Fatigue and Immune Dysfunction Syndrome
Chronic Fatigue Syndrome
Chronic Kidney Disease
Chronic Thyroiditis
Circumscribed Scleroderma
Cirrhosis
CKD
Coagulopathy
Cobalamin Deficiency
Colon Cancer
Colorectal Cancer
Community-Acquired Pneumonia
Congenital Adrenal Hyperplasia
Congenital Alactasia
Congestive Heart Failure
Conn Syndrome
Consumption Coagulopathy
Copper Storage Disease
CREST
Crohn Disease
Crushing Syndrome
Cutaneous anthrax
CVD
Cystic Fibrosis
Degenerative Joint Disease
Dehydration
Dermatosclerosis
Diabetes
Diabetes mellitus
Diarrhea
DIC
Diffuse Cutaneous Scleroderma
Diffuse Thyrotoxic Goiter
Disaccharidase Deficiency
Discoid Lupus
Disseminated Intravascular Coagulation
Disseminated Intravascular Coagulopathy
Disseminated Lupus Erythematosus
DJD
Double Pneumonia
Down Syndrome
Drug-induced Lupus
DS
Dysmetabolic Syndrome
Ebola Hemorrhagic Fever
Ebola Virus Disease
Ebola Virus Infection
Encephalitis
End Stage Renal Disease
Endocrine Syndromes
Endocrine System and Syndromes
Epilepsy
ESRD
EVD
Excessive Clotting Disorders
Extraseasous Pleomacytoma
Fibromyalgia
Flu
Folate Deficiency
Folic Acid or B9 Deficiency
Food and Waterborne Illness
Food Poisoning
Fungal Infections
Gastroenteritis
Gluten-Sensitive Enteropathy
Gonorrhea
Gout
Gouty Arthritis
Graves Disease
GSE
Guillain-Barré Syndrome
H1N1
H3N2
HSN1
HTN9
Hashimoto Thyroiditis
HBP
HD
Healthcare-Associated Pneumonia
Heart Attack
Heart Attack and Acute Coronary Syndrome
Heart Disease
Heart Failure
Hematuria
Hemochromatosis
Hemoglobin Abnormalities
Hemoglobin Barts
Hemoglobin C Disease
Hemoglobin E Disease
Hemoglobin S
Hemoglobin Variants
Hemoglobinopathy
Hepatic Disease
Hepatitis
Hepatolenticular Degeneration
Hereditary Persistence of Fetal Hemoglobin
Herpes
Herpes Zoster
High Blood Pressure
HIV
HIV Infection and AIDS
HL
Hodgkin Disease
Hodgkin Lymphoma
Hospital-Acquired Pneumonia
HPTH
HPV
Hughes Syndrome
Huntington Disease
Huntington's Chorea Disease
Hypercoagulable Disorders or States
Hyperparathyroidism
Hypersensitivity
Hypertension
Hyperthyroidism
Hypoparathyroidism
Hypothyroidism
IBD
Icterus
Infectious Arthritis
Infectious Polyneuritis
Infertility
Inflammatory Bowel Disease
Influenza
Influenza A
Influenza B
Inhalation anthrax
Inherited Copper Toxicity
Insulin Resistance
Insulin Resistance Syndrome
Iron Overload Disease
Iron Storage Disease
Jaundice
JIA
JRA
Juvenile Idiopathic Arthritis
Juvenile Rheumatoid Arthritis
Keratoconjunctivitis Sicca
Kidney Disease
Lactase Deficiency
Lactose Intolerance
Landry's Ascending Paralysis
LE
Lead Poisoning
Leukemia
Limited Cutaneous Scleroderma
Linear Scleroderma
Liver Disease
Lobar Pneumonia
Localized Scleroderma
Lower Respiratory Tract Infection
Lung Cancer
Lung Diseases
Lupus
Lupus Anticoagulant Syndrome
Lupus Erythematosus
Lyme Disease
Lymphocytic Thyroiditis
Lymphoma
Malabsorption
Malaria
Malignancy
Malignant tumor
Malnutrition
MDS
ME
Melanoma
Meningitis and Encephalitis
Meningococcal Meningitis
Menopause
Metabolic Syndrome
MG
MI
Morphea
MCTT
MPDs
MPNs
MRSA
MS
Multiple Myeloma
Multiple Sclerosis
Myalgic Encephalomyelitis
Myasthenia Gravis
Mycobacteria other than tuberculosis
Mycoses
Myelocele
Myelodysplasia
Myelodysplastic Syndrome
Myelomeningocele
Myeloproliferative Disorders
Myeloproliferative Neoplasms
Myocardial Infarct
Neonatal Lupus
Nephrotic Syndrome
Neural Tube Defects
Neuropathy
NHL
Non-Hodgkin lymphoma
Non-Small Cell Lung Cancer
Nontuberculous Mycobacteria
Nontuberculous Mycobacteria Infections
NTD
NTM
OA
Obesity Syndrome
Osteoarthritis
Osteoarthrosis
Osteoporosis
Ovarian Cancer
PA
Pancreatic Cancer
Pancreatic Diseases
Pancreatic Insufficiency
Pancreatitis
Parathyroid Cancer
Parathyroid Diseases
PCOS
Pelvic Inflammatory Disease
Peptic Ulcer
PID
Pituitary Disorders
Plasma Cell Dyscrasia
Plasma Cell Myeloma
Plasma Cell Neoplasm
Plasmacytoma
Plasmacytoma of Bone
Pneumonia
Polycystic Ovary Syndrome
Porphyria
Post-infectious Arthritis
Pre-eclampsia
Pregnancy
Pregnancy-induced Hypertension
Presenile Dementia
Primary Aldosteronism
Primary Hyperaldosteronism
Prinzmetal's angina
Prostate Cancer
Protein in urine
Proteinuria
RA
Reactive Arthritis
Reaven Syndrome
Renal Disease, Kidney Failure
Rheumatoid Arthritis
Rheumatoid Spondylitis
Sarcoidosis
SCD
Scleroderma
SEID
Seizure Disorder
Sepsis
Septic Arthritis
Sexually Transmitted Diseases
Sexually Transmitted Infections
Shingles
Sicca Syndrome
Sickle Cell Anemia
Sickle Cell Disease
Sjögren Syndrome
SLE
Small Cell Lung Cancer
Spina bifida
Spinal dysraphism
Spinal Meningitis
SSc
Stable angina
Staph
Staph aureus
Staph Infections
Staph Infections and Methicillin-Resistant Staphylococcus aureus
Staphylococcus aureus
STDs
Stein-Leventhal Syndrome
Sticky Blood Syndrome
STIs
Stomach Flu
Stroke
Subacute Cutaneous Lupus
Swine Flu
Syndrome X
Syphilis
Systemic Exertion Intolerance Disease
Systemic Lupus Erythematosus
Systemic Scleroderma
Systemic Sclerosis
TB
Testicular Cancer
Thalassemia
Thrombophilia
Thyroid Cancer
Thyroid Diseases
Toxemia
Toxic Diffuse Goiter
Travelers' Diseases
Trich
Trichomonas
Trichomoniasis
Trisomy 21
Tuberculosis
Types of Liver Disease
Ulcerative Colitis
Unstable angina
Urinary Tract Infection
UTI
Vaginal Infection
Vaginitis and Vaginosis
Vaginitis/Vaginosis
Variant angina
Vasculitis
VD
Venereal Diseases
Vitamin B12 and Folate Deficiencies
Vitamin B12 Deficiency
Vitamin K Deficiency
Vulvovaginitis
Walking Pneumonia
West Nile Virus
Wilson Disease
WNV
Wound and Skin Infections

"It is commonly thought that laboratory tests provide two-thirds to three-fourths of the information used for making medical decisions. If so, test results had better tell the truth about what is happening with our patients."

Clinica Chimica Acta 2004;346:3-11

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MY THESIS

"For much in medicine, we knowingly sell preeminent precision even though we all know in our heart of hearts we can only deliver educated estimates.
I believe most patients would be very understanding about this imprecision if we were just more open about it."
-James McCormack, Pharm D (1959 - hopefully not soon)

"We also CAN'T be precise about the imprecision"

I am speaking in general, and do realise there are always some exceptions

I am presenting concepts

I will be providing ball-park estimates

Two Problems with Faking Precision

FALSE BELIEFS

BELIEF #1 - the good/bad thresholds are relatively black and white

BELIEF #2 -when the numbers change these changes are real

These beliefs can potentially lead to inappropriate feelings of fear, happiness, frustration, confusion…

Both in patients AND clinicians

Sources of Imprecision

Lab Error

Analytic variation

Biologic variation

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Actual LAB errors

Lab Error

0.3%

~60% pre-analytical
~15% analytical
~ 25% post analytical

Table 1. Laboratory errors in stat testing.

Defects: detection steps	Defects found No.	Frequency, %
Preanalytical		
Specimen collected from infusion route	3	1.9
Sample contaminated	1	0.6
Tube filling error	21	13.1
Empty tube	11	6.9
Inappropriate container	13	8.1
Nonrefrigerated sample	3	1.9
Missing tube	5	3.1
Digoxin test timing error	1	0.6
Patient identification error	14	8.8
Request procedure error	12	7.5
Data communication conflict	6	3.8
Physician's request order missed	3	1.9
Order misinterpreted	2	1.3
Check-in not performed (in the Laboratory Information System)	4	2.5
Subtotal	99	61.9
Analytical		
Instrument-caused random error	3	1.9
Analytical inaccuracy not recognized	21	13.1
Subtotal	24	15
Postanalytical		
Results communication breakdown	32	20
Lack of communication within laboratory	3	1.9
TAT excessive	2	1.3
Subtotal	37	23.1

Clinical Chemistry 2007;53:1338-42

Dispensing errors ~1-2%

Measurement Landscape

Assuming no pre-analytic issues - timing/labelling etc

Population-based reference intervals

Analytic variation

Analytical Variation
CVA - analytical variation

Biologic variation

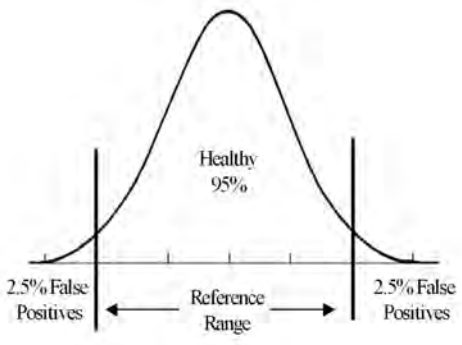
Biological Variation
CVI - within subject
CVG - between subject

Reference change values (RCV)

Population-based reference intervals

Population-based reference intervals

The interval/range where 95% of healthy people fall



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Number of Tests Ordered	Probability of at Least One Abnormal Test
1	5%
2	10%
5	23%
10	40%
15	54%
20	64%

Lab results report
exact numbers
BUT
Every test result is
really only a range
that hopefully includes
the true result
+/- 1-2% up to
+/-20-30% or more

YOU CANNOT BE SERIOUS!!
That ball was on the line

When we do tests, typically we are wondering

what are the results NOW, and/or

have they changed from PREVIOUS measurements

Analytic variation

Biologic variation

Every “measurement” will be “different”

Analytic variability
Biologic variability

Reference Change Values (RCV)

a tool for assessment of the significance of differences in serial results from an individual

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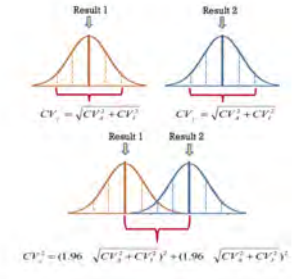
Reference Change Values

Used with SERIAL results to help deal with the analytic imprecision and biologic variation

Coefficients of Variation (total) = analytic PLUS biologic variation



MINIMUM DIFFERENCE between two consecutive results which needs to be EXCEEDED in order for one to state a STATISTICALLY SIGNIFICANT change has taken place

$$RCV = \sqrt{2} * 1.96 * \sqrt{(CV^2_{Analytical} + CV^2_{Intraindividual})}$$

How good, analytically speaking, does a “test” need to be

“The analytical CV (CVA) should be less than one-half the average within-subject biological variation (CVI)”

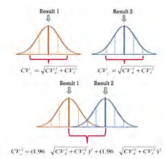
When it is, the CVA has almost no impact on the RCV - the RCV is pretty much determined by the CVI

Reference Change Values

findings of a “significant difference" JUST means we are ruling out that the difference seen is due to chance

NOT

THAT THE MAGNITUDE OF THE DIFFERENCE SEEN IS THE ACTUAL MAGNITUDE OF THE DIFFERENCE



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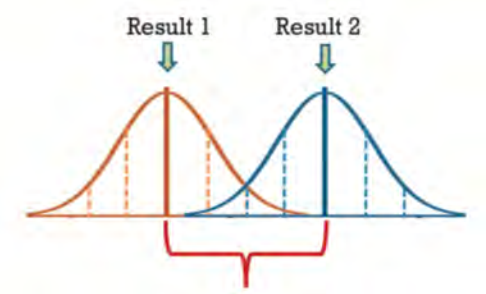
We believe these two results are different



can't necessarily quantify this difference with any precision

What about multiple measurements?

Table 1. RCV using multiple estimates of the initial and new set points, expressed as a fraction of traditional RCV from two singleton measurements.

		Number of results estimating initial set point				
		1	2	3	4	5
Number of results estimating new set point	1	1.00	0.87	0.82	0.79	0.77
	2	0.87	0.71	0.65	0.61	0.59
	3	0.82	0.65	0.58	0.54	0.52
	4	0.79	0.61	0.54	0.50	0.47
	5	0.77	0.59	0.52	0.47	0.45

with 4 measurements before and 4 afterwards
(vs 1 before and 1 after)
you can lower the RCV by 50%

Annals of Clinical Biochemistry 2016;53:413-4

Lab Error

Analytic variation

Biologic variation

This is the problem and it is NOT fixable, it is only KNOWABLE

Cholesterol
Glucose

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Cholesterol

2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult

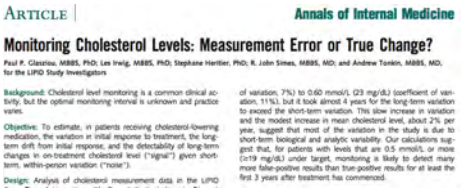
"In individuals with a modified FRS of 5%-9%, yearly monitoring could be used to evaluate change in risk"

AACE 2017 Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE

"Lipid status should be re-assessed 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved."

"While on stable lipid therapy, individuals should be tested at 6-to 12-month intervals"



ARTICLE | Annals of Internal Medicine

Monitoring Cholesterol Levels: Measurement Error or True Change?

Paul P. Glasziou, MBBS, PhD; Les Irwig, MBBS, PhD; Stephane Heritier, PhD; R. John Simes, MBBS, MD; and Andrew Tonkin, MBBS, MD, for the LIPID Study Investigators

Background: Cholesterol level monitoring is a common clinical activity, but the optimal monitoring interval is unknown and practice varies.

Objective: To estimate, in patients receiving cholesterol-lowering medication, the variation in initial response to treatment, the long-term drift from initial response, and the detectability of long-term changes in on-treatment cholesterol level ("signal") given short-term, within-person variation ("noise").

Design: Analysis of cholesterol measurement data in the LIPID

of variation, 7%) to 0.60 mmol/L (23 mg/dL) (coefficient of variation, 11%), but it took almost 4 years for the long-term variation to exceed the short-term variation. This slow increase in variation and the modest increase in mean cholesterol level, about 2% per year, suggest that most of the variation in the study is due to short-term biological and analytic variability. Our calculations suggest that, for patients with levels that are 0.5 mmol/L or more (>19 mg/dL) under target, monitoring is likely to detect many more false-positive results than true-positive results for at least the first 3 years after treatment has commenced.

Ann Intern Med 2008;148:656-61

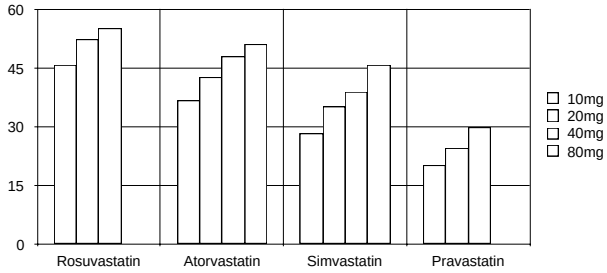
VARIATION
Total chol ~ - 0.80 to 0.80 mmol/L (~30 mg/dL)
LDL chol ~ - 0.5 to 0.5 mmol/L (~20 mg/dL)

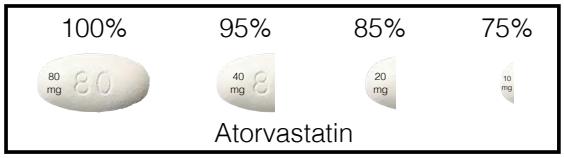
Average increase in cholesterol is 0.5-1%/year

"After initial change only measure every 3-5 years"

DOSE increases do not lead to proportional EFFECT increases

% reduction in LDL cholesterol





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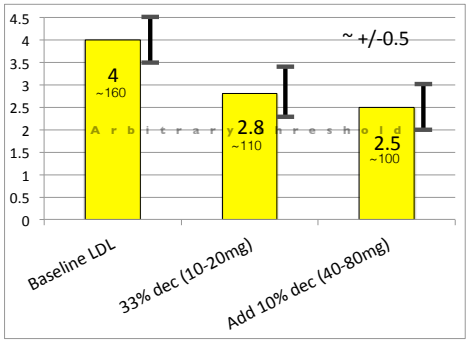
LDL cholesterol - 2 mmol/L ~80mg/dL



RESEARCH

When to remeasure cardiovascular risk in untreated people at low and intermediate risk: observational study

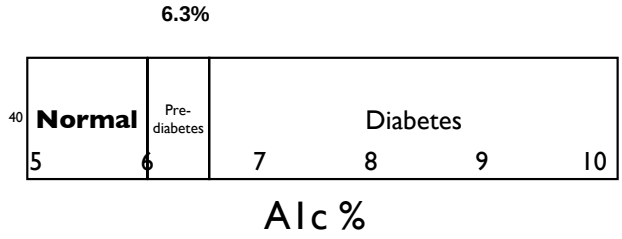
BMJ 2013; 346 doi: http://dx.doi.org/10.1136/bmj.f1895 (Published 3 April 2013)
Cite this as: *BMJ* 2013;346:f1895

"Repeat risk estimation before 8-10 years is not warranted for most people initially not requiring treatment"

Glucose

Precisely Imprecise

What an A1c result really means



Typical A1c change seen with a medication = 0.7%⬇

Seasonal variation 0.2-0.5%
Higher in the winter
Am J Epi 2004;161:565-74

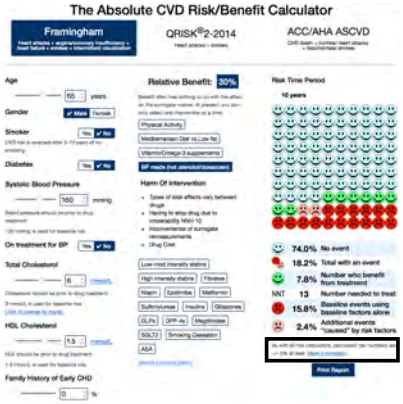
James McCormack

Yet another IMPORTANT issue for measurements pf glucose, cholesterol, blood pressure and bone density

These are RARELY measures of any disease

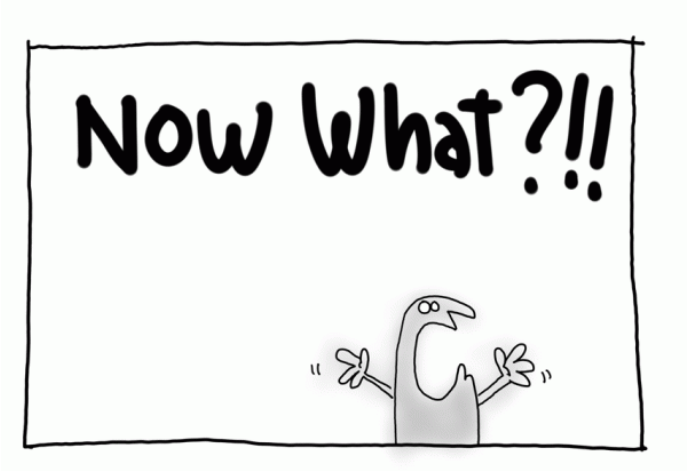
They are simply RISK FACTORS

They should be presented in the context of the risk of developing important clinical outcomes - heart attacks, strokes, ESRD etc



cvdcalculator.com

Calculate ballpark 10-yr risk of CVD - BP, chol, diabetes
Make estimate of benefit based on the best available evidence
Gives a list of adverse effects to discuss



The Problem
is
NOT Fixable,
it is
Only
KNOWABLE

James McCormack

Just the facts, Ma'am

Should we…

Openly explain and present lab variability - YES

Openly discuss the potentially black and white things about lab variability - ABSOLUTELY

Continue to use words like low, medium, high, significant - NO, NO, NO, NO

Use a 95% or a 90% or an 85% significance threshold - UNKNOWABLE

Get hung-up on the fact the evidence-base isn't perfect - NO - USE THE BEST AVAILABLE EVIDENCE

Care who is the driver of change - WHOEVER CAN DO IT RIGHT

Report SDs, levels of significance, error bars - IN GENERAL, NO

Discuss the variability or the exceptions to the rule - OF COURSE

Be OK with "ball parking" - WELCOME TO HEALTH CARE

Care if improved lab reporting improves patient outcomes - IT'S REALLY ABOUT DECISIONS AND THE "TRUTH"

Believe it is just the "other" lab's problem not ours - THAT'S ADORABLE

If I was the boss of "LAB" result reporting

All of this could be done today

Shift from a laboratory perspective to a patient-centered viewpoint

Using BALLPARK estimates

ALWAYS provide the imprecision

Provide MUCH more definitive guidance

Stop using terms like low, medium, high or significant

If they are "risk factor" measurements then they should only be provided with "risk" estimates

Do not do a test without discussion of a pre-test probability and then provide a post-test probability

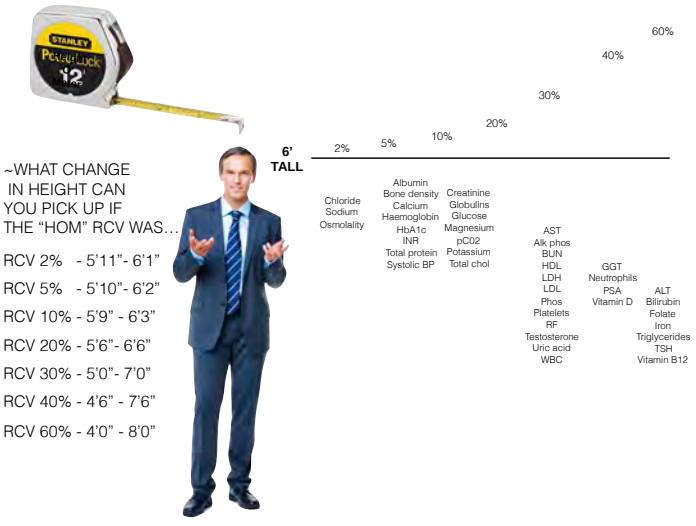
Make many tests more "inconvenient"?

The magnitude of the imprecision around routinely ordered medical measurements*

MEASUREMENT						
	Chloride Sodium Osmolality	Albumin Bone density Calcium Hematocrit Hemoglobin HbA1c INR MCH MCV Total protein Systolic BP	Creatinine Globulins Glucose Magnesium pC02 Potassium PTT Total cholesterol T4	AST Alkaline phosphatase BUN HDL LDH LDL Phosphorous Platelets Rheumatoid factor Testosterone Uric acid WBC	GGT Neutrophils PSA Vitamin D	Aldosterone ALT Bilirubin Folate Iron Lactate Triglycerides TSH Vitamin B12
Approximate +/- range for a single measurement	~1-3%	~3-7%	~7-15%	~15-30%	~30-50%	~>50%
The magnitude of the change required between two serial measurements so one can be reasonably confident there has been a change**	~2-5%	~5-10%	~10-20%	~20-40%	~40-60%	~>60%

* based on the analytic and biologic variation
** also known as the reference change value

Data collated primarily from here - https://www.westgard.com/biodatabase1.htm
but some also taken and confirmed from a few other sources - numbers rounded off for ease of use
James McCormack BSc (Pharm), Pharm D - therapeuticseducation.org



Kam Shojania

Thermal detonator vs light sabre. How to order rheumatology tests without hurting civilians.

Kam Shojania, MD, FRCPC
Clinical Professor and Head, UBC
Division of Rheumatology

a place of mind

Faculty/Presenter Disclosure

- **Faculty:** Kam Shojania
- **Relationships with commercial interests:**
  - **I have stock options in Augurex where I have been a consultant since 2008 – a Vancouver biotech company that has made a new test for Rheumatoid Arthritis – Called 14-3-3 eta (Jointstat).**
  - **I am the local PI of a vasculitis study funded by BMS.**
  - **I work with the Provincial Blood Coordinating Office to manage IVIG use in rheumatology.**

Mitigating Potential Bias

- I am probably biased regarding 14-3-3-eta because I have been working with it for 10 years.
- But I don't recommend that you order this test as a screening test for RA at this time (not covered by MSP anyway).
- I limit my interaction with industry – no talks, no honoraria, no consulting, no office access.

29th Annual Best Science Medicine Course:

Learning Outcome Objective Slide

Participants will understand the use and limitation of commonly ordered rheumatologic lab tests in their patients with inflammatory arthritis.

Kam Shojania

My workup – for REAL inflammatory arthritis documented on physical exam

- CBC, U/A
- CK, Creat
- ANA (ENA, antiDNA, C3,C4 only if ANA is pos)
- Anti CCP, CRP, RF (14-3-3 eta if CCP and RF negative)
- SPEP, Hep B, C, HIV
- AST, ALT, Albumin, ASMA (for AI hepatitis)
- Uric Acid, Ca, P04
- Ferritin (TIBC)

Warning

- If I catch you do this workup for osteoarthritis or generalized soft tissue pain….
- You will have to:
- 1. Pay for the tests yourself
- 2. If it is for one of those executive physical screenings, you will have to endure a 10min lecture from me while you buy me lunch.

Goals

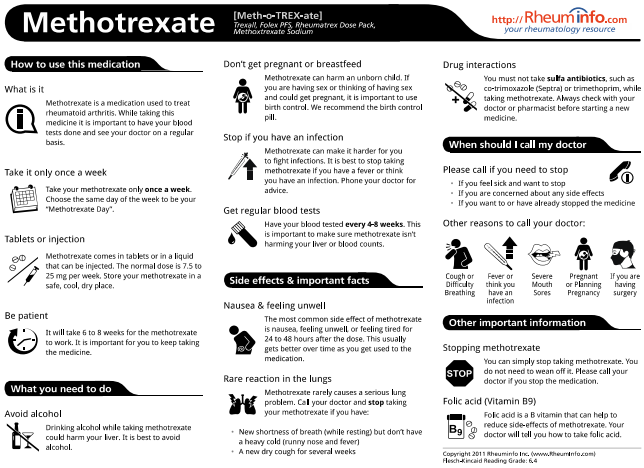
- ANA, ENA, CCP
- RF
- CH50, C3, C4
- ESR, CRP
- ANCA
- HLA-B27

- Which tests ?
- when to order them?
- What are the test limitations ?

RESOURCES

- www.rheuminfo.com
- Great site for medication and disease information for patients
- RACE line (new email service Dr2Dr)

Kam Shojania



Methotrexate [Meth-o-TREX-ate]
Trexall, Folex PFS, Rheumatrex Dose Pack, Methotrexate Sodium

http://RheumInfo.com your rheumatology resource

How to use this medication

What is it
Methotrexate is a medication used to treat rheumatoid arthritis. While taking this medicine it is important to have your blood tests done and see your doctor on a regular basis.

Take it only once a week
Take your methotrexate only **once a week**. Choose the same day of the week to be your "Methotrexate Day".

Tablets or injection
Methotrexate comes in tablets or in a liquid that can be injected. The normal dose is 7.5 to 25 mg per week. Store your methotrexate in a safe, cool, dry place.

Be patient
It will take 6 to 8 weeks for the methotrexate to work. It is important for you to keep taking the medicine.

What you need to do

Avoid alcohol
Drinking alcohol while taking methotrexate could harm your liver. It is best to avoid alcohol.

Don't get pregnant or breastfeed
Methotrexate can harm an unborn child. If you are having sex or thinking of having sex and could get pregnant, it is important to use birth control. We recommend the birth control pill.

Stop if you have an infection
Methotrexate can make it harder for you to fight infections. It is best to stop taking methotrexate if you have a fever or think you have an infection. Phone your doctor for advice.

Get regular blood tests
Have your blood tested **every 4-8 weeks**. This is important to make sure methotrexate isn't harming your liver or blood counts.

Side effects & important facts

Nausea & feeling unwell
The most common side effect of methotrexate is nausea, feeling unwell, or feeling tired for 24 to 48 hours after the dose. This usually gets better over time as you get used to the medication.

Rare reaction in the lungs
Methotrexate rarely causes a serious lung problem. Call your doctor and **stop** taking your methotrexate if you have:
- New shortness of breath (while resting) but don't have a heavy cold (runny nose and fever)
- A new dry cough for several weeks

Drug interactions
You must not take **sulfa antibiotics**, such as co-trimoxazole (Septra) or trimethoprim, while taking methotrexate. Always check with your doctor or pharmacist before starting a new medicine.

When should I call my doctor

Please call if you need to stop
- If you feel sick and want to stop
- If you are concerned about any side effects
- If you want to or have already stopped the medicine

Other reasons to call your doctor:
Cough or Difficulty Breathing; Fever or think you have an infection; Severe Mouth Sores; Pregnant or Planning Pregnancy; If you are having surgery

Other important information

Stopping methotrexate
STOP
You can simply stop taking methotrexate. You do not need to wean off it. Please call your doctor if you stop the medication.

Folic acid (Vitamin B9)
Folic acid is a B vitamin that can help to reduce side-effects of methotrexate. Your doctor will tell you how to take folic acid.

Flesch-Kincaid Reading Grade: 6.4

General approach to inflammatory arthritis

- Inflammatory pain is
  - Worse in the morning
  - Associated with prolonged stiffness, followed by period of loosening with activity
  - Worse at night
  - Associated with swelling and sometimes warmth of the joints involved
  - A red joint however, is septic or crystal arthritis

Inflammatory arthritis – joint distribution

- The distribution of pain helps differentiate Rheumatoid Arthritis and Ankylosing Spondylitis
- RA classically involves
  - The small joints of hands and feet
  - Symmetrical pattern
  - Can have skin nodules, lung involvement.
- AS classically involves
  - The spine: sacroiliac and up to cervical spine
  - The large joints: knees, hips
  - Asymmetrical pattern
  - Don't forget uveitis, inflammatory bowel disease

Remember Psoriatic Arthritis

- PsA is an hybrid
  - can look like RA:
    - Peripheral joints involvement and erosions
  - can look like AS:
    - Sacroiilitis
    - Enthesitis
  - History of psoriasis: personal or familial
  - Dactylitis is quite specific
  - Enthesitis (heel pain, typically)
  - And, by the way, there are no diagnostic lab tests!

Kam Shojania

Best approach to acute mono-arthritis

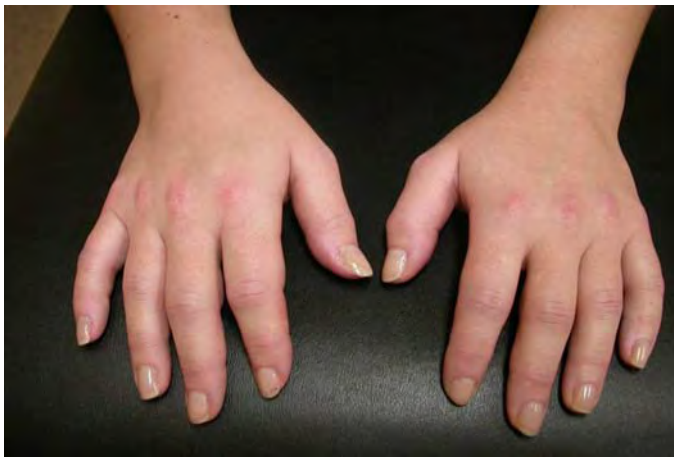
- CBC, Creat, Uric Acid, CRP
- Joint aspiration for 3 'c's culture, crystal, cell count:
  - Rule out infection and crystal arthropathy mainly
  - However monoarthritis could be:
    - Trauma
    - Psoriatic Arthritis
    - Ank Spond or early RA

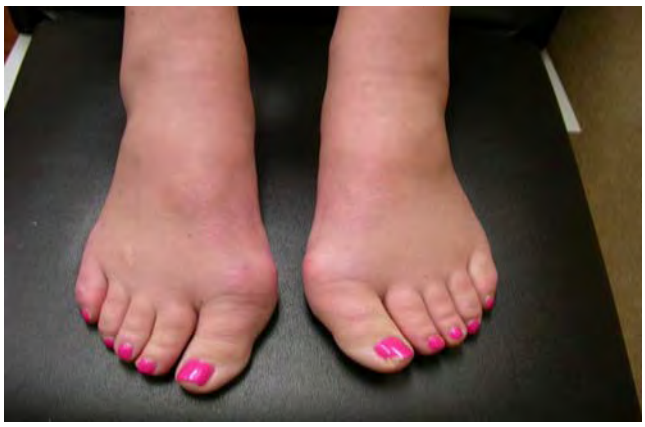
I forgot to mention

- Is it lupus?

Very unlikely. 1/1000 (compared to 1/100 RA, PsA)

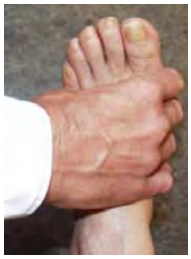
Screening for ANA will usually just bring you grief

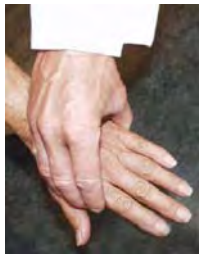




Physical Examination – MCP/MTP Squeeze Test

- Compress a group of small adjacent MCP or MTP joints between your thumb and forefinger
- Pain elicited by mild compression of the MCP or MTP joints as a group may be diagnostic of early RA





General approach to inflammatory arthritis

- Match the test to the disease

	Rheumatoid Arthritis	Ankylosing Spondylitis	Psoriatic Arthritis
Rheumatoid factor	+	-	-
Cyclic Citrullinated Peptide (CCP)	+	-	-
HLAB27	-	+	+
Antinuclear Antibody (ANA)	-	-	-

General approach to inflammatory arthritis

- Match the test to the disease

	Rheumatoid Arthritis	Ankylosing Spondylitis	Psoriatic Arthritis
Rheumatoid factor	70-80 %	-	-
Cyclic Citrulinated Protein (CCP)	50-70%	-	-
HLAB27	-	90 %	30 %
Antinuclear Antibody (ANA)	30%	-	-

Physical signs suggestive of psoriatic arthritis

Kam Shojania

My workup for acute monoarthritis

- CBC, Creatinine, Uric acid, CRP
- Possibly blood cultures, urinalysis
- Aspirate the joint
- Send for 3 'c's – Culture, Crystals, Gram stain

My workup for inflammatory back pain

- CBC, Creat, CRP
- SI joint x-rays
- Consider low radiation CT SI joints if radiologist have expertise in this area (cheaper and faster than MRI)
- HLA B27 only in selected cases where the pretest probability is around 50%.
- (downside of genetic testing includes disruption of patients ability to obtain life/disability insurance

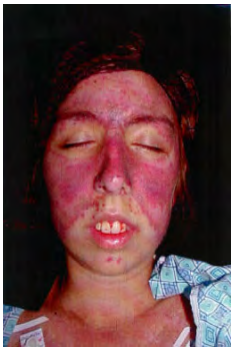
There are no good tests for OA

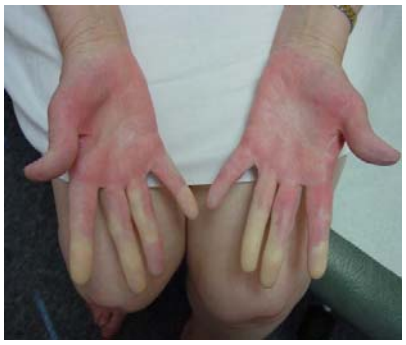
- History
- Physical exam
- X-rays may be deceiving

Case #1

- A 46 year old woman is referred to you with a symmetrical polyarthritis, pleuritic chest pain, alopecia and malar rash.
- What serological tests would you order?

Kam Shojania





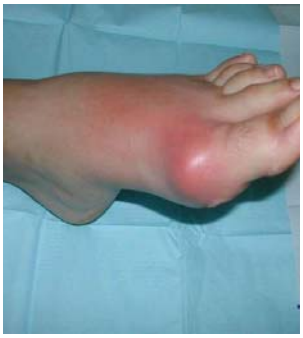
Testing

- ANA
- ENA – automatic if ANA elevated
- Anti-DNA
- Complement C3, C4

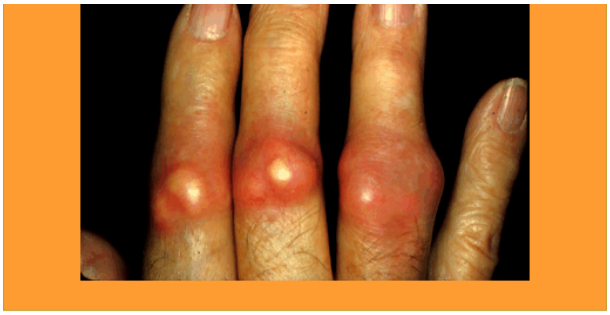
- Don’t forget CBC, U/A, Creat, LFTs

Case #2

- A 48 year old man with acute monoarthritis of the left 1st toe comes into the ER. CBC was normal. No fevers or chills. This has happened once before.
- On exam, Red shiny swollen warm 1st MTP.
- Uric acid level is normal. What do you do?



A red joint is septic or crystal arthritis (or both)



Inflamed tophaceous gout Three inflamed tophi over the proximal

UpToDate 2004

Case #3

- A 45 year old woman has a 3 month history of inflammatory polyarthritis (MCPs, wrists, knees, MTPs). She has 2 hours of morning stiffness.
- Her RF is negative. She has a mild anemia.
- The CRP is 41. Hepatic and renal function are normal.

- What other tests would you do?

Case #3

- The anti-CCP is highly positive.
- Does that change your diagnosis?
- Does that change the prognosis?

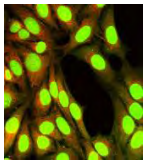
Case #4

- A 27 year old man has been involved in a MVA 4 months prior. He has had diffuse back pain since then with activity and cannot work. He has no morning stiffness. He has full back ROM but complaints of pain and there is tenderness over the muscles. All tests are normal. Someone ordered an HLA-B27 and it is positive.
- Does he have ankylosing spondylitis?

Review of tests

Antinuclear Antibodies

- Diverse collection of antibodies directed against macromolecules which are normal components of the cell nucleus.
- Associated with CTD, neoplasms, drug reactions, endocrine diseases
- Extractable nuclear antibodies (ENA) may be helpful if ANA is positive



Prevalence of ANA

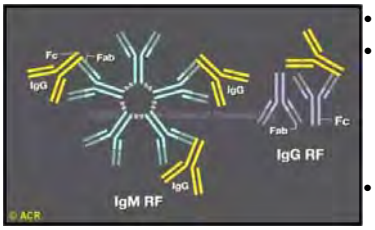
- The ANA is positive in 98% of SLE patients.
- It is positive in 40 - 70% of other CTD's.
- It is also positive in 5% of healthy adults with a titre less than 1/160. It is likely higher in the geriatric population.

Extractable nuclear antigens (ENA)

- anti Sm
- anti Ro
- anti La
- anti RNP
- anti Jo
- anti dsDNA
- anti histone
- anticentromere Ab

- Can be ordered if ANA positive
- May help in diagnosis of CTD
- Do not order with negative ANA
- Best to just leave this one for rheumatology

Rheumatoid Factor



- Anti-IgM and/or IgG
- Non-specific as it is elevated in other diseases like SLE, Infections and Malignancy
- Increases with normal aging
- 15% have a positive RF
- Most common cause of high RF is chronic infection (hepatitis, Tb)

Kam Shojania

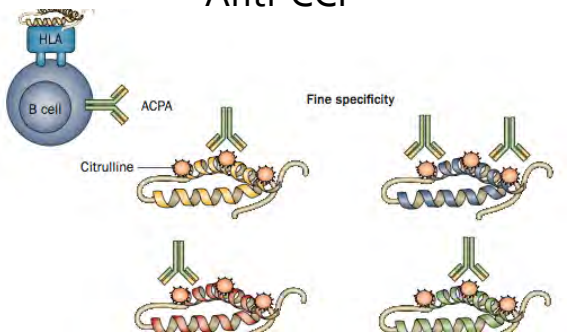
Rheumatoid factor

Utility of Rheumatoid Factor

- Rheumatoid factor (RF)
  - Antibody against Fc portion of IgG
  - May by IgG, IgA, or IgM isotype

Disease	Frequency
Rheumatoid arthritis	70% to 90%
Mixed CTD	50% to 60%
SLE	15% to 35%
Systemic sclerosis	20% to 30%
Healthy individuals < 50 yo	5% to 10%
Healthy individuals > 70 yo	10% to 25%

Anti-CCP



- Highly specific for RA
- Can be present for years before the first clinical sign of disease
- Associated with greater radiological joint damage

ESR

- Non-specific
- Upper limit of normal is age/2 for men and (age+10)/2 for women.
- Helpful for PMR or GCA but up to 10% may have normal ESR
- Can be useful in following the course of disease in RA, GCA, PMR
- Mostly supplanted by the CRP now.

C-Reactive Protein (CRP)

- Better than ESR because it is not affected by age or anemia.
- Also useful in following GCA, PMR, Ra
- Now cheaper than ESR in most locations

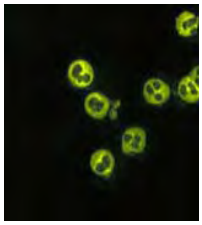
- Do the CRP instead of the ESR.
- In ER, if you are considering Giant Cell Arteritis, best do both.

Guidelines: ANA, CCP and RF

- You should order an ANA or a RF only for suspected connective tissue disease.
- They should not be ordered to:
  - 'screen' a patient with no symptoms.
  - 'follow' someone with a known CTD to assess disease activity.
- Once a patient is diagnosed with a CTD, you need not order these tests again unless the clinical situation in the future does not fit with the Dx.

Antineutrophil cytoplasmic antibodies (ANCA)

- Antibodies to the cytoplasmic constituents of granulocytes.
- Originally detected by indirect immunofluorescence on ethanol-fixed neutrophils.
- c-ANCA - cytoplasmic fluorescence
- p-ANCA - perinuclear fluorescence



- Now you simply order ANCA
  - You get ant-PR3 or antiMPO
  - Useful for vasculitis (1/10,000)

Final word on ANCA

- I suggest you do not order ANCA in primary care.
- If you suspect vasculitis, refer urgently. ANCA may be negative in vasculitis so don't wait for this test.

Complement

- High in infection - not useful
- Low complement triggered by immune complex formation and consumption of complement
- SLE, MPGN, vasculitis, serum sickness, cryoglobulinemias
  - Serum Complements. Inappropriate use in patients with suspected rheumatic disease. Archives of Internal Medicine 153(20):2363-6, 1993, Oct 25.
- I suggest that complement should not be ordered in the primary care setting.

HLA-B27 is common, AS is not

- There is a limited use of HLA-B27 in making the diagnosis of AS.
  - North European Caucasian patients 10% prevalence of B27 but only 0.1% prevalence of Ank Spond
  - AS only (not PsA, Reiter's syndrome)
  - 50:50 pretest likelihood – good time to get the test
  - children - poor history and X-ray findings
  - Early symptoms – x-ray features are often late

The best lab test in rheumatology:

For acute monoarthritis or oligoarthritis:

- Joint aspiration
  - cell count
  - gram stain, culture
  - crystal analysis
    - best to do yourself on fresh specimen

Recap: My workup for acute monoarthritis

- CBC, Creatinine, Uric acid, CRP
- Possibly blood cultures, urinalysis
- Aspirate the joint
- Send for 3 'c's – Culture, Crystals, Gram stain

Recap: My workup for inflammatory back pain

- CBC, Creat, CRP
- SI joint x-rays
- Consider low radiation CT SI joints if radiologist have expertise in this area (cheaper and faster than MRI)
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- (downside of genetic testing includes disruption of patients ability to obtain life/disability insurance

Recap: My workup – for REAL inflammatory arthritis

- CBC, U/A
- CK, Creat
- ANA (ENA, antiDNA, C3,C4 if pos)
- Anti CCP, CRP, RF
- SPEP, Hep B, C, HIV
- AST, ALT, Albumin (ASMA)
- Uric Acid, Ca, P04
- Ferritin (TIBC)

Conclusion

- Still no good replacement for Hx and Px
- Make a diagnosis of inflammatory polyarthritis or monarthritis first.
- Know what you want to rule in or out with any test
- You could probably never order ANCA, CCP, Complement and you wouldn't miss anything.
- Screening bloodwork has not been shown to be helpful in rheumatology

Tina Korownyk

Opioids for pain "Your focus determines your reality"

Tina Korownyk

Faculty/Presenter Disclosure

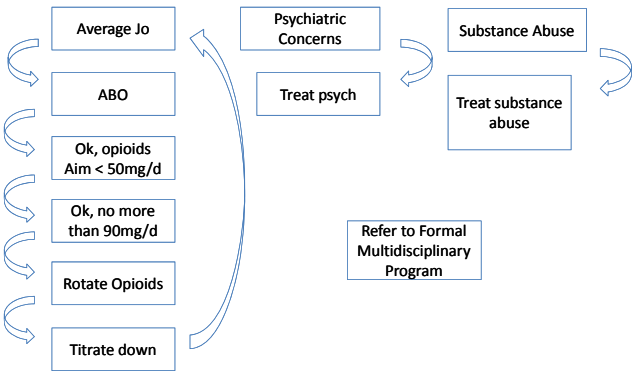
- **Faculty/Presenter:** Tina Korownyk
- **Where I get Personal $:** U of A, Alberta Health
- **Where I get Grant/ Program $:** Alberta College of Family Physicians, Other Colleges of Family Physicians, Toward Optimized Practice, Other non-profit organizer

- **Relationships with commercial interests:**
  - **Grants/Research Support:** Not applicable
  - **Speakers Bureau/Honoraria:** Not applicable
  - **Consulting Fees:** Not applicable
  - **Other:** None

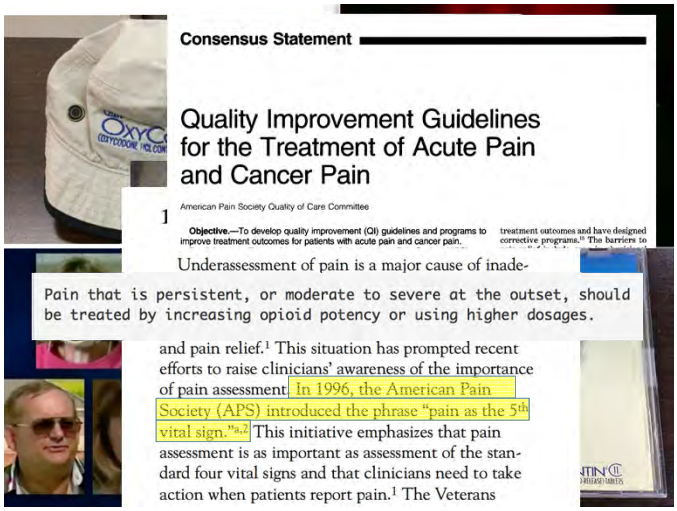
Objectives

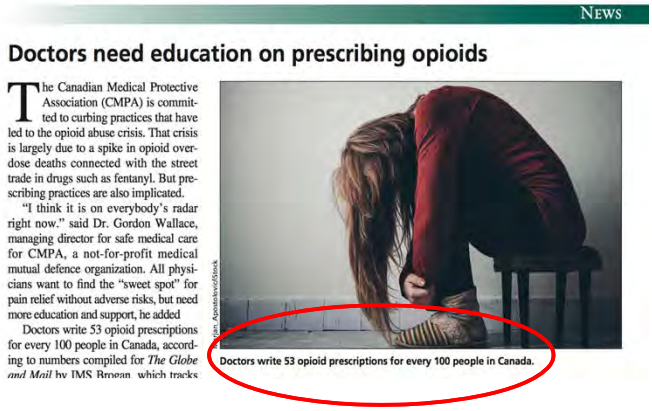
- Discuss evidence for opioids:
  - Acute pain
    - Do they work? For what? How long?
  - Chronic pain
    - Long term risks and benefits

2017 Chronic Non-Cancer Pain Guidelines



Tina Korownyk





CMAJ Oct 2016

Pediatric Acute Pain

MSK Injuries[1]

- 3 RCTs, 740 children, IB versus aceta, codeine, or both
  - IB > either alone for pain, IB = combination
  - IB improved function, fewer AEs
- RCT 134 kids, IB (10mg/kg) vs morphine (0.5mg/kg)
  - No difference pain 24 hrs
  - Morphine ↑ AE 56% vs 31%, NNH = 4
- RCT 456 kids, morphine (0.2mg/kg) + IB, IB, or morphine[4]
  - No difference in achieving <30mm VAS at 60 mins (~30%)
  - Morphine ↑ AE 21% vs 7%, NNH = 8

Outpatient Post Operative Pain[2,3]

- RCT 154 children, orthopedic surgery (ORIF, cysts, hardward removal)
- IB vs Morphine
  - No difference pain scores up to 48 hrs
  - Morphine NNH = 4
- Similar for post-tonsillectomy pain

1) TFP #14, updated July 8 2013 2) CMAJ 2017 October 10;189:E1252-8 3) Pediatrics 2015;135:307-13. 4) Pediatrics. 2017 Nov;140(5). pii: e20170186.

Acute Pain in Adults

Back Pain < 2 weeks[1]

- RCT, Naprosyn 500 BID: + cyclobenzaprine 5mg, oxycodone/acetaminophen 5/325mg, or placebo (1-2 TID)
  - No difference frequent/always back pain day 6: 29%, 28%, 35%
    - Return to normal activities: 4d, 4d and 5d.

Soft Tissue Injury[2]

- Cochrane (4 RCTs, 958 pts): No difference opioid vs NSAID for pain outcomes
- Improved function at 7d with NSAIDs

MVC Pain[3]

- ER Cohort: NSAID vs Opioid – no difference in pain at 6 weeks
- Those prescribed opioids 20% more likely to report opioid use at 6 weeks

1) JAMA. 2015;314(15):1572-1580 2) Cochrane Database Syst Rev. 2015 Jul 1;(7):CD007789. 3) Pain. 2017 Feb;158(2):289-295.

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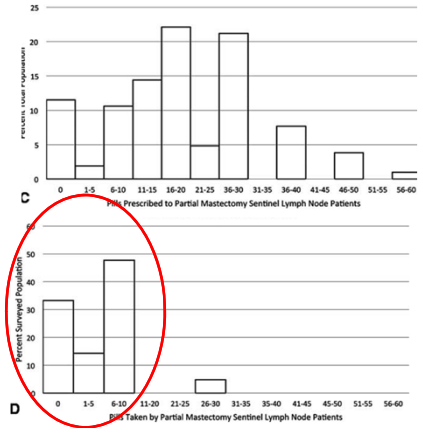
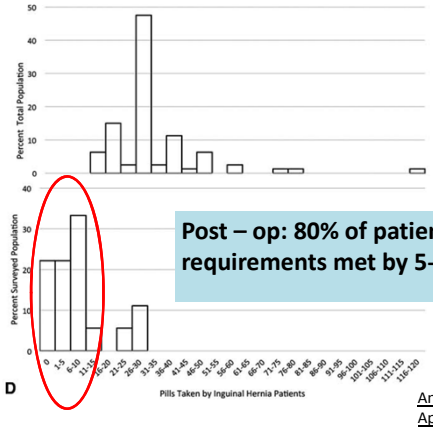
How Many Opioids Do We Need?



Ann Surg. 2017 Apr;265(4):709-714.

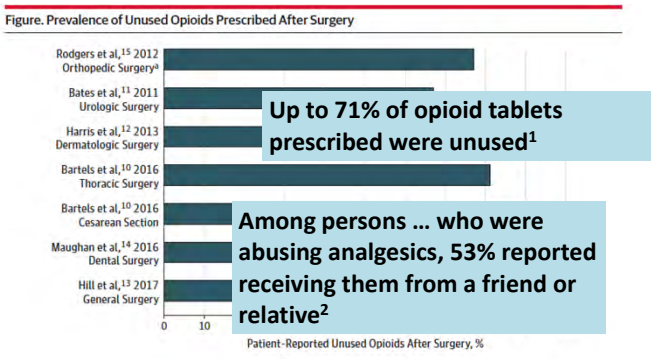
How Many Opioids Do We Need?



Post – op: 80% of patient requirements met by 5-15 pills

Ann Surg. 2017 Apr;265(4):709-714.

Unused Opioids After Surgery



Up to 71% of opioid tablets prescribed were unused[1]

Among persons … who were abusing analgesics, 53% reported receiving them from a friend or relative[2]

JAMA Surg. 2017 Aug 2. doi: 10.1001/jamasurg.2017.0831. 2) Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. NSDUH series H-48. HHS publication no. (SMA) 14-4863.Rockville, MD

Acute Pain

- Ambulatory care: no strong evidence that opioids are superior[1]
- Specific end date (sunrise, sunset)
- Reconsider length of Rx – is "2 weeks" or "30 tabs" really necessary? (more likely 5-15 tabs)
- Review dispensing interval, storage, disposal

1) Ann Emerg Med. 2012 Oct;60(4):499-525.
2) https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm
3) http://www.mdacep.org/MD%20ACEP%20Pamphlet%20FINAL_April%202014.pdf

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Are Long Acting Opioids Better?

Study	Pain	Time	Pts	Findings
Oxycodone				
Caldwell 1999	OA	30d	107	Equal for pain and sleep
Hale 1999	Back	6d	47	Equal for pain
Salzman 1999	Back	10d	57	Equal for pain
Codeine				
Hale 1997	Back	5d	83	LA better pain (but higher doses)* 200mg vs 71mg / day
Dihydrocodeine				
Gostick 1989	Back	14d	61	Equal for pain
Lloyd 1992	OA	14d	86	Equal for pain
Morphine				
Jamison 1998	Back	112d	36	LA better pain (but higher doses) * LA group titrated up as needed

Carson S, Thakurta S, Low A, Smith B, Chou R. *Drug Class Review: Long-Acting Opioid Analgesics: Final Update 6 Report*. Portland, OR: Oregon Health and Science University; July 2011. http://www.ncbi.nlm.nih.gov/books/NBK62335/. Accessed Oct 2017.

Long Vs Short Acting Opioids

- Cohort, 319 **Unintentional Overdoses,** 2000-2009 veterans admin healthcare system[1]
  - ↑ Risk Overdose with long acting: HR 2.33
  - Highest in 1st 2 weeks: HR 5.25
- ↑**Mortality** with Long acting compared to other pain medications[2]

"Because of **the greater risks of overdose and death with extended-release opioid formulations, reserve [these medications] for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective…"** **(FDA 2013)**

1) JAMA Intern Med. 2015;175(4):608-615. 2) JAMA. 2016;315:2415-23


REVIEW ARTICLE

What is th

ACKNOWLEDGEMENTS

Editorial assistance in the preparation of this article was provided by the McMahon Group and funded by King Pharmaceuticals, Inc. King Pharmaceuticals, Inc.,

ronic Pain?

Critical Review

Richard L. Rauck, MD

Medical Director, Carolinas Pain Institute, Center for Clinical Research, Winston-Salem, North Carolina, U.S.A.

Opioids for Chronic Pain

- **Abuse or dependence**[1]:
  - 0.7% with ≤36 MME/d, 6.1% with ≥ 120 MME/d
- **Overdose**[1]:
  - ↑ risk with ↑ dose:
    - 20-49 MME/d HR 1.44
    - 50-99 MME/d HR 3.79
    - >100 MME/d HR 8.87
- **Road trauma**: ~ 20% ↑odds with ≥20MME/d[2]
- **Mortality**: (LA Opioid vs TCA or anticonvulsant)[3]
  - <30 d: 260/10,000 vs 63/10,000 (HR = 4.16)
  - Overall: 167/10,000 vs 108/10,000 (HR = 1.64)
- Mixed evidence for fractures, MI, & sexual dysfunction

1) Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1–49. 2) JAMA Intern Med 2013;173:196–201. 3) JAMA. 2016;315:2415-23

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Opioids for Chronic Pain

- Cochrane systematic reviews
  - **Chronic back pain**[1]: Majority < 4weeks, opioids better than placebo, no better than NSAIDs or antidepressants
  - **Neurologic pain**[2]: half the studies <24hrs. Opioids > placebo for pain but not function. No diff with gabapentin or TCAs
  - **OA pain**[3]: small benefit vs placebo, trials <4 weeks demonstrated significantly greater pain benefit (p=0.001)
- Sys Rev, opioids >3 mo[4]
  - No placebo controlled RCTs > 3 months
  - **No study opioids vs no opioids evaluated >1 yr outcomes of pain, function or quality of life**

. 2) Cochrane 2013; 8: CD004959 3) Cochrane Database of Systematic Reviews 2013, CD006146 4) Cochrane 2014; 9: CD003115. 4) Ann Intern Med. 2015 Feb 17;162(4):276-86

Opioids for Chronic Pain

- As highlighted by an on the National Institutes of Health Pathways to Prevention panel:
- **"Particularly striking … was the realization that evidence is insufficient for every clinical decision that a provider needs to make about the use of opioids for chronic pain."**
- **Bottom Line: Evidence of long term benefit on pain, function and QOL with opioids is lacking.**

Ann Intern Med 2015;162:295–300.

SPACE Trial

- RCT, 240 pts, mean age 58 years, Veterans Affairs primary care clinics
- Moderate to severe chronic back or hip/knee OA pain despite analgesic use (exclude current opioid users)
- Randomized to:

	Opioids (Max 100 MME)	Non Opioids
Step 1	IR morphine /Oxycodone	Acetaminophen & NSAIDS
Step 2	SA morphine/Oxycodone	Nortriptyline, Amitriptyline, Gabapentin Topicals
Step 3	Transdermal fentanyl	Pregabalin, Duloxetine, Tramadol

JAMA. 2018 Mar 6;319(9):872-882.

SPACE Trial

Results

(BPI) at 12 months	Opioids	Non-Opioid	Diff?
Function	3.4	3.3	NS
Pain Intensity	4.0	3.5	p=0.03
≥ 30% improvement Function	59%	61%	NS
≥ 30% improvement Pain	41%	54%	p=0.05
Medication related symptoms	1.8	0.9	0.03

- No difference in adverse events, "doctor-shopping," diversion, or opioid use disorder diagnoses were detected.

JAMA. 2018 Mar 6;319(9):872-882.


HALT!
Save the date!
The
30th Annual Best Science
Medicine Course
will be held on
Friday, May 3rd and
Saturday, May 4th, 2019

Thanks for your questions and discussion.

Thank you for completing your course evaluations.

“The Force will be with you… always.”

Star Wars: Episode IV - A New Hope (1977)