26TH ANNUAL
BEST SCIENCE MEDICINE COURSE

April 17th and 18th, 2015

Fairmont Waterfront Hotel
Vancouver, B.C.

FRIDAY SYLLABUS

Sponsored by

The THERAPEUTICS EDUCATION COLLABORATION
In Cooperation with the
DEPARTMENT OF FAMILY MEDICINE,
UNIVERSITY OF BRITISH COLUMBIA

COURSE DIRECTORS
DRS. ROBERT RANGNO, JAMES MCCORMACK and
MICHAEL ALLAN

"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

Best Science Medicine Course 2015

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
Scott Garrison, Assoc. Prof., Family Medicine, University of Alberta
Mike Kolber, Assoc. Prof., Family Medicine, University of Alberta
Tina Korownyk, Assoc. Prof., Family Medicine, University of Alberta
Janet Nuth, Physician Risk Manager, CMPA, Ottawa, Ontario

Local Faculty

Keyvan Hadad, Clin. Assoc. Prof., Pediatrics, Medicine, UBC & BCWH
Peter Loewen, Assoc. Prof., Pharm. Sciences, UBC & VCHA
Val Montessori, Clin. Assoc. Prof., Medicine, Infectious Diseases, UBC & PHC
Alnoor Ramji, Clin. Assoc. Prof., Medicine, Gastroenterology, UBC & PHC
Launette Rieb, Clin. Assoc. Prof., Family Medicine, UBC & PHC
Kam Shojania, Clin. Prof., Medicine, Head, Rheumatology, UBC & PHC
Adil Virani, Assoc. Prof., Pharmaceutical Sciences, UBC, & Director, LMPS

BCWH – BC Women's Hospital
LMPS - Lower Mainland Pharmacy Services, FHA, PHSA, PHC, VCH
PHC – Providence Health Care
UBC – University of British Columbia
VCHA – Vancouver Coastal Health Authority
VGH – Vancouver General Hospital

BSMC
BEST SCIENCE MEDICINE COURSE

26th Annual Best Science Medicine Course

Formerly The Drug Therapy Decision Making Course – 25 years

Friday, April 17, 2015

07:00 Registration (Muffins & Coffee)
Program Chairs – Bob Rangno/James McCormack /Mike Allan

"Common Sense is a Super Power"

08:00	Up, up and away	Bob Rangno and James McCormack
08:10	The Dynamic Duo – which one is Robin?	Mike Allan and James McCormack

"It's Clobbering/Best Science Time"

08:40	Holy Bat Logic – how to decipher the medical literature	James McCormack
09:00	Questions	
09:10	Dealing with uncertainty – It's an imperfect world, but it's the only one we got	Mike Allan
09:30	What to do when Superheroes get old – the uncertainly principle	Rita McCracken
09:50	Questions	
10:00	Refreshment Break	

"To the Batmobile"

10:20	What to do when pain stops you from being able to leap tall buildings	Launette Rieb
10:40	The Periodic Health Exam – the arch-nemesis of primum non nocere?	Mike Allan
11:10	Questions	
11:20	Medical marijuana – Flame On!	Launette Rieb
11:40	Asthma – if you can't breathe it really doesn't matter what other superpowers you have	Tina Korownyk
12:00	Questions	
12:10	Lunch	

"Unwanted pathogens – human Kryptonite?"

13:00	What if Peter Parker had been bitten by a tic instead of a spider? – Lyme Disease	Val Montessori
13:20	STI, HPV, GC, STD, BV – shielding us from the genital villains	Mike Kolber
13:40	Hepatitis C – unmasking the new agents	Alnoor Ramji and Adil Virani
14:00	Questions	
14:20	Refreshment Break	

"Holy Heartburn"

14:40	Constipation – The Incredible Bulk to the rescue	Mike Kolber
15:00	Reflux and jaundice in your Superbaby	Keyvan Hadad
15:20	Anemia – Iron Man to the rescue	Peter Loewen
15:40	Questions	
16:00	Adjourn	

James McCormack and G. Michael Allan

Welcome!!

BSMC

26TH ANNUAL

Best Science Medicine Course

Formerly The Drug Therapy Decision Making Course – 25 years

Friday, April 17, 2015 and Saturday, April 18, 2015

The Fairmont Waterfront – 900 Canada Place Way, Vancouver, BC

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

#dtc26

@medmyths

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

"With Great Power Comes Great Responsibility"

Faculty/Presenter Disclosure

- **Presenter: James McCormack/Mike Allan**
- **Relationships that may introduce potential bias and/or conflict of interest:**
  - No relationships to declare

Learning Outcome Objective Slide

Provide at least one learning objective.

"Dynamic Duo" Talk

1) List the top 10 reasons for MD visits

2) Briefly describe the best available evidence around 3 of these conditions.

Patient's values vary

Evidence comes in different forms

The 10 New Therapeutic Commandments

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

James McCormack and G. Michael Allan

We are all KNOWLEDGE brokers

17

OBJECTIVES

Top 10 reasons for MD visits

RISK REDUCTION
Cholesterol problems
High blood pressure
Diabetes

PAIN CONTROL
Joint disorders, including osteoarthritis
Back problems
Headaches and migraines

SKIN DISORDERS
Cysts, acne and dermatitis

PSYCH/NEURO
Anxiety, bipolar disorder and depression
Chronic neurologic disorders

INFECTIOUS DISEASES
Upper respiratory conditions

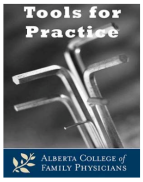
Describing Benefits

The chance of "X"

WITH NO TREATMENT

The chance of "X"

WITH TREATMENT



Children with Acute Otitis Media: Benefits and Risks of Antibiotics

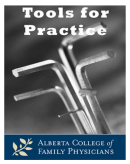
Clinical Question: In children with Acute Otitis Media (AOM) what are benefits and risks of antibiotics?

Antibiotics improve outcomes for 1 in 3 to 1 in 10, depending on outcome and complicating factors

Adverse events, particularly diarrhea, in roughly 1 in every 5

Delayed prescriptions
4 studies - 2 found no difference and 2 found immediate prescriptions superior (NNT 6-7)

James McCormack and G. Michael Allan



What can't they do: Steroids for my sore throat?

Question: Do corticosteroids reduce pain in patients with acute pharyngitis?

Corticosteroids added to antibiotics

Pain free at 24 hours - NNT =4

Especially in adults with documented streptococcus pharyngitis and more severe symptoms

Flu Shot

~ 70-90% effective - using antibodies as the diagnosis
~ 60% effective - if use culture endpoints
~ 85% effective - nasal spray in children 6 months to 6 years old

Every year 1-10% adults get the flu

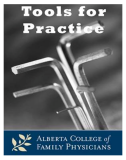
~ 5% - therefore reduced to 1% - less if unmatched

5-20% per year in children

~10% - therefore reduced to 2%

5% down to 2% (1%) in adults

10% down to 4% (2%) in children



Will the flu shot help my Grandma and Grandpa?

Clinical Question: Does the seasonal trivalent influenza vaccine (flu shot) prevent influenza or its complications in patients age ≥65 years old?

One high quality randomized controlled trial

Vaccinating 40 community dwelling seniors will prevent one case of influenza

Influenza (influenza-like illness plus serology)
Vaccine 1.7%, placebo 4.2%

Cohort studies demonstrating mortality benefits are biased by healthy user effect

Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

2,283 patients (Netherlands) - median age 70, 57% male, 20% CVD, 40% COPD/asthma

Hospitalized (non-ICU) with CAP

Three arms - beta-lactam (39% amox, 40% amox/clav, 15% ceftriaxone) vs beta-lactam/macrolide vs fluoroquinolone (60% moxi) strategies - 25% deviation for "medical reasons"

90-day mortality (~10%) and hospital stay (6 days)- all groups non-inferior - looked at the data in numerous ways

N Engl J Med 2015;372:1312-23

Heartburn

Indication	Outcome	Placebo/ no treatment	H2RA (%)	PPI (%)	NNT (PPI vs placebo)
GERD-like symptoms (CD002095)	Heartburn remission	25-40	55	70*	2-3
NSAID ulcer prevention (CD002296)	Clinical ulcers over 6-12	0.5-2	No studies	No studies	-
	Endoscopic ulcers at 12 weeks or	35	15 high dose H2RA	15	5

*high dose provides approximately a 5% absolute increase in benefit

Pain

The best non-narcotic acute pain killer - dental pain, headache etc

NSAID plus acetaminophen 1000 mg

Naproxen 250 mg/Ibuprofen 400 mg

FULL glass of water - lie on right side

James McCormack and G. Michael Allan

Neuropathic pain

post herpetic neuralgia/diabetic

Gabapentin

Moderate improvement 43% (G) vs 26% (P) - NNT~6

Substantial improvement 31% (G) vs 17% (P) - NNT~7

Dizziness, sedation, confusion, ataxia, peripheral edema - NNH ~8

CD007938

A test of benefit/harm can be made after 1-2 days at a low dose (100-900 mg/day)

Benefit is unlikely to increase with higher doses or longer treatment - TI letter #75

Erectile dysfunction

"Successful" attempts in the sildenafil group ≈ 70%

"Patients" who "responded" in the placebo group ≈ 20%

7/10 "patients" will "respond" each time to sildenafil

2 of these 7 "responded" not because of the drug - NNB of 2

10% headache, 15% flushing, 10% dyspepsia - <1% stopped drug due to side effects

N Engl J Med 1998;338:1397-404

Depression

Patients who respond in the SSRI group ≈ 60%

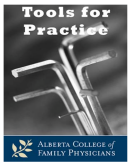
40% in primary care? Am J Psychiatry 2009; 166:599–607

Patients who respond in the placebo group ≈ 45%

6/10 patients will respond to an antidepressant

4-5 of these 6 improved not because of the drug - NNT of 6-7

CD007954



Zoster vaccine: Zoster loster or imposter coster?

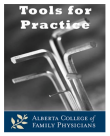
Clinical Question: What are the benefits of the zoster vaccine to our patients?

Study	Placebo	Zoster Vac	Benefit	NNT (3 yrs)
Age 50-59 (3 yrs)	2%	0.6%	1.4%	71
Age ≥60 (3 yrs)	3.4%	1.7%	1.7%	59

"60 / 360 @ 60"

Bottom-Line: Over 3 years, one in 60-70 patients will avoid shingles due to the vaccine

- One in 350 for post-herpetic neuralgia



Statins and the elderly: The Who, What and When?

Clinical Question: Which elderly patients should be offered what type of statin for cardiovascular disease (CVD) prevention?

Secondary prevention

9 RCTs, 19,569 patients age 65-82

All cause mortality - RR 0.78 (0.65-0.89) NNT = 28

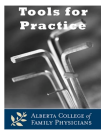
Non-fatal MI NNT = 38, Stroke NNT=58

Primary prevention

8 RCTs 24,674 patients age 65-82

MI NNT = 84, Stroke NNT =143 - no reduction in mortality

NNH musculoskeletal events NNH 77



Can I get my cholesterol checked fast (without fasting)?

Clinical Question: Can non-fasting lipid levels be used to predict future cardiovascular disease (CVD) risk?

Lipid results

Cross sectional study of >200,000 Canadians

Fasting changed lipid levels by:
<2% for TC and high density lipoprotein (HDL)
~10% for low density lipoprotein (LDL)
~20% for triglycerides
Similar in Danish cohort

Non-fasting and fasting HDL and non-HDL cholesterol similarly predicted CVD risk

James McCormack and G. Michael Allan

Accutane/Epuris

10, 20 and 40 mg capsules

Therapeutic Choices - 0.5-2 mg/kg/day for 12-16 weeks
60 kg = 30 to 120 mg/day
“Low dose” was considered 0.5 mg/kg/day and there was a cumulative dose of 120-150 mg/kg

Start with 10 mg a day and continue until all lesions are gone and then continue for 2-4 months at 5 mg/day or 10 mg every other day

Australasian J of Dermatol 2013;54:157–62
Indian J Dermatol Venereol Leprol 2010;76:7-13

ORIGINAL ARTICLE

Isotretinoin 5 mg daily for low-grade adult acne vulgaris – a placebo-controlled, randomized double-blind study

Journal of the European Academy of Dermatology and Venereology 2

General Sports Injur

Recommend

R = rest

I =

C = +/- NSAIDs/acetaminophen

Heat after 48 hours

RICE - coined in 1978

“Coaches have used my “RICE” guideline for decades, but now it appears that both Ice and complete Rest may delay healing, instead of helping.” – Gabe Mirkin, MD, March 2014

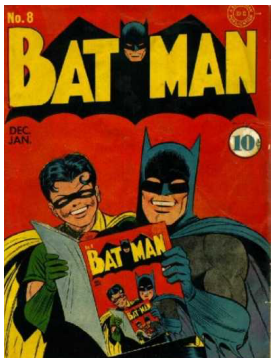
M - Move safely when you can as much as you can
C - Compress
E - Elevate

Questioning Ice/Cryotherapy

J Strength Con Res 2013;27:1354-61
Am J Sport Med 2004;32:251-61
Sports Med 2012;42:69-87
J App Phys 2011;110:382-8
J Athl Train 2012;47:435-4

James McCormack

Holy Bat Logic



How to Decipher the Medical Literature

Faculty/Presenter Disclosure

- **Presenter: James McCormack**
- **Relationships that may introduce potential bias and/or conflict of interest:**
  - No relationships to declare

26th Annual Best Science Medicine Course:

Learning Outcome Objective Slide

Provide at least one learning objective.

"How to decipher the medical literature" Talk

1)List seven sources of bias in the medical literature

2)Show how to calculate relative and absolute risk and NNT

We compare one thing to another

1) Always find differences

2) Report the differences - numbers
(RR/OR/HR/RRR, AR/ARR/NNT/NNH)

3) If there was NO difference how often would we see such a difference - statistics
(p-values/confidence intervals)

4) Could the difference be because of other things - believable/trust
(bias/systematic error)

5) Is the difference important - magnitude
(values and preferences)

For dichotomous (yes/no) outcomes, each study reports the differences found

You will see differences presented as either

- a RELATIVE difference - always ratios
  - relative risk = risk ratio (RR) ~odds ratio (OR) if events occur <10% - OR typically used in case-control studies
  - hazard ratio (HR) - when a survival analysis has been done
  - relative risk reduction (RRR)
- an ABSOLUTE difference
  - absolute risk (AR)
  - absolute risk reduction (ARR)
  - numbers needed to treat/harm (NNT/NNH)

For each difference found we want to know

p-value - sort of like a false positive
- if the two groups have the SAME MEAN what is the chance of observing a difference this big, or larger

confidence interval - sort of like a +/-
- a plausible range of values for the true effect - NOT a probability

James McCormack

Sources of bias

Bias - systematic error that causes inaccurate research findings

Information

Observer

Recall

Selection

Confounding

Publication

Reporting bias

Lower Risk of Bias

Randomized - most trials are randomized

Blinded - more important for symptom trials than long-term CVD trials

Allocation concealment - mention of this is a measure of trial quality

Intention-to-treat - most conservative - most trials are now being analyzed this way

Follow-up - less loss to follow-up - another measure of trial quality

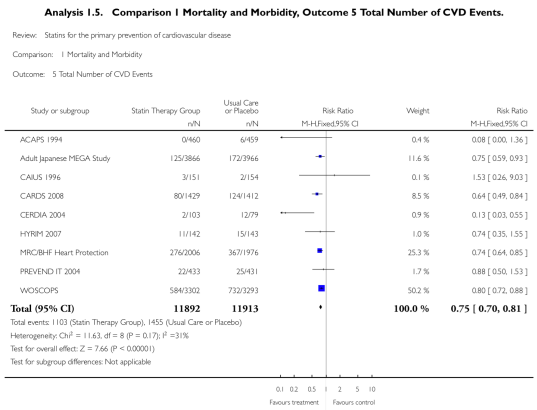
Conflicts of interest - it's about declaration - most studies now present financial conflicts of interest

Table 2. Primary and Secondary Outcomes.*

Outcome	LCZ696 (N = 4187)	Enalapril (N = 4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	−2.99±0.36	−4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

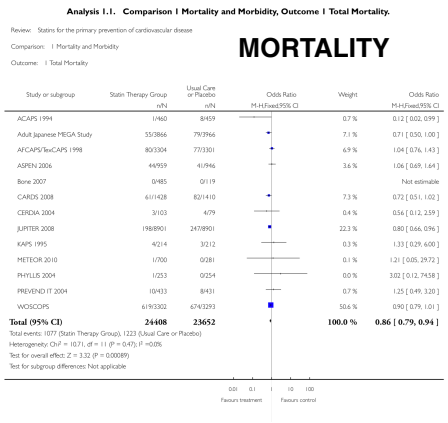
	LCZ696	Enalapril	HR Point estimate	HR Confidence interval
Primary composite	21.8	26.5	0.80	0.73-0.87
Decline in renal function	2.2	2.6	0.86	0.65-1.13

Statins for the primary prevention of cardiovascular disease (Review)



THE COCHRANE

Statins for the primary prevention of cardiovascular disease (Review)



THE COCHRANE

Study	Number of Trials in Meta-analysis (Number of Patients)	Point Estimate (95% Confidence Intervals)	Relative Risk Overall Mortality
Studer 2005	9 (26,641)	0.86 (0.76 – 0.99)	
Thavendiranathan 2006	6 (39,937)	0.92 (0.84 – 1.01)	
Mills 2008	19 (63,899)	0.93 (0.87 – 0.99)	
Brugts 2009	9 (67,476)	0.88 (0.81 – 0.96)	
Ray 2010	11 (65,229)	0.91 (0.83 – 1.01)	

0.6 0.65 0.7 0.75 0.8 0.85 0.90 0.95 1 1.05 1.1

Figure 1 Comparison of 5 meta-analyses examining relative risk of overall mortality with statin use in primary prevention. Footnote: Brugts 2009 point estimate and confidence intervals are odds ratios (not relative risks).

G. Michael Allan

Dealing with Information Uncertainty

It's an imperfect world but it's the only one we got

"Medicine is a science of uncertainty and an art of probability."
- William Osler

Faculty/Presenter Disclosure

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26th Annual Best Science Medicine Course

Learning Outcome Objective Slide

Provide at least one learning objective.

"Dealing with uncertainty - It's an imperfect world, but it's the only one we got" Talk

1)Explain how studies are "statistically significant".

2)Explain clinically significant versus statistically significant

3)Explain misinterpretation of confidence and false disagreement.

4)Explain the misuse of meta-analyses and how it is misleading

5)All will include practical examples with clinical application.

Ignore Media Reports?

Research
Recherche

Drugs in the news: an analysis of Canadian newspaper coverage of new prescription drugs

Alan Cassels, Merrilee A. Hughes, Carol Cole, Barbara Mintzes, Joel Lexchin, James P. McCormack

193 articles - 5 selected "new"drugs

100% - mentioned at least one benefit

2/3 - made no mention of possible side effects or harms

1/4 - of mentions of drug benefits and harms presented quantitative information

1/4 - of cases in which drug benefits and harms were quantified, the magnitude was presented only in relative terms

2/3 - of the articles gave no quantification of the benefits or harms

1/5 - reported only surrogate benefits

1/20 - mentioned contraindications - 1/3 mentioned drug costs

After exclusion of industry and government spokespeople, for only 3% was there any mention of potential COI

CMAJ 2003;168:1133-7

CHRISTMAS 2014: MEDIA STUDIES

Televised medical talk shows—what they recommend and the evidence to support their recommendations: a prospective observational study

	No (%) of recommendations	
	The Dr Oz Show **(n=479)**	*The Doctors* **(n=445)**
Benefit of recommendation mentioned	453 (94.6)	402 (90.3)
Benefit was specific	204 (42.6)	184 (41.3)
Magnitude of benefit mentioned	79 (16.5)	49 (11.0)
Possible harms mentioned	47 (9.8)	34 (7.6)
Cost mentioned	60 (12.5)	14 (3.1)
Potential conflict of interest declared or mentioned	1 time	3 times

BMJ 2014;349:g7346

G. Michael Allan

"Believable" Evidence for Recommendations

The Dr Oz Show

evidence supported 46%

contradicted 15%

not found for 39%

believable or somewhat believable evidence 33%

The Doctors

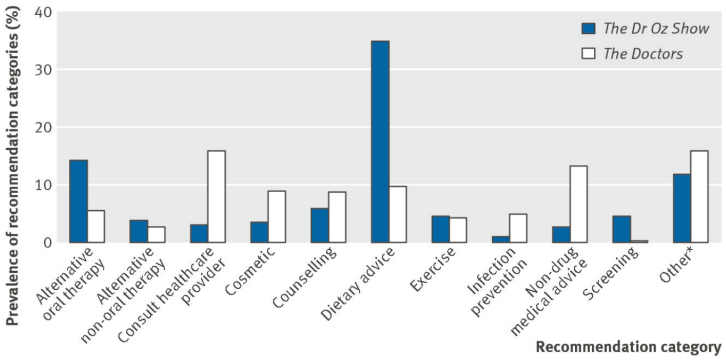
evidence supported 63%

contradicted 14%

not found for 24%

believable or somewhat believable evidence supported 33%

BMJ 2014;349:g7346



* Other includes recommendations pertaining to: medications, drugs of abuse, dental care, diagnosis, lifestyle, motherhood statements, physiotherapy, sex related topics, tests, vitamins and vaccines

BMJ 2014;349:g7346

BMJ Open **Representations of the health value of vitamin D supplementation in newspapers: media content analysis**

Timothy Caulfield,[1] Marianne I Clark,[1] James P McCormack,[2] Christen Rachul,[3] Catherine J Field[4]

Reviewed Canada, US and UK newspapers for 5 years

294 articles

80% suggested supplementation is or may be necessary for the general population

almost none discussed the potential harms of vitamin D supplementation in any detail

BMJ Open 2014;4: e006395. doi:10.1136/ bmjopen-2014-006395

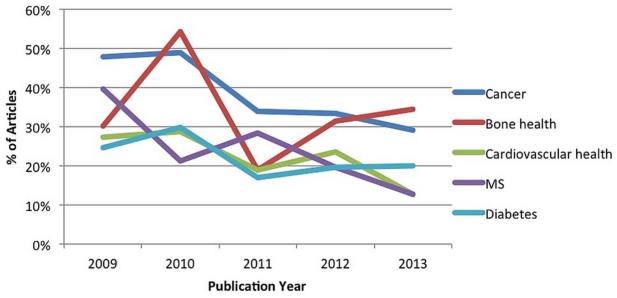


Figure 1 Most frequently named health conditions discussed in relationship to vitamin D in newspapers over 5 years.

Articles stated supplementation may be beneficial or is necessary

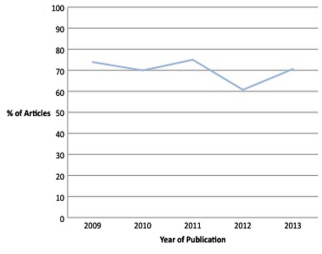


Figure 2 Percentage of articles that utilised one or both of the frames 'supplementation may be beneficial' and/or 'supplementation is necessary' by year.

Articles interpreted research as endorsement of supplementation

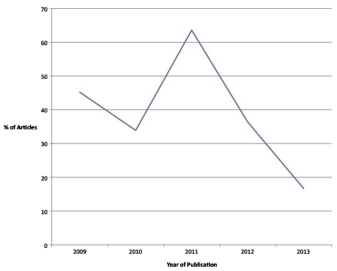


Figure 3 Percentage of articles citing research about vitamin D that interpreted research as endorsement of supplementation by year.

Ignore Most Associations?

G. Michael Allan

Essay

Why Most Published Research Findings Are False

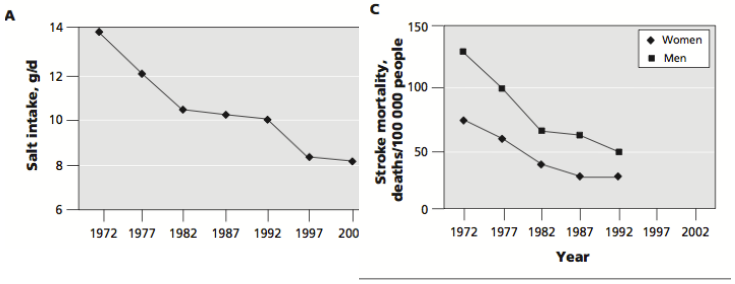
John P. A. Ioannidis

PLoS Med: 2005

"a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance."

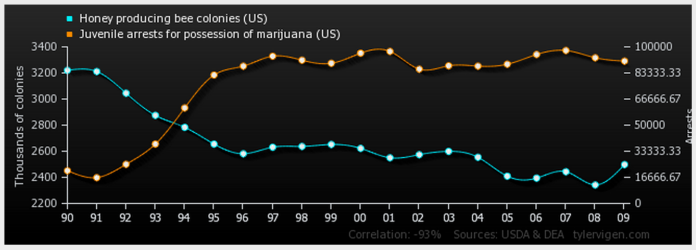
CMAJ ANALYSIS

Effective population-wide public health interventions to promote sodium reduction



CMAJ 2009. DOI:10.1503/cmai.090361

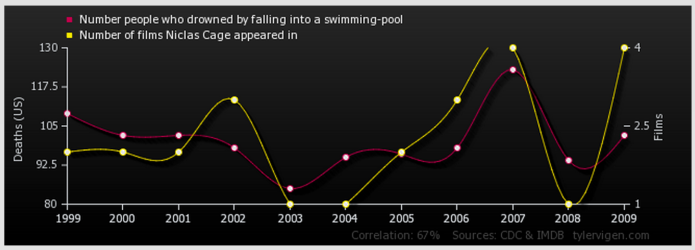
Honey producing bee colonies (US)
inversely correlates with
Juvenile arrests for possession of marijuana (US)



Honey producing bee colonies (US) *Thousands of colonies (USDA)*	'90: 3,220; '91: 3,211; '92: 3,045; '93: 2,875; '94: 2,783; '95: 2,655; '96: 2,581; '97: 2,631; '98: 2,637; '99: 2,652; '00: 2,622; '01: 2,550; '02: 2,574; '03: 2,599; '04: 2,554; '05: 2,409; '06: 2,394; '07: 2,443; '08: 2,342; '09: 2,498
Juvenile arrests for possession of marijuana (US) *Arrests (DEA)*	'90: 20,940; '91: 16,490; '92: 25,004; '93: 37,915; '94: 61,003; '95: 82,015; '96: 87,712; '97: 94,046; '98: 91,467; '99: 89,523; '00: 95,962; '01: 97,088; '02: 85,769; '03: 87,909; '04: 87,717; '05: 88,909; '06: 95,120; '07: 97,671; '08: 93,042; '09: 90,927

Correlation: -0.933389

Number people who drowned by falling into a swimming-pool
correlates with
Number of films Nicolas Cage appeared in



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Number people who drowned by falling into a swimming-pool *Deaths (US) (CDC)*	109	102	102	98	85	95	96	98	123	94	102
Number of films Nicolas Cage appeared in *Films (IMDB)*	2	2	2	3	1	1	2	3	4	1	4

Correlation: 0.666004

What can we study?

Implausible results in human nutrition research

Definitive solutions won't come from another million observational papers or small randomized trials

John P A Ioannidis *professor of medicine, health research and policy, and statistics*

Stanford Prevention Research Center, Stanford, CA 94305, USA

BMJ 2013;347:f6698

Objectively speaking, we can't get definitive answers from more studies because they all have important biases, there are numerous confounders and evaluating surrogate markers is fraught with problems

Single Nutrients

"on the basis of dozens of randomized trials, single nutrients are unlikely to have relative risks less than 0.90 for major clinical outcomes …"

"… most are greater than 0.95"

In other words,if differences exist they are <10% and may be <5%

"Observational studies and even randomized trials of single nutrients

seem hopeless,

with rare exceptions"

BMJ 2013;347:f6698

G. Michael Allan

Multiple Nutrients and Behaviours

"Larger effect sizes [ie. >10%] are more plausible for complex dietary patterns that sum the effects of multiple nutrients and behaviors"
PREDIMED, Lyon Diet Heart Study

Now, it is possible to *"identify nutrition related interventions that produce a 5-10% relative risk reduction in overall mortality in the general population"*

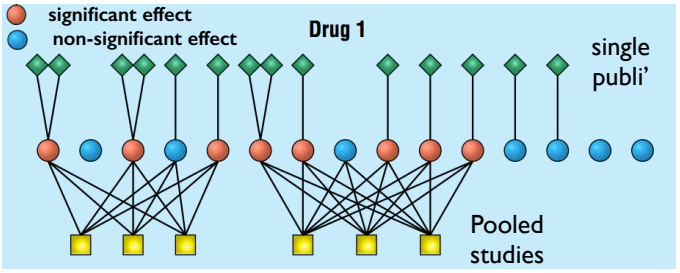
However, this would require
>10 times the sample size of PREDIMED
(n = 80,000 and 4,000 endpoints)

BMJ 2013;347:f6698

SSRI: Super Selective Release of Information

Step 2: Re-publish the positive!

Three Trials find their way into 12 publications (5 each)



Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B. Evidence b(i)ased medicine--selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. BMJ. 2003 May 31;326(7400):1171-3.

The evidence for effect differences between industry and non-industry sponsored studies

Cochrane review 2013 - Lexchin and Bero

STUDIES THAT SHOW NO INFLUENCE ON EFFECT SIZE

4 papers ~ 800 studies -pain medication, antipsychotics, and antidepressants
JAMA 2003;290(7):921–8 Pain 2006;121(3):207–18. Neuropsychopharmacology 2008;33(5):971–5,The British Journal of Psychiatry 2000;177:292–302

1 additional paper - statin trials ~180 studies
http://www.bmj.com/content/349/bmj.g5741

STUDIES THAT SHOW AN INFLUENCE ON EFFECT SIZE

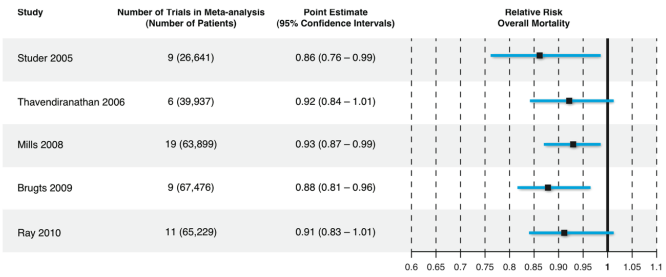
3 papers ~50 studies - clozapine, glucosamine and nicotine replacement
difficult to tease teasing out the actual effect size differences - around 40% for glucosamine, 15% for NRT and clozapine??
British Journal of Psychiatry 2003;183:161–6.Arthritis and Rheumatism 2007;56(7):2267–77 Addiction 2007;102(5):815–22

BOTTOM LINE – evidence not overwhelming nor consistent and the magnitude is unclear

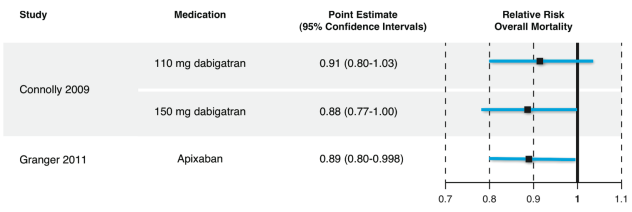
1) 5 papers ~1000 studies have shown no influence of industry on effect size
2) 3 papers ~50 studies suggest an influence on effect size
3) seems very much to depend on the class of drugs
4) can't easily put a magnitude on the effect if there is one

Ignore Many Conclusions?

Comparison of 5 meta-analyses examining relative risk of overall mortality with statin use in primary prevention



Comparison of 2 randomized controlled trials examining the relative risk of overall mortality with 3 novel oral anticoagulants versus warfarin in atrial fibrillation



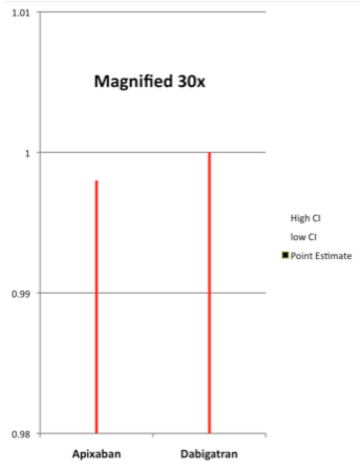
G. Michael Allan

Novel Anti-Coagulants

"ARISTOTLE: A major win for apixaban in AF"

"the most positive yet"

"first of the three new oral anticoagulants to show a clearly significant reduction in all-cause mortality"



http://www.theheart.org/article/1268723.do, Dabigatran (150mg): N Engl J Med 2009;361:1139-51. Apixaban: N Engl J Med. 2011;365(11):981-92

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441

Diabetes Care

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

January 2015 Volume 38, Supplement 1

Standards of Medical Care in Diabetes—2015

Diabetes Care January 2015

113 PAGES

Risk estimation

no mention or discussion of the magnitude, in relative or absolute terms, of any adverse clinical endpoints associated with elevated glucose

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441

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THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

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Standards of Medical Care in Diabetes—2015

Diabetes Care January 2015

Impact of treatment

no mention of the magnitude with regards to retinopathy/ kidney disease/neuropathies

CVD - "16% reduction in events" and "reductions in MI" (15% sulfony/insulin, 33% met) and "in all-cause mortality (13% and 27%, respectively) from the UKPDS/ 10 year follow-up

"every HbA1c reduction of 1% may be associated with a 15% relative risk reduction in nonfatal myocardial infarction, but without benefits on stroke or all-cause mortality" and a 9% "reduction in major CVD outcomes"

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441

Diabetes Care

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

January 2015 Volume 38, Supplement 1

Standards of Medical Care in Diabetes—2015

Diabetes Care January 2015

Potential Harms

12 classes of medications mentioned

~50 disadvantages/harms are listed in tables nowhere in the tables, and only twice in the documents, are absolute numbers for side effects provided (SGLT2 inhibitors/mycotic infections and DPP-4/heart failure)

Ignore Most New Things?

New and improved

vs.

Unsafe/withdrawn

The last decade (2000s)

Drugs considered to provide substantial improvements (PMPRB)

19

Drugs removed from the market (FDA etc)

Xigris - for severe sepsis

23

Became one of these

G. Michael Allan

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)	1 sodium phenylbutyrate coated granules (urea cycle disorders)

We Are All Individuals

Every patient is an “n of 1” study
Every treatment is an experiment

Rita McCracken

What to do when superheroes get old - the uncertainty principle -

(or: frailty, polypharmacy and how they (might) impact prescribing)

Dr. Rita McCracken
Family Physician
PhD Candidate
rita.mccracken@ubc.ca
@DrRitaMc

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty/Presenter:** [Rita McCracken]
- **Relationships with commercial interests:**
  - **Grants/Research Support:** n/a
  - **Speakers Bureau/Honoraria:** n/a
  - **Consulting Fees:** n/a
  - **Other:** n/a

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

- **This program has NOT received ANY financial support**.
- **This program has NOT received ANY in-kind support**.
- **Potential for conflict(s) of interest:**
  - n/a
  - n/a

CFPC CoI Templates: Slide 3

Mitigating Potential Bias

- I will provide a published source to support every statement that I make.
- I welcome feedback if bias is noted by any audience member. (please be specific about what you heard me say and why you think it is biased).

Learning objectives

1. Describe state of literature/evidence regarding prescribing to frail elders.
2. Understand how frailty is a prognostic signpost and helpful in de-prescribing decisions.
3. Review de-prescribing process(es).

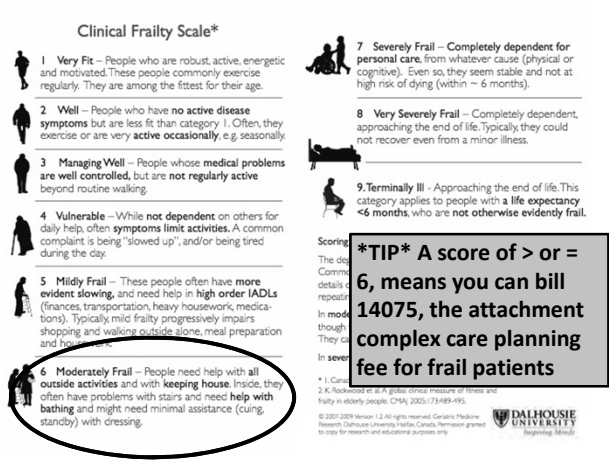
Polypharmacy in elderly, *(literature review in one slide)*

1. Physiology in frail elders is different and comorbidities are common.
2. Frailty common (and prognostic factor).
3. More drugs increases chances of more adverse events (mathematical reality).
4. Limited life span.
5. Frail elders typically excluded from most trials.
6. Chronic Dz guidelines based on available trials.
7. EVERYONE SAYS “MORE RESEARCH NEEDED”

References, please see POLYPHARMACY reference slide at end of this presentation.

Rita McCracken

What do we mean by frail?



Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

***TIP* A score of > or = 6, means you can bill 14075, the attachment complex care planning fee for frail patients**

What does the frailty scale tell us?

- Not perfect, but helps predict
  - Time to nursing home admission and
  - Time to death
- Many other frailty scales and comprehensive geriatric assessment tools.
- Canadian research suggests this tool has a high correlation (r=0.80) to more complicated assessments in predicting that more frail people die faster and go to nursing homes earlier.

Rockwood, K, et al, CMAJ. Aug 30, 2005; 173(5): 489–495

Problems with the "evidence"

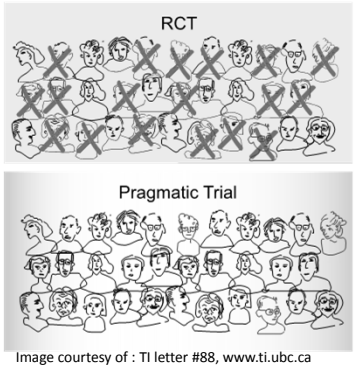


Image courtesy of : TI letter #88, www.ti.ubc.ca

Won't medications HELP or IMPROVE frailty?

Rita McCracken

Let's talk about hypertension

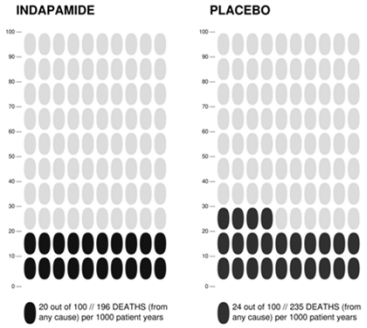
HYVET : who they studied

Inclusion criteria:
- Aged 80 or more,
- Systolic BP 160-199 mm Hg
- + diastolic BP <110 mm Hg,
- Informed consent

Exclusion criteria:
- Standing SBP <140 mm Hg
- Stroke in last 6 months
- Dementia
- Need for daily nursing care

Reference: Beckett NS, et al. N Engl J Med. 2008;358(18):1887-98.

HYVET – all cause death/1000 pt years



Active therapy **reduced** total mortality:

ARR = 2.2%,
NNT = 48 for 2 years

TREATMENT GROUP
mean BP 144/78
(48% reached target)

PLACEBO
Mean BP 159/84
(20 % achieved target)

Beckett NS, et al. N Engl J Med. 2008;358(18):1887-98

Leiden 85+ (no one gets left out)

"Overall, **90-year-old participants with SBP of 150 mmHg or less had a 1.62 times increased mortality risk** compared to those with SBP more than 150 mmHg (95%CI:1.21–2.20), independent of the SBP trend in preceding years. This applied to those with and without antihypertensive drugs and those with and without history of cardiovascular disease or noncardiovascular disease."

Older patients with LOWER Blood Pressure had HIGHER RISK OF DEATH.

Reference: Poortvliet RK, et al. Journal of Hypertension. 2013;31(1):63-70.

Mossello, Florence, Italy

(JAMA Intern Med, 2 March 2015)

Prospective cohort, n= 172 outpatients, 1 June 2009 - 31 May 2011, baseline ax + f/u (6-18 months)

Inclusion criteria:
- Aged 65 or more,
- Dx MCI or Dementia, MMSE 10-27
- Informed consent ((family member if need be)

Exclusion criteria:
- MMSE<10
- A. Fib (bc automated machines not reliable)
- Refusal to wear BP cuff

At baseline and follow up they assessed:
1. Vascular comorbidities (incl HTN, DM2, CHF, CHD, arrhythmias (not A.Fib), CV Dz, CKD)
2. List of all hypertension medications.
3. Office SBP/DBP
4. Cognitive Ax
5. BADL's and IADL's

Fastidious attention to BP monitoring, including:
24hr ABPM @ baseline
- Mean
- Variability
- Nighttime "dipping"

Office BP @followup

What did they find in Florence?

At mean of 9 months to follow up

- DECREASE in MMSE (baseline **22.1** (SD 4.4) to **20.7** (SD 5.8) (p=<0.001)
- Using daytime SBP, compared tertiles
  - <128 (MMSE -2.8 (SD 3.8))
  - 128-144 (MMSE – 0.7 (SD 2.5)) (p<0.002)
  - >145 (MMSE -0.7 (SD 3.7)) (p<0.003)

There is not much data on blood pressure in people with cognitive impairment, said lead author Dr. Enrico Mossello of the University of Florence in Italy. This study is the first to suggest that **cognitive declines might happen faster in older people on blood pressure medicine** whose systolic pressure – […] – is low, he said.

Mossello et al, JAMA Intern Med, 2 March 2015
http://www.theglobeandmail.com/life/health-and-fitness/health/low-blood-pressure-linked-to-faster-cognitive-decline/article23287122/

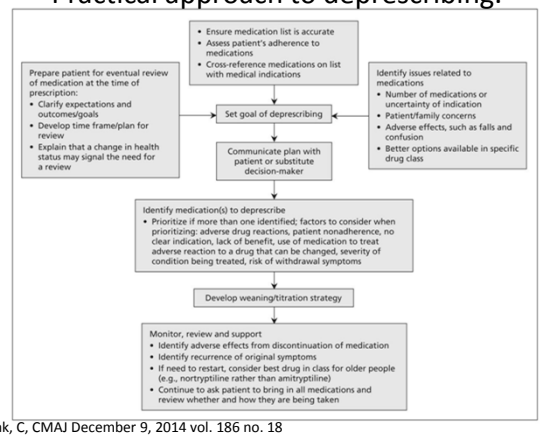
Rita McCracken

So how do you actually trim a medication list?

Figure Legend:

Algorithm for Deciding Order and Mode in Which Drug Use Could Be Discontinued

"Practical approach to deprescribing."



Frank, C, CMAJ December 9, 2014 vol. 186 no. 18

What makes a good day for our patient?

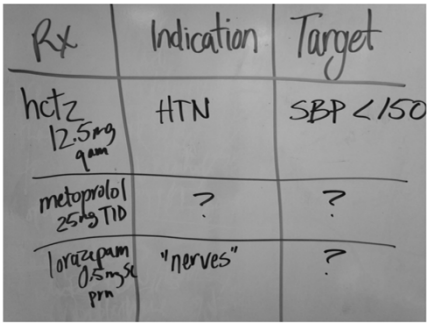
- Good enough mobility
- Regular bowel movements and a manageable bladder habit.
- Clarity of thought
  - (minimal daytime drowsiness, can have a conversation, go to Bingo, read the paper, etc)
- Enjoyment of foods and drinks that are meaningful and pleasurable for them
  - (as opposed to adhering to a "special diet")
- Time with loved ones (usually).
- Days NOT consumed by doctors appointments, trips to the pharmacy and pill taking.

Where to start

- Make an accurate list of all medications (+OTC's) being taken
- Know what the indication is for each and what the target for each is and
- Ensure patient (or family) understands and can help assess targets.

Rita McCracken

Where to start



Basic Plan

1. Avoid cold turkey drug-ectomies
   - Except in case of e.g. vitamins, statins, bisphosphonates
   - **Special attention needs to be paid to benzo and opiate tapers (you may do a smaller reduction and over a much longer period)
2. If you are going to reduce, **decrease dose by ½ and reassess in 7-14 days .**
   - Are things better, worse, the same?
   - If worse, consider restarting,
   - If better or the same, then reduce by ½ again, etc until med discontinued OR symptoms reappear.

Bottomline

- You need to know **which of your patients are frail** and prescribe to them differently.
  - There is no trial data to say exactly what is best
  - Drugs for treating specific symptoms should be used at the **lowest possible dose** and be reviewed often.
- **Communication** with patients and family will take time, but is needed.
- The **14075 fee code** helps reimburse practicing the ART of medicine with this population.

In summary

1. Review frail elders medication list frequently
2. Be honest about the quality of evidence and what a patient/family can expect from a pill.
3. Existing trials/guidelines RARELY include frail elders.
4. Consider reducing medications.
5. Monitor what happens when you do.
6. PARTICIPATE IN PRAGMATIC TRIALS when invited
   - Dr. Scott Garrison
7. Call me!
   - Mobile: 778 996 6894 (also through St. Paul's switchboard)

Acknowledgements

- My family – for supporting this academic adventure.
- My PhD supervisor - Scott Garrison and the rest of my committee (Dr. James McCormack and Margaret McGregor)
- My medical student research assistant, Ms. Charmaine Lam.
- Dr. Jonathan Berkowitz for helping me make sense of the math.
- PHC's Dept of Family and Community Medicine and the BC College of Family Physicians for financial support of my research.
- My patients and their families for daily reminders about why this work is valuable

A BIG TOOLBOX

Rita McCracken

Good questions to ask yourself (and your patient) about the med list and how s/he feels

- Are you prescribing a medication that is:
  - Impairing appetite?
  - Changing tastes of favorite foods?
  - Affecting balance?
  - Changing sleep patterns? (? nocturia 2° to diuretic?)
  - Causing leg cramps/pain?
  - Increasing constipation? Diarrhea?

  What if this patient really only wants to visit with her grandchildren, watch Family Feud and eat pistachio ice cream

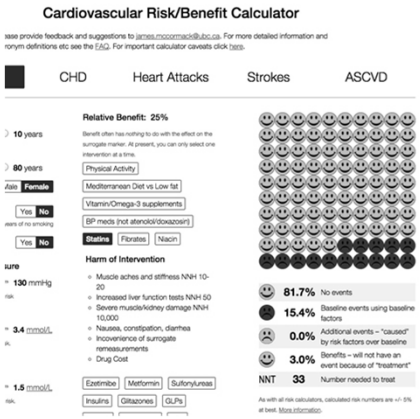
More ideas to consider when decreasing meds.

a) Flag meds that may be CAUSING a problem from Step One.
- E.g. Ca++ and constipation, SBP too low and dizziness and fatigue, statin and lower limb muscle pain.

b) Make sure you are **using age/frailty appropriate guidelines**
- E.g. PATH, CFP, RX Files (see reference list, at end of presentation)

c) Are targets and **patient expectations realistic**?
- Many patients believe benefits of medications are much higher than they actually are (remember the ARR slide in this presentation)?

d) What is the NNT and/or NNH for this medication?
- (short answer, it likely doesn't exist for your frail person, but even using trial data from younger people, what is it?)
- For CV risk drugs, try using http://bestsciencemedicine.com/chd/calc2.html



Best Science Medicine Risk Calculator
(example of tool to help explain potential benefit using all avail CV risk data)

http://bestsciencemedicine.com/chd/calc2.html

GP Resources for managing de-prescribing (1 of 2)

- **FRAILTY SCALE**
  - Canadian made and easy to use clinically. Also used for GPSC frailty attachment fee evaluation.
  - Frailty Complex care fee code = 14075 = $315 // http://www.gpscbc.ca/system/files/GPSC%20FEES%20General%20and%20Attachment%20Quick%20Reference.pdf
  - http://geriatricresearch.medicine.dal.ca/pdf/Clinical%20Faily%20Scale.pdf
- **Best Science Risk Calculator**
  - This is the only risk calculator you need. Simply amazing, summarizes RCT evidence and displays it in a way that you and patients can understand.
  - http://bestsciencemedicine.com/chd/calc2.html
- **Best Science Medicine (on iTunes)**
  - Podcasts that distill evidence, new and old into useable clinical pearls
  - http://therapeuticseducation.org/bs-medicine-podcast

GP Resources for managing de-prescribing (2 of 2)

- **PATH Clinic**
  - innovative scientific research being done in Canada about how to BETTER care for frail elders
  - http://pathclinic.ca/resources/
- **Choosing Wisely Canada**
  - Collection of recommendations (from Colleges of FP and Specialists) to stop doing things and the evidence that supports them.
  - http://www.choosingwiselycanada.org/recommendations/canadian-geriatrics-society-2/
- **The NNT**
  - GREAT website to remind you about what NNT is and to tell you what NNT's are known about certain treatments.
  - http://www.thennt.com/
- **Rx Files** – Elderly LTC Pearls
  - (needs a subscription)
- **CONTACT ME!** Happy to try and help as a GP consult, or a GP conference.
  - Email: rita.mccracken@ubc.ca

Polypharmacy References, page 1

(to support the "polypharmacy lit review in one slide" slide)

1. Sera LC, McPherson ML. Pharmacokinetics and pharmacodynamic changes associated with aging and implications for drug therapy. Clin Geriatr Med. 2012;28(2):273-86.
2. Jyrkka J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Polypharmacy status as an indicator of mortality in an elderly population. Drugs Aging. 2009;26(12):1039-48.
3. Therapeutics-Initiative. Reducing polypharmacy: A logical approach. Therapeutics Initiative Letter [Internet]. 2014; (90).
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Rita McCracken

Polypharmacy References, page 2

(to support the "polypharmacy lit review in one slide" slide)

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The Test Answers.

Learning Objective # 1 Review

Describe state of literature/evidence regarding prescribing to frail elders.

What I said:

- RCT's usually exclude frail elders.
- Guidelines are based on RCT's and expert opinion.
- Polypharmacy is well described as a concern, but there is also no RCT evidence of its harm.
- Everyone thinks we need more research that includes frail elders.
  - (I am trying to do this)

Learning Objective # 2

Understand how frailty is a prognostic signpost and helpful in de-prescribing decisions.

What I said:

- Ken Rockwood's Frailty Scale is easy to use.
- We should apply it to all older patients, and monitor shifts.
- Frailty is an indicator of "MULTI SYSTEM FAILURE" and time for us to really start focusing on the person as a whole, for the time they have left.

Learning Objective #3 Review

Review a 4 Step process to de-prescribing.

What I said:

1. Check the patient
2. Make a list of all meds with indication and target
3. Identify drugs to stop or decrease.
4. Decrease by ½ for 7-14 days and reassess often.

(I also mentioned it was harder than it sounds and that you have to communicate A LOT with your patient)

Launette Rieb

What to do when pain stops you from being able to leap tall buildings?

Launette Rieb, MSc, MD, CCFP, CCSAM, FCFP, dip ABAM
Clinical Associate Professor, Dept. of Family Practice, UBC

Best Medicine Conference April 17, 2015 - Vancouver, BC, Canada

Faculty/Presenter Disclosure

- Faculty: Launette Rieb
- Relationship with commercial interests:
  - No commercial interests

Disclosure of Commercial Support

- No financial support or in-kind support for this program
- No potential conflicts of interest for Dr. Rieb

Mitigating Potential Bias

- There is no bias to mitigate

Learning Objectives

- Review evidence for medications used to treat persistent pain
- Reflect on key points of the Canadian opioid guidelines for chronic non-cancer pain
- Point out evidence on non-pharmacological pain treatments

Acetaminophen for Osteoarthritis Cochrane Review (Towheed, 2006)

- 15 studies, 6000 people, 4g/d vs placebo
- Less pain (when resting, moving, sleeping and overall) and felt better overall than people who took a placebo, modest effect size
- In OA subjects with moderate-to-severe levels of pain, NSAIDs appear to be more effective than acetaminophen
- Trial duration only 6 weeks
- Long term studies needed

Launette Rieb

Topical NSAIDs for chronic musculoskeletal pain. Cochrane Review (Derry, 2012)

- Topical NSAIDs can provide good levels of pain relief; topical diclofenac solution is equivalent to that of oral NSAIDs in knee and hand osteoarthritis
- There is no evidence for other chronic painful conditions
- Formulation can influence efficacy
- The incidence of local adverse events is increased with topical NSAIDs, but gastrointestinal adverse events are reduced compared with oral NSAIDs

Antidepressants for neuropathic pain, Cochrane Review (Saarto, 2007, 2012)

- Limited evidence for the role of SSRIs
- Both TCAs and venlafaxine have NNTs = 3 for moderate pain relief
- There is evidence to suggest that other antidepressants may be effective but numbers of participants are insufficient to calculate robust NNTs
- SNRIs are generally better tolerated by patients than TCAs

Clonazepam for neuropathic pain and fibromyalgia in adults. Cochrane Review (Corrigan, 2013)

- This review uncovered no evidence of sufficient quality to support the use of clonazepam in chronic neuropathic pain or fibromyalgia

Antipsychotics for acute & chronic pain. Cochrane Review (Seidel 2013)

- 11 studies, 770 pts
- Significant reduction in pain (NNT=2.6) after administration of the new antipsychotic compared to placebo or another medicine
- Results were based on small studies and heterogeneous, therefore may be unreliable
- Consider unwanted effects
- Antipsychotics might be used as an add-on therapy in the treatment of painful conditions.

Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews (Wiffen, 2013)

- Only for **gabapentin and pregabalin** - evidence that they worked in long-term nerve pain with painful diabetic neuropathy and postherpetic neuralgia
- **Pregabalin** had evidence of efficacy in central neuropathic pain (typically pain after stroke) and in fibromyalgia.
- NNT = 4-10 for 50% reduction in
- S/Es could not be tolerated in 1 in 4 - so they stopped taking
- Serious side effects were no more common with antiepileptic drugs than with a harmless placebo
- Evidence of lack of effect for lacosamide and lamotrigine, insufficient evidence for the other anitiepileptic drugs

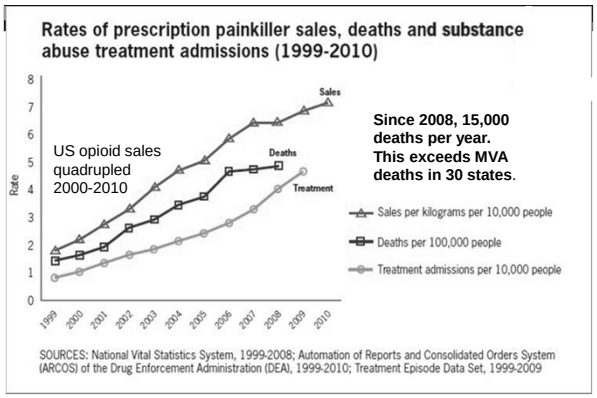
Neuropathic Pain - CPS

- Moulin et al. Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society. Pain Res Manag vol 19 No 6; Nov-Dec, 2014

- 1st line: TCAs, SNRIs, gabapentinoids
- 2nd line: tramadol, weak opioids
- 3rd line: cannabinoids (oromucal nabiximols)
- 4th line: methadone, strong opioids

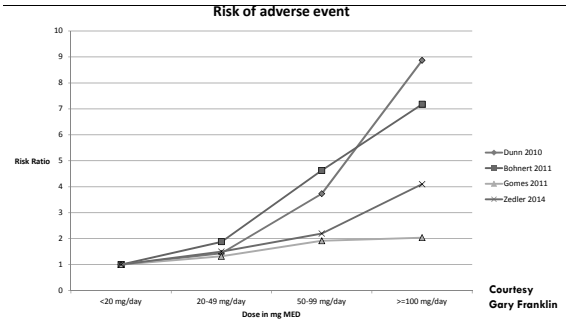
Muscle Relaxants

- Leite et al. **Cyclobenzaprine** for the treatment of myofascial pain in adults. Cochrane Database 2009 and May 16, 2012
- There was **insufficient** evidence to support the use of cyclobenzaprine in the treatment of MP
- We identified only two small studies in which a total of 35 participants were given cyclobenzaprine, and it was not possible to estimate risks for benefits or harms



Slide courtesy Mark Sullivan

Dose-related risk of opioid overdose



Opioid Abuse, Addiction, Misuse: Dose-Dependent Effect

- One fair-quality study of a large claim databased found long-term prescribed opioid use (>90 days' supply) associated with increased risk of an opioid abuse or dependence diagnosis vs. no opioid treatment
  - Low dose (1-36 mg MED/day): OR 15 (95% CI 10 to 21)
  - Moderate dose (36-120 mg MED/day): OR 29 (95% CI 20 to 41)
  - **High dose (≥120 mg MED/day): OR 122** (95% CI 73 to 206) *(Edlund, 2014)*

Evidence on effectiveness of LOT for chronic non-cancer pain

- Short-term efficacy
  - 62 RCT's in one recent meta-analysis, duration <16 weeks in 61 (Furlan, 2011)
  - Opioids more effective than placebo for nociceptive and neuropathic pain (effect sizes 0.55-0.60)
  - Maximum dose ≤180 mg MED/day in all trials except for 3
- Long-term effectiveness
  - Cochrane review included 26 studies >6 months (Nobel 2010)
  - 25 studies case series or uncontrolled long-term trial continuations
  - Many discontinuations due to adverse effects (23%) or insufficient pain relief (10%), but some evidence that patients who continue on opioids experience long-term pain relief

Other limitations of the evidence on effectiveness of LOT

- Effects on function generally smaller than effects on pain, with some trials showing no or minimal benefit
- High loss to follow-up
- Trials typically excluded patients at higher risk for abuse or misuse, psychological comorbidities, and serious medical comorbidities
- Limited evidence on commonly treated conditions
  - Low back pain, fibromyalgia, headache, others
- No trials compared LOT vs. CBT-based exercise therapy or interdisciplinary rehabilitation

Launette Rieb

Opioids … for chronic low-back pain. Cochrane Review (Chaparro 2013)

- 15 trials which included 5540 participants
- More pain relief and fxn in short term
- No information from RCTs supporting the efficacy and safety of opioids used for more than four months
- The **current literature does not support that opioids are more effective than other groups of analgesics** for LBP such as anti-inflammatories or antidepressants

Opioid Use Guidelines (Furlan, 2010; Chou 2009)

- Do complete hx + px, DDx, screen – SUD,MDD
- Opioid Manager, Pharmanet, UDS, contract
- **Watchful Dose** CND+AAPM **= 200 mg MEDD**
- WSBC + Washington state **= 120 mg MEDD**
- Establish realistic expectations
  - Only 1 in 4 pts with CNCP get relief from opioids
  - **2/10 drop is a successful result** – do not chase up the dose past one or 2 increases without benefit
  - Function must change for prescribing to continue

Oxycodone for neuropathic pain and fibromyalgia. Cochrane Review (Gaskell 2014)

- Oxycodone was not convincingly shown to help relieve the pain (very low quality evidence)
- Compared with placebo, fewer people stopped taking oxycodone because they felt it was not effective, but more people experienced adverse effects (very low quality evidence)
- Oxycodone has not been shown to work as a pain medicine in diabetic neuropathy or postherpetic neuralgia. No studies have examined its use in other types of neuropathic pain, or in fibromyalgia

Methadone for chronic non-cancer pain. Cochrane Review (Haroutiunian 2012)

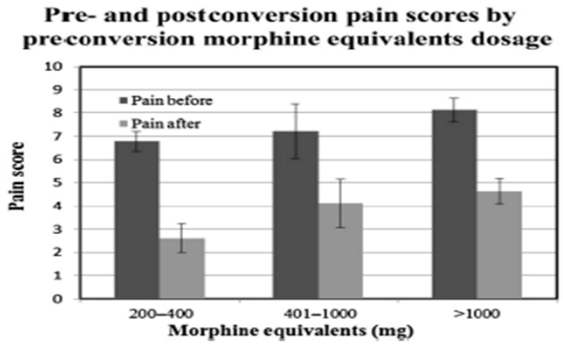
- 3 studies provide very limited evidence of the efficacy of methadone for CNCP
- Too few data for pooled analysis of efficacy or harm, or to have confidence in the results of the individual studies
- No conclusions can be made regarding differences in efficacy or safety between methadone and placebo, other opioids, or other treatments

Bup/nx and Pain

Pain Medicine 2014; *: **–**
Wiley Periodicals, Inc.

Conversion from High-Dose Full-Opioid Agonists to Sublingual Buprenorphine Reduces Pain Scores and Improves Quality of Life for Chronic Pain Patients Daitch D et al. Pain Medicine. 2014

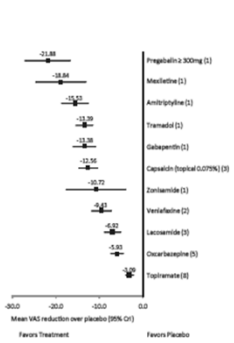
Retrospective chart review of CNCP patients on over 200 MEDD
- converted from other opioids to bup/nx
- pain scores averaged 8/10 pre-conversion, 4/10 post conversion



Daitch D et al. Pain Medicine. 2014

Meds for Diabetic Neuropathy

(SNEDECOR. 2013)



Non-pharmacological Therapies Cochrane Reviews

- Psychological therapies – CBT
  - Mild-mod effect: depression, disability, +/- pain (Williams, 2012)
- Physical therapy –
- TENS – conflicting evidence (Khadilkar, 2008)
- Prolotherapy – Not effective alone, unclear with co-interventions (Dagenaise 2007)
- Spinal manipulation for CLBP – no better/worse than tx like PT/exercise, unclear compared to sham (Rubinstein 2011)
- Massage – Beneficial, especially combined with stretching and education (Furlan 2008)

Medications are a fantastic tool, but if they are not working…

- Review the diagnosis – Repeat Hx/Px
- Tolerance, opioid induced hyperalgesia, substance dependence or diversion?
- Screen for depression, anxiety, and PTSD
- Explore perception of disability & meaning
- Consider somatoform disorders
- Avoid iatrogenic pain and suffering

Harmony

Sunyata

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Launette Rieb

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- Franklin et al, Am J Industrial Med 2011
- Some slides courtesy of Roger Chou – used with permission

G. Michael Allan

A Healthy Examination of the Periodic Health Exam: The Dos and Do Not Dos

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Faculty/Presenter Disclosure

- **Faculty/Presenter:** G Michael Allan
- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** None

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

- **This program has received financial support from** None **in the form of** nothing.
- **This program has received in-kind support from** None **in the form of** nothing.
- **Potential for conflict(s) of interest:**
  - Not Applicable

CFPC CoI Templates: Slide 3

Mitigating Potential Bias

- Not Applicable

26th Annual Best Science Medicine Course

Learning Outcome Objective Slide

Provide at least one learning objective.

PHE Talk

1) Identify patient & doctor expectations in the PHE
2) Explain what the PHE has shown to do or not do.
3) Discuss the broader implications (like opportunity costs)
4) Based on the best available evidence:
   1) Review what is recommended for the PHE
   2) Review what is not recommended on the PHE

What do patients want?

- 62% want a PHE (older research – 90%)
- Almost all (>90%) want diet, exercise, smoking talk
  - Two thirds want to talk about sexual health or seatbelts

Physical	Percent
BP	99%
Heart & Lung	99%
Reflex testing	95%
Abdominal exam	93%
Prostate exam	91%
Breast Exam	89%
Pap smear	78%

Test	Percent
Urinalysis	50-78%
Cholesterol	63-92%
Glucose	43-89%
PSA	67-90%
FOB	44-58%
Mammogram	68-71%
Pap	75%

Ann Intern Med. 2002;136:652-659.J Fam Pract. 1984 Aug;19(2):191-5.

G. Michael Allan

What do doctors think?

- Survey of 783 US Primary care doctors (47% of 1679)
- 65% felt PHE necessary & 78% felt wanted by pts
- PHE improves the Doctor-Patient relationship 94%

- 74% felt PHE detected subclinical disease
- 63% felt PHE had proven value

Include	Percent
Glucose	46%
Lipid Panel	48%
CBC	39%
Urinalysis	44%
TSH	21%
ECG	6%

Arch Intern Med. 2005;165:1347-1352

Is there time Preventive Services?

- Following US Preventive Task Force Based on Patient for big panel (2500),….
  - 7.4 hours a day.
  - Even smaller panel like ~1250, would still be half a work-day ever day.

1) Am J Public Health. 2003;93(4):635-41.

Potential Harms of Screening

1. Over-diagnosis,
2. Overtreatment,
3. Distress or injury from invasive follow-up tests,
4. Distress due to false positive test results,
5. False reassurance due to false negative test results,
6. Possible continuation of adverse health behaviours due to reassuring test results,
7. Adverse psychosocial effects due to labeling,
8. Difficulties with getting insurance.

BMJ 2012;345:e7191

How are we doing,…?

55 y.o. healthy woman Tests ordered by Colorado MD	
Test	**% Ordered**
CBC	67%
Urinalysis	55%
TSH	57%
ECG	30%

55 y.o. healthy woman Tests ordered by Canadian FM Residents	
Test	**% Ordered**
CBC	77%
Urinalysis	30%
TSH	48%
ECG	19%
Bone Mineral Density	32%

Templates no better

Am J Prev Med 2007;32(1):59–62. & Fung et al, Can Fam Physician 2014 in-press.

Does the PHE work?

- 3 systematic reviews have looked at this
- Best: 14 RCT (182,880pts), x1-22 yrs
  - Good methods, good description of studies, etc.
- Result: Total mortality Risk Ratio 0.99 (0.95-1.03)
  - CVD mortality: 1.03 (0.91-1.17)
  - Cancer mortality: 1.01 (0.92-1.12)
  - Other outcomes (e.g. CVD): No better.
- So, General Internal Med (US) "Choose Wisely" state "Don't Perform Routine General Health Checks for Asymptomatic Adults." (Rec #2)

BMJ 2012;345:e7191. http://www.choosingwisely.org/doctor-patient-lists/society-of-general-internal-medicine/

Is the research believable?

- Lots of issues:[1]
  - Half had only 1 round of screening,
  - ≥80% cholesterol screening but ⅔ too old for statins
  - Only ~20% had Cancer screening.
- Other studies: 2 Systematic review
  - What's Good: PAP, Colon Ca screen, & Cholesterol (?)[2]
  - Reduced "High risk" markers, few statistically significant
    - Tot Chol (0.63, 0.50-0.79) & DBP (0.63, 0.53-0.74)[3]
- Bottom-Line: Still not great, research does not mirror practice but not clear that absolutely does not work.

1) BMJ 2012;345:e7191 2) Ann Intern Med. 2007;146:289-300. 3) Health Care Financ Rev. 1999;20(4):25-43.

G. Michael Allan

Summing up: General PHE

1) PHE research has not been great and it is not clear it works or does not work.
2) There are risks to screening & it takes a lot of time.
3) Patients want "Annual Physical" with lots of Px/tests
4) Most doctors want to do PHEs and we frequently over order

- Bottom-Line: If you are going to do PHEs, focus on what works, find some common-ground with patients, minimize extra tests.

Physical Exam DO: BP & PAP

DON'T

- Pelvic Exam (ovarian Ca)
- Abdominal Exam (Pancreatic Ca, AAA or hepatosplenomegaly)
- Thyroid Exam (Thyroid Ca)
- Testicular Exam (Testicular Ca)
- Lung Auscultation (COPD)
- Carotid Auscultation (Stenosis)
- Peripheral pulses
- Lymph node palpation
- Reflexes / sensation testing
- Spine mobility

Insufficient evidence

- Oral exam
- Screening hearing loss >50yrs
- Whole body skin exam
- Eye exam for visual loss/ glaucoma.
- DRE (prostate or colon)
- Breast Exam
- Heart Auscultation (mixed one yes valvular disease another no)

Bloomfield HE, Wilt TJ. Evidence Brief: Role of the Annual Comprehensive Physical Examination in the Asymptomatic Adult, VA-ESP Project #09-009;; 2011.

Do

- Hypertension (CHEP): Whenever is "appropriate"[1]
- Lipids: Age 40 q 5 yrs, non-fasting. Do Risk Assess.[2]
  - CCV: age 40 in males, 50 in females. q 1-3 years[3]
- Sugar (CDA): Age 40 (likely A1c) q 3 yrs[4]
  - Task force: if high risk of DM q3-5 yrs, if very high q yr[5]
- BMD: OST (wgt - years) = if >5, low risk[6]
  - (CO CPG) Age 65 all, Consider from 50 onward if at risk?[7]

1) https://www.hypertension.ca/en/chep 2) Unpublished Alberta Simplified Lipid Pathway. 3) Can J Cardiol. 2013;29(2):151-67. 4) Can J Diabetes. 2013;37 Suppl 1:S12-5. 5) http://canadiantaskforce.ca/ctfphc-guidelines/2012-type-2-diabetes/ 6) TFP #44 March 21, 2011. http://www.fpnotebook.com/ 7) CMAJ. 2010 Nov 23;182(17):1864-73.

Do

- Cervical cancer (TOP): age 21, after 3 normal in 5 yrs, then q3 years[1]
  - Task force: Age 25, q3 years to Age 69.[2]
- Breast Cancer (Task force): Mammogram age 50 q 2 years (to 74)[3]
  - Breast exam (task force): Don't do
- Colon Cancer (TOP): FIT soon q 1-2 year. Age 50 - 74

1) http://www.topalbertadoctors.org/download/578/Cervical%20cancer%20summary%20nov%202811.pdf & 2) http://canadiantaskforce.ca/ctfphc-guidelines/2013-cervical-cancer/ 3) http://www.topalbertadoctors.org/download/301/colorectal_summary.pdf

New or controversial

- AAA (US Task force & TFP): U/S once for male ever-smokers, age 65-75.[1]
- Lung Cancer (US Task force): Low-dose CT q1yr 55-80, with 30 pack yrs (unless ex-smoker x 15yrs).[2]
  - TFP: No
- Prostate Cancer (TOP)[3]: discuss age 50. If screening PSA +/- DRE q1-2 yrs, stop if <10 yrs life expect

1) http://www.uspreventiveservicestaskforce.org/uspstf/uspsaneu.htm & https://www.acfp.ca/wp-content/uploads/tools-for-practice/1397838891_20121015_093820.pdf 2) http://www.uspreventiveservicestaskforce.org/uspstf/uspslung.htm & https://www.acfp.ca/wp-content/uploads/tools-for-practice/1397839118_20121126_091132.pdf 3) http://www.topalbertadoctors.org/download/276/Prostate%20Cancer%20Guideline%20Eval%20&%20Referr.pdf

Last bits: Advice

- Lifestyle (US Task Force)
  - Ask abut smoking and encourage
  - Weight - Yes
  - If CVD risk increased, then diet and activity advice.
- Vitamin D and calcium
  - Unclear (US Task Force): Insufficient evidence.

1) Diet and activity: http://www.uspreventiveservicestaskforce.org/uspstf13/cvdhighrisk/cvdriskfinalrsfact.pdf
1) Tobacco: http://www.uspreventiveservicestaskforce.org/uspstf/uspstbac2.htm
2) http://www.uspreventiveservicestaskforce.org/uspstf/uspsvitd.htm

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Preventive test by Age: When to Start

Age	Males	Females
21/25+	Smoking	Smoking, PAP q 3 yrs
40	Lipid & Risk q5, Glucose q3-5, ? hypertension	Lipid & Risk q5, Glucose q3-5, ? hypertension
50	FIT q1-2 , PSA (?)	FIT q 1-2, Mammogram q2 OST (for BMD) q 5
65	OST (for BMD)	
70		STOP PAP
75	STOP FIT Lipid & Risk, likely PSA; Rest unclear	STOP FIT, Mammo, Lipid & Risk; Rest unclear

DON'T: Seven Deadly (PHE) Sins

1) Review of Systems (mike's rule)
2) Screen for depression (or virtual anything)
3) Urinalysis, CBC, LFT, creatinine, any biomarker, etc
4) Chest x-ray, ECG, virtual anything
5) Cholesterol or sugar in "young" (<40) healthy
6) Other time wasters: like Waist circumference.
   - Or even mention metabolic syndrome.
7) Don't recommend Vitamins, ASA, low salt, etc.

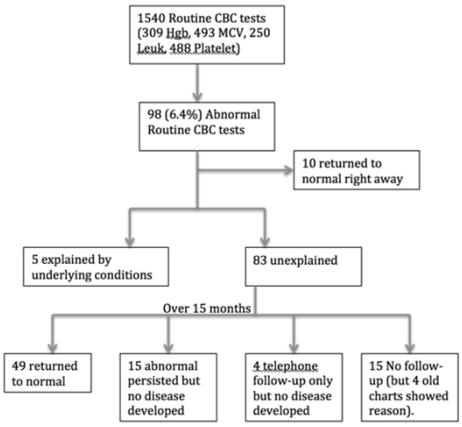
http://canadiantaskforce.ca/?content=pcp

CBC: an example of limits

- Community screening (+ long-term care) 8 studies[1]
  - 6.4-13.5% abnormal (~ ¾ mildly abnormal)
    - 1 study institutional elderly (age 83) =30% abnormal
  - <2% management change (mostly iron def)
  - 0-0.09% something serious
- Pre-op & Admission screening x 9 studies[2]
  - Overall 0.8% to 3.0% abnormal
  - 0-1.9% changed management.
  - Small African study admission 38% abnormal, 1.9% change

1) BMJ 1967;4:714-717. JAMA 1983: 249:633-636. Lancet 1980; 1: 552. Ann Intern Med 1992; 116:44-50. Am J Med. 1996; 101: 142-152 Am J med Sci 1995;309(4): 194-200. Am J Public Health 1985; 75: 243-245 JAMA. 1983; 249:633-6. 2) four studies from Health Technology Assessment 2012; Vol. 16: No. 50 . J Gen Intern Med 1987;2:373- 6. Postgrad Med J 1989: 65:525-7 N. S Afr Med J 1997;87:734-7 JAMA 1985; 253: 3576-81 JAMA 1984;252: 231-234.

Figure 1 (of Ruttimann, Ann Intern Med 1992; 116:44-50.)



Case 1: Christine Robbin

- A 38 year old female with BMI of 25. Otherwise well
  - What history do you want?
- Family history: None Cancer or Heart Disease. & She has never had any screening. Smoking
- What would you do in an exam?
  - What would you order?

Case 2: Winnie Pooh

- A 55 year old male with a BMI of 31. Otherwise well.
  - What history do you want?
- Family history: None Cancer or Heart Disease. & He has never had any screening. Smoking
- What would you do in an exam?
  - What would you order?

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Case 3: Tigra Bounce

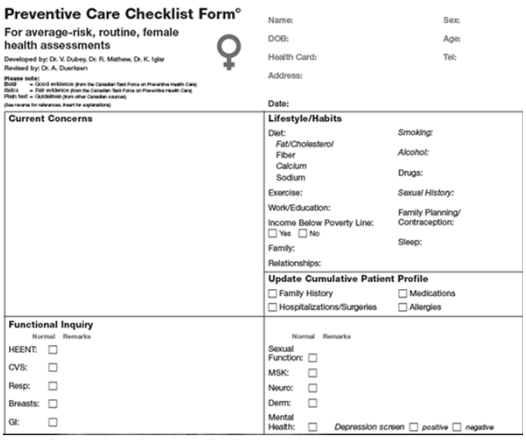
- A 72 year old female with a BMI of 31. Otherwise well. On Ramipril and Chlorthalidone.
  - What history do you want?
- Family history (?): None Cancer or Heart Disease. & She has had regular screening. Non-Smoker

- What would you do in an exam?
  - What would you order?

RESOURCES

- College of Family Physicians of Canada
- Toward Optimized Practice
- Task Force:
  - Screening for DM
  - Discussion tools
- Tools for Practice
- Risk calculators:

Can College Fam Phys



Preventive Care Checklist Form©

For average-risk, routine, female health assessments

Developed by: Dr. V. Dubey, Dr. R. Mathew, Dr. K. Iglar
Revised by: Dr. A. Duerksen

Please note:
Bold = Good evidence (from the Canadian Task Force on Preventive Health Care)
Italics = Fair evidence (from the Canadian Task Force on Preventive Health Care)
Plain text = Guidelines (from other Canadian sources)
(See reverse for references, insert for explanations)

Name: Sex:
DOB: Age:
Health Card: Tel:
Address:
Date:

Current Concerns

Lifestyle/Habits
Diet:
Fat/Cholesterol
Fiber
Calcium
Sodium
Exercise:
Work/Education:
Income Below Poverty Line: ☐ Yes ☐ No
Family:
Relationships:
Smoking:
Alcohol:
Drugs:
Sexual History:
Family Planning/ Contraception:
Sleep:

Update Cumulative Patient Profile
☐ Family History ☐ Medications
☐ Hospitalizations/Surgeries ☐ Allergies

Functional Inquiry

	Normal	Remarks
HEENT:	☐	
CVS:	☐	
Resp:	☐	
Breasts:	☐	
GI:	☐	
Sexual Function:	☐	
MSK:	☐	
Neuro:	☐	
Derm:	☐	
Mental Health:	☐	*Depression screen* ☐ *positive* ☐ *negative*

http://www.cfpc.ca/ProjectAssets/Templates/Resource.aspx?id=1184&langType=4105

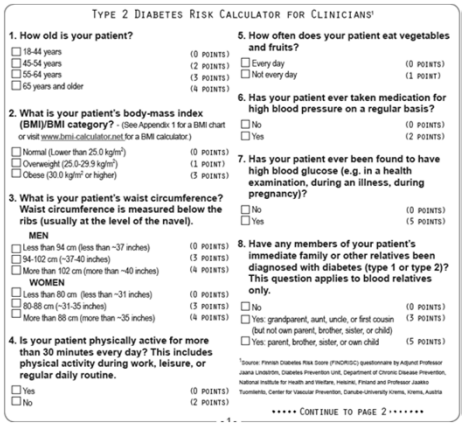
Please note:
Bold = Good evidence (from the Canadian Task Force on Preventive Health Care)
Italics = Fair evidence (from the Canadian Task Force on Preventive Health Care)
Plain text = Guidelines (from other Canadian sources)

≥ 65 years

- ☐ **Mammography** (50-69 yrs, q1-2)
- ☐ **Hemoccult Multiphase q1-2 years** (age 65-74)
  OR ☐ *Sigmoidoscopy* OR ☐ Colonoscopy
- ☐ *Audioscope (or inquire/whispered voice test)*
- ☐ Fasting Lipid Profile
- ☐ *Fasting Blood Glucose, at least q3 yrs (more often if at risk)*
- ☐ *Bone Mineral Density* (reassess risk in 1-3 yr if moderate risk, in 5 yr if low risk)

http://www.cfpc.ca/ProjectAssets/Templates/Resource.aspx?id=1184&langType=4105

Task Force & Diabetes



TYPE 2 DIABETES RISK CALCULATOR FOR CLINICIANS[1]

1. How old is your patient?
☐ 18-44 years (0 POINTS)
☐ 45-54 years (2 POINTS)
☐ 55-64 years (3 POINTS)
☐ 65 years and older (4 POINTS)

2. What is your patient's body-mass index (BMI)/BMI category? - (See Appendix 1 for a BMI chart or visit www.bmi-calculator.net for a BMI calculator.)
☐ Normal (Lower than 25.0 kg/m²) (0 POINTS)
☐ Overweight (25.0-29.9 kg/m²) (1 POINT)
☐ Obese (30.0 kg/m² or higher) (3 POINTS)

3. What is your patient's waist circumference? Waist circumference is measured below the ribs (usually at the level of the navel).
MEN
☐ Less than 94 cm (less than ~37 inches) (0 POINTS)
☐ 94-102 cm (~37-40 inches) (3 POINTS)
☐ More than 102 cm (more than ~40 inches) (4 POINTS)
WOMEN
☐ Less than 80 cm (less than ~31 inches) (0 POINTS)
☐ 80-88 cm (~31-35 inches) (3 POINTS)
☐ More than 88 cm (more than ~35 inches) (4 POINTS)

4. Is your patient physically active for more than 30 minutes every day? This includes physical activity during work, leisure, or regular daily routine.
☐ Yes (0 POINTS)
☐ No (2 POINTS)

5. How often does your patient eat vegetables and fruits?
☐ Every day (0 POINTS)
☐ Not every day (1 POINT)

6. Has your patient ever taken medication for high blood pressure on a regular basis?
☐ No (0 POINTS)
☐ Yes (2 POINTS)

7. Has your patient ever been found to have high blood glucose (e.g. in a health examination, during an illness, during pregnancy)?
☐ No (0 POINTS)
☐ Yes (5 POINTS)

8. Have any members of your patient's immediate family or other relatives been diagnosed with diabetes (type 1 or type 2)? This question applies to blood relatives only.
☐ No (0 POINTS)
☐ Yes: grandparent, aunt, uncle, or first cousin (but not own parent, brother, sister, or child) (3 POINTS)
☐ Yes: parent, brother, sister, or own child (5 POINTS)

[1]Source: Finnish Diabetes Risk Score (FINDRISC) questionnaire by Adjunct Professor Jaana Lindström, Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland and Professor Jaakko Tuomilehto, Center for Vascular Prevention, Danube-University Krems, Krems, Austria

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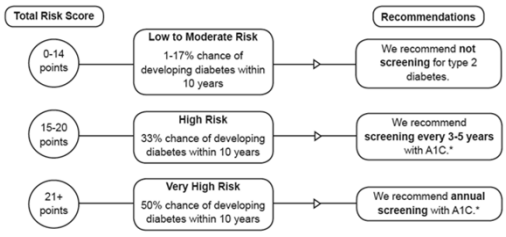
- 1 -

Screening for Diabetes



- Or CDA states: Screen every 3 years in individuals 40 years of age or in individuals at high risk using a risk calculator.

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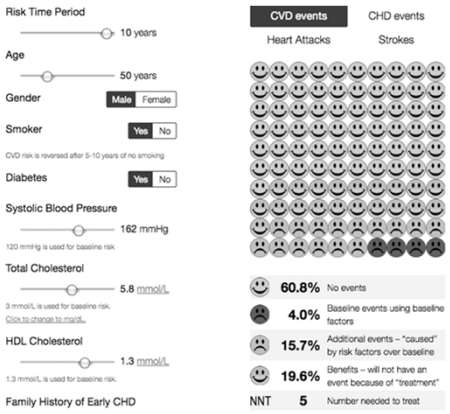
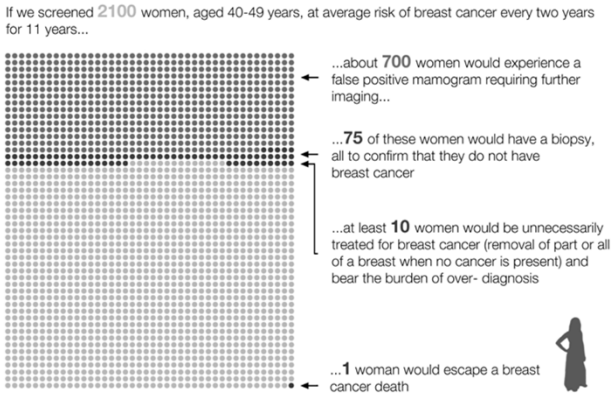
New Calculator with actual effects



http://bestsciencemedicine.com/chd/calc2.html

Patient Discussion Tools



Bonus Slides

- Cancer Screening Summary slides
- Benefits of Lifestyle info

Smoking Cessation

- Weekly counseling x 3 months +/- Bupropion/NRT
- Comparing intensive intervention vs usual
  - 2 yr continued abstinence 39% vs 9% (NNT 4)
    - Normal cessation rates in highest risk pts. is 9%
    - Even a low cessation rate (30%) is better than nothing!
  - Hospitalization 23% vs 41% (NNT 6)
  - Mortality 3% vs 12% (NNT 11)
- Other Studies find mortality reductions as well.

Chest 2007; 131: 446–52 Ann Intern Med. 2005;142:233-9.

Activity

- RCT 101 males (~61), stable angina
  - PCI single vessel vs Bike to 70% HR of Sx for 10 min/d x 2 wks, then 20 min/d + one 60 min/wk
- Exercise ↓ ischemic outcomes
  - RRR 61%, AR 18%, NNT 6, (At 50% cost).
- Similar to others:
  - Cochrane exercise review found 31% CAD mortality reduction & other papers find the same
  - In CHF over 10 years, Mortality down from 16% to 6%

Circulation 2004;109:1371-8. Cochrane 2011;(7):CD001800. J Am Coll Cardiol 2012;60:1521–8.

Lifestyle

	Countries	Risk	CVD	Mortality
Lancet 1994	France	Secondary (MI within 6 months)	0.27 (0.12-0.59)	0.30 (0.11-0.82)
Lancet 2002	Northern India	Mixed (≥ 1 risks (BP, Chol, DM), or angina or MI)*	0.50 (0.34-0.73)	0.63 (not sign, p=0.064)
N Engl J Med 2013	Spain	Primary (had DM or 3 risks: smoking, BP, LDL, HDL, wgt, family Hx)	0.70 (0.55–0.89)	0.89 (0.71–1.12)

Lancet 1994; 343: 1454-59. Lancet 2002;360(9344):1455-61 N Engl J Med 2013;368:1279-90.

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Prostate Cancer Screening:

Time	Number Needed to Screen	Number benefiting per 1000 screened	Number Needed to Treat
9 yrs	1410	0.7	48
14 yrs	293	3.4	12

- Positive PSA (<10ng/ml) are 70% false positive
- False +ve: "worry about prostate cancer" 1 yr (26% vs 6%)
- Biopsy: 7.5% pain, 3% Antibiotic, 0.5% hospitalization,
- Approximate Harms of Treatment
  - For every prostate Ca death prevented: 4 will have sexual function difficulties and 1 will have urinary incontinence.

Can Urol Assoc J. 2011 Dec;5(6):416-21.

Summary for mammography: risks and benefits over 10 to 16y

		Risks and benefits per million women screened for 10-16 years		
	NNS to prevent one BrCa death	BrCa deaths prevented	Unnecessary biopsies	Unnecessary mastectomy
40 – 49 y	2108	474	36,000	5,000-10,000**
50 – 69 y	721	1387	37,000	
70 – 74 y	451*	2218*	26,000	

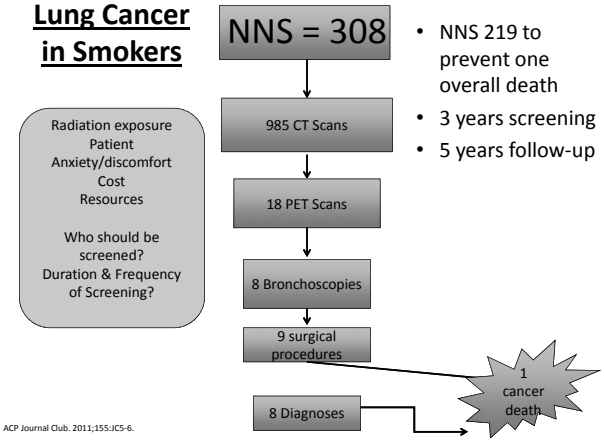
- **Ontario Cohort Data**: CBE detected Breast Ca in an additional 4/10 000 women (missed by mammogram)[1]
  - 219 additional false positives

Does screening for CRC make a Difference?

- FOBT:
  - ~1200 x 10 years to prevent 1 CRC death[1,2]
- Flex sigmoid[3]:
  - ~200 x 11 yrs to prevent 1 CRC
  - ~500 x 11 years to prevent 1 CRC death
- Colonoscopy: no data to show prevents CRC death
- 10,000 patients screened x 10 years with FOBT
  - 9 fewer CRC deaths, 2800 colonoscopies, ~2 perforations

[1] Towler, Cochrane 1998; [2]Hewitson, Cochrane 2007: CD001216 [3] Lancet 2010;375:1624–33

Lung Cancer in Smokers



- NNS 219 to prevent one overall death
- 3 years screening
- 5 years follow-up

ACP Journal Club. 2011;155:JC5-6.

Launette Rieb

Medical Marijuana - Flame-On!

Launette Rieb
MD, MSc, CCFP, FCFP, dip ABAM
Clinical Associate Professor, UBC
Best Medicine Conference 2015

Faculty/Presenter Disclosure

- Faculty: Launette Rieb
- Relationship with commercial interests:
  - No commercial interests

Disclosure of Commercial Support

- No financial support or in-kind support for this program
- No potential conflicts of interest for Dr. Rieb

Mitigating Potential Bias

- There is no bias to mitigate due to commercial interest
- Any "bias" I may have comes from treating thousands of people with addiction and pain conditions

Learning objectives

- Summarize adverse health risks
- Overview literature on cannabinoids for medical use, focus on pain
- Review new CFPC guidelines for dried cannabis "prescribing" including indications, contraindications

Cannabinoids

- **Nabilone** (Cessemet) – synthetic delta 9 THC
  - Dosing 0.25 - 4mg/d divided tid to qid
  - Does not show up on urine drug screen
  - Approved in Canada: Chemotherapy induced N+V
- **Nabiximols** (Sativex) – plant extract of delta-9-tetrahydrocannabinol 2.7 mg and cannabidiol 2.5 mg in an oromucosal spray
  - Dosing 1-12 buccal sprays/d divided tid to qid
  - Approved in Canada for advanced cancer pain, MS associated pain and spasticity

Cannabiniods, cont'd

- **Dronabinol** (Marinol) delta-9-THC
  - 2.5-20 mg/d in divided dosing tid to qid
  - Approved in Canada: For chemotherapy induced N+V, and for anorexia associated with HIV/AIDS
- **Ingested marijuana**
  - Usually about 1/3 more than smoked, baked
  - Harder to titrate than smoked, but longer lasting
- **Smoked marijuana = "dried cannabis"**
  - Patients' use huge range – few puffs to many grams/d
  - This is why guidelines have been developed
  - Health Canada exemption, many states in US have marijuana for medical purposes exemptions

Pharmacokinetics

- **Inhalation**
  - Peak effect 10-30 min, duration 2-3+ h
- **Oral Ingestion**
  - Peak effect 1-2 h, duration 4-6+ h
  - First pass hepatic metabolism
- Highest [THC] found in heart & fat
- Metabolism by cytochrome P450
- Half-life 2-60 h
- Excretion 1/3 urinary, 2/3 fecal
- **UDS**: Single use 5-7 d, chronic use 45+ d

Adverse Health Reactions

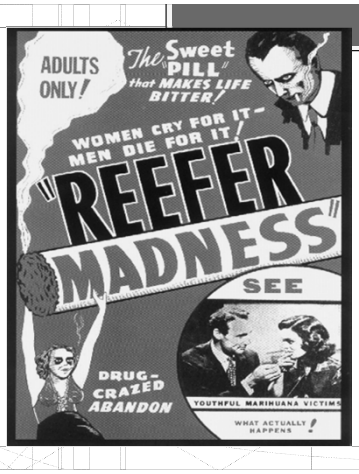
Acute

- Dry mouth, conjunctival injection
- ↓BP, ↑HR, arrhythmias
- Decreased exercise time to onset of **angina** (Aronow, 1974)
- Attention, motivation, **memory**, false novelty, paranoia, derealization, hallucinations
- THC ↑**anxiety**, acute psychosis; CBD may ↓anxiety (Fusar-Poli 2009)
- Altered depth perception, coordination, **driving impairment** (Robbe, 1998)

Adverse Health Reactions

Chronic

- ↑Risk of **COPD** (Tan, 2009)
- ↑Risk of **lung CA**: 1 joint/d = 1 PPD tobacco (Aldington, 2008)
- **Brain changes**: Heavy daily users 5+ joints/d:↓hippocampal and amygdala volume (Yucel, 2008)
- Lowers **IQ**: If initiation prior to age 18 - IQ does not recover when detoxed; if adult initiation, can normalize REF
- ↑Risk of **psychotic disorder** - dose dependent, age dependent, genetically influenced (VM=2x, VV=10x), CBD may be protective (Andereasson 1987, and Zammit 2002, Henquet 1995, Caspri, 2005)
- **Hormonal effects** – ↓testosterone, LH and FSH
- ↑Risk of cannabis use disorder = **addiction**
- ↑Risk of **diversion**



Estimated Relative Risk of Death from Illicit Drugs

Opioids	14.7
Cocaine	4.7-7.6
Amphetamines	6.2
Cannabis	1

(Dagenhardt & Hall, 2012)

Note: Cannabis deaths likely underestimated (e.g. motor vehicle accidents & respiratory disease)

Launette Rieb

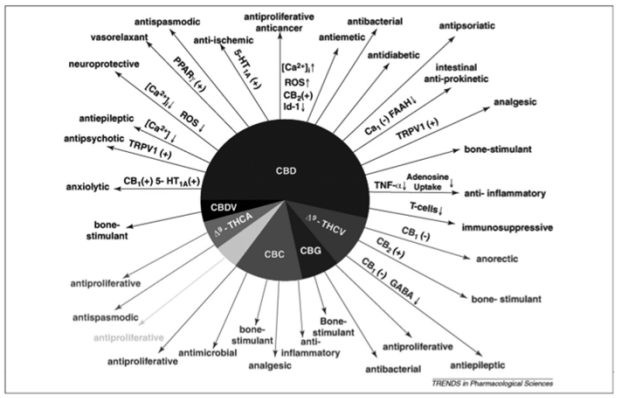


Figure 1. Pharmacological actions of non-psychotropic cannabinoids (with the indication of the proposed mechanisms of action). Abbreviations: Δ^9-THC, Δ^9-tetrahydrocannabinol; Δ^8-THC, Δ^8-tetrahydrocannabinol; CBN, cannabinol; CBD, cannabidiol; Δ^9-THCV, Δ^9-tetrahydrocannabivarin; CBC, cannabichromene; CBG, cannabigerol; Δ^9-THCA, Δ^9-tetrahydrocannabinolic acid; CBDA, cannabidiolic acid; TRPV1, transient receptor potential vanilloid type 1; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; 5-HT$_{1A}$, 5-hydroxytryptamine receptor subtype 1A; FAAH, fatty acid amide hydrolase. (+), direct or indirect activation; ↑, increase; ↓, decrease.

Potential Medical Uses

- Antiemetic: Effective chemo N+V; rebound N +V
- Appetite stimulant in HIV/AIDS: evidence "lacking" on Cochrane Review (Lutage 2014)
- Antispasmodic for MS: Reduced spasticity with oral whole plant extract(Wade 2010)
- Anticonvulsant: Small controlled trials - not effective, anecdotal evidence of help
- Glaucoma: Modest ↓ intraocular pressure of short duration (2-4 h), followed by rebound hypertension. Chronic use leads to tolerance of IOP effect (Jones et al,1981)
  - Topical synthetic cannabinoids may decrease IOP (Porcella, 2001)

Analgesia

Possible mechanism:

- Amygdala activity contributes to the dissociative effect of cannabis on pain perception (Lee, 2013)

Systematic Review and Meta-analysis of Cannabis Treatment for Chronic Pain

- Martin-Sanchez et al. Pain Medicine Vol 10 (8) 2009: 1353-1368
- Double blind RCTs comparing any cannabis preparation to placebo in pts with chronic pain (>6mo) published to Feb 2008
- 18 studies included

Meta-analysis of cannabis for CP

- Baseline=0, scale: -10 to +10
- Efficacy -0.61 SMD (-0.84 to -0.37), modest
- Altered perception OR: 4.51, NNH: 7
- Altered motor fxn, OR: 3.93, NNH: 5
- Altered cognitive fxn, OR: 4.46, NNH: 8
- **"Beneficial effects may be partially (or completely) offset by potentially serious harms"**

Cannabis and Prescribed Opioids

- Reisfield et al. Pain Medicine Vol 10 (8) 2009: 1434-1441
  - Analysis of published studies on patients using opioids for CNCP that looked at aberrant drug related behavior and UDS results:
  - Cannabis use is prevalent: 6.2 - 39% in pain pop.
  - Cannabis use - Significant association with present and future **aberrant opioid related behaviors** – diversion, cocaine in UDS, prescription forgery, no opioid in UDS
  - **6x** more likely to have the above behaviors than someone on opioids not using cannabis

Launette Rieb

Neuropathic Pain - Review

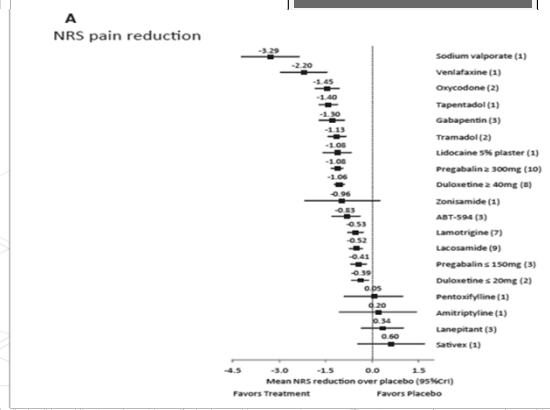
- Lynch, 2011 – looked at studies from 2003-2010
- Systematic review of RCTs on cannabinioids for CNCP
- 80 reviewed, 18 meet PRISM criteria (15 neuropathic), 766 people combined
- "Overall there is evidence that cannabinoids are safe and **modestly effective in neuropathic pain** with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis"

Neuropathic Pain - CPS

- Moulin et al. Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society. 2014
- 1st line: TCAs, SNRIs, gabapentinoids
- 2nd line: tramadol, weak opioids
- **3rd line: cannabinoids – oromucal nabiximols**
  - Note: Did **not** recommend smoked cannabis
- 4th line: methadone, strong opioids

Diabetic Neuropathy

- Snedecor et al. Systematic Review and Meta-Analysis of Pharmacological Therapies for Painful Diabetic Peripheral Neuropathy. 2014
- Oro-mucosal **nabiximols** (Sativex) scored worse than placebo for pain relief



So what is the evidence for smoked cannabis?

- 5 RCTs on smoked cannabis
- Total subjects = 180
- Duration range 3-15 days
- Subjects had severe neuropathic pain from MS or HIV or other causes
- The trials compared smoked cannabis to placebo, not to other treatments or to oral cannabis
- One trial that compared smoked cannabis to dronabinol
  - dronabinol had a longer duration of analgesia

Dried Cannabis Guidelines from College of Family Physicians of Canada (CFPC):

- Kahan M, et al. 2014
- Disclaimer: Dried cannabis differs from prescribed products in that Health Canada has not reviewed data on its safety or effectiveness and has not approved it for therapeutic use. CMA and CMPA does not endorse its use. "Prescribe" with discretion or not at all.

Launette Rieb

Indications for smoked cannabis

- **Severe neuropathic pain,** not responding to other treatments including oral cannabinoids
- NOT indicated for MSK pain

Recommendation 3

- Dried cannabis is not an appropriate therapy for anxiety or insomnia (Level II)

Recommendation 4

Dried cannabis is not appropriate for patients who:

- a) Are under the age of 25 (Level II)
- b) Have a personal history or strong family history of psychosis (Level II)
- c) Have a current or past cannabis use disorder (Level III)
- d) Have an active substance use disorder (Level III)
- e) Have cardiovascular disease (angina, peripheral vascular disease,
- cerebrovascular disease, arrhythmias) (Level III)
- f) Have respiratory disease (Level III) or
- g) Are pregnant, planning to become pregnant, or breastfeeding (Level II)

Recommendation 5

Authorized *with caution* in those patients who:

- a) Have a concurrent active mood or anxiety disorder (Level II)
- b) Smoke tobacco (Level II)
- c) Have risk factors for cardiovascular disease (Level III) or
- d) Are heavy users of alcohol or taking high doses of opioids or benzodiazepines or other sedating medications prescribed or available over the counter (Level III)

Recommendation 8

Before signing a medical document authorizing dried cannabis for pain:

a) Conduct a **pain assessment** (Level II)
b) Assess the patient for **anxiety** and **mood disorders** (Level II)
c) Screen (including urine drug screen) and assess the patient for **substance use disorders** (Level II)

Recommendation 10

- **Patients taking dried cannabis should be advised not to drive for at least:**

a) 4 hours after inhalation (Level II)
b) 6 hours after oral ingestion (Level II)
c) 8 hours after inhalation or oral ingestion if the patient experiences euphoria(Level II)

Launette Rieb

Harm Reduction Advice

- Use **vaporizer** instead of joint or pipe
  - Much lower levels of carbon monoxide
- **Don't mix with tobacco**
- Caution with alcohol, opioids, and other drugs
- Don't breath hold
- Caution with edibles

****Dosing****

- Start with 1 inhalation before bed, go slow
- **Maximum** "script" (document) typically should specify dose, percent THC, days, amount:
- **"Dried cannabis 500 mg/day, 9% THC maximum, for 30 days, dispense 15 g"**
- Not clear if producers have to honor 9% THC direction but important to list

Average joint = 0.5 gm

Monitoring

- **See patient – weekly** to biweekly until dose established
- **Then monthly** monitoring x three to six months before visits every 1- 3 months
- Include an **agreement**, monitor for psychiatric symptoms, cannabis use disorder, functional changes
- Do **random urine drug screens** for THC and other addictive substances

Discontinuation

Taper off

- If no functional benefit is derived
- If impaired in the office
- If psychotic symptoms appear
- If driving under the influence
- If safety sensitive work or play impaired
- If diverting

Launette Rieb

Thanks

- Questions?

References

Key

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- Elizabeth E Lutge[1,2,*], Andy Gray[3], Nandi Siegfried[4]**The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS.** Editorial Group: Cochrane HIV/AIDS Group, Published Online: 30 APR 2013. Assessed as up-to-date: 30 JUL 2012 DOI: 10.1002/14651858.CD005175.pub3

Launette Rieb

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Tina Korownyk

Asthma

(If you can't breathe, it really doesn't matter what other superpowers you have)

Tina Korownyk

Faculty/Presenter Disclosure

- **Faculty/Presenter:** Tina Korownyk
- **Relationships with commercial interests:**
  - **Grants/Research Support:** I have received funding from non-profit sources such as the Alberta College of Family Physicians, Alberta Primary care networks and the College of Family Physicians Canada
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** None

CFPC CoI Templates: Slide 3

Disclosure of Commercial Support

- **None**
- **Potential for conflict(s) of interest:**
- None

Mitigating Potential Bias

N/A

Objectives

To review evidence for asthma management including

Inhaled corticosteroids, Long acting beta-agonists, Leukotriene receptor antagonists, and newer agents.

1st Line Treatment Anti-Leukotrienes vs ICS

- Sys rev, 56 RCTs (19 Pediatric), mild-mod asthma
- Results: ICS superior
  - NNT ICS to prevent 1 exacerbation (oral steroids) = 28
  - Those receiving LTRA had 3x ↑ risk of being hospitalized for exacerbation
  - ICS ↑ FEV_1, ↑% symptom free days, ↓ symptoms, ↓ night–time awakenings, ↓rescue β-agonist use.
- No difference kids vs adults
- Difference more impressive for moderate asthma

Cochrane Database Systematic Rev 2012 May 16;5:CD002314

Tina Korownyk

Double The Dose, Double the Benefit?

2 RCTs:

- 1) 390 pts, mean 49 yrs, asthma, on 100-2000ug corticosteroid /day
- Randomized to 2nd puffer (double the dose or placebo) with ↓ PEF/↑ symptom scores.

Outcomes: no difference in need for po prednisolone, peak flow or sx scores

- 2) 290 pts, no benefit with doubling dose of inhaled steroids.

Lancet. 2004;363:271-5. Thorax. 2004 Jul;59(7):550-6.

Quadruple the dose!

- 403 pts with asthma
- Instructed to use additional inhaler (placebo or 4x corticosteroid dose) when FEV fell by 15-30%
- Number requiring PO corticosteroids (tx vs placebo):
  - ITT: 9% vs 14% RR 0.64 (0.37-1.11)
  - PP: 21% vs 50% RR 0.43 CI 0.24-0.78
    - NNT = 4
- Cochrane: self initiated ICS increase not associated with statistically significant reduction in risk of exacerbations.

Am J Respir Crit Care Med. 2009 Oct 1;180(7):598-602. Cochrane Database Syst Rev. 2010 Dec 8;(12):CD007524.

Suboptimal Control with ICS
Increase ICS vs LABA

- Sys Rev 48 RCTs, 15 155pts
- LABA + ICS 400ug vs ICS ~1000ug/d
- LABA + ICS:
- ↓exacerbations, NNT = 73
  - No diff a/es (RR 0.99)
    - ↑ risk tremor RR 1.84 (1.20 to 2.82)
    - ↓oral thrush RR 0.58 (0.40 to 0.86)
- **Peds**: 3 RCTs, trend ↑ risk
  - Exacerbation RR 1.24 (0.58 to 2.66),
  - Hospital admission RR 2.21 (0.74 to 6.64)

Cochrane Database Syst Rev. 2010 Apr 14;(4):CD005533

Suboptimal Control with ICS
LABA vs Placebo

- Systematic Review, 77 RCTs, 21 248 pts[1]
- Low-dose ICS (200-400 ug/d beclo or equiv) + LABA vs placebo
- LABA ↓ exacerbations from 15% to 11%, NNT =41
  - Range 17-435 depending on baseline CER
- Also ↓SABA use, ↑ FEV(1), ↑symptom free days
- Not sign in children RR 0.89 (0.58-1.39)

Peds: (25 rcts, 5572 pts)[2]

- No diff exacerbations RR 0.92 (0.60 to 1.40)
- No diff symptom-free days, hospital admission, quality of life, use of reliever medication, and adverse events

1) Cochrane Database Syst Rev. 2010 May 12;(5):CD005535. 2) Cochrane Database Syst Rev. 2009 Jul 8:(3):CD007949.

Suboptimal Control with ICS
LABA vs LTRA

- 18 RCTs, 8 contributed to 1° outcome (n=6257)
  - 1 included children (n=334)
  - ICS + either LABA or LTRA
- ICS/LABA: ↓exacerbations RR 0.87 (0.76 - 0.99)
  NNT = 62
  - Single inhaler combination RR=0.64 (0.45 to 0.91)
  - Two separate inhalers RR=1.06 (0.80 to 1.41)
- **Peds:** Not significant RR 0.84 (0.53 -1.34)

Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta-agonists versus anti-leukotrienes for chronic asthma. Cochrane Database Syst Rev 2014;1:CD003137.

Suboptimal control with ICS
Pediatrics & LTRAs

- RCTs, children 1-18yrs, symptomatic on ICS, randomized to ICS + LTRA or ICS
- 4 RCTs (559 children), > 6yrs
- No difference exacerbations LTRA +ICS vs ICS
  - RR 0.8 (0.34-1.91)
- No difference exacerbations (RR 0.82) or hospitalizations in trial comparing LTRA + ICS vs higher doses ICS
- No data on preschoolers
- Bottom Line: Data does not support addition of LTRAs to ICS in pediatrics

Cochrane Database Syst Rev. 2013 Oct 2;10:CD009585

Tina Korownyk

Single Inhaler Therapy
(formoterol & budesonide)

Cochrane systematic review:

- 13 RCTs, (SIT vs steroids + separate LABA)
  - 13 152 patients, all industry sponsored
- No difference hospital admission
- Single inhaler therapy:
  - ↓ exacerbations requiring oral corticosteroids: NNT = 90
  - ↓ daily dose ICS (107 to 385 µg/day).
  - More likely to have withdrawals due to adverse events (OR 2.85)
  - ↓ corticosteroids used in peds, annual height gain 1 cm greater
- Limits: not blinded, unknown adherence in best practice arm

Cochrane Database Syst Rev. 2013 Apr 30;4:CD007313.

LABA the Difference!

- **Salmeterol**: slow onset bronchodilation, not recommended for reliever therapy
  - (Advair: salmeterol & fluticasone)
- **Formoterol**: fast onset, recommended for reliever therapy
  - (Symbicort: formoterol & budesonide)
- Cochrane Systematic Review, 5 RCTs, Symbicort vs Advair.[1] No difference in exacerbations, hospitalizations, serious events or other outcomes
- Safety in Adults: Review of Reviews[2]
  - 89 RCTs, 61 366 adults
  - Absolute increase mortality 3/10 000
  - (For MONOTHERAPY absolute increase 7/10 000)

1) Cochrane Database Syst Rev. 2011 Dec 7;(12):CD004106. 2) Cochrane Database Syst Rev. 2014 Feb 6;2:CD010314.

Single Inhaler Therapy
Maintenance & Relief

- Is SIT effective & safe as both maintenance & reliever?
- Sys Rev, 4 RCTs, 9130 pts, mean 636 to 888 ug/d
- SIT vs combination inhalers + SABA
  - Ie budesonide/formoterol 160/4.5 bid
  - fluticasone/salmeterol 500/50 µg bid
- SIT: ↓ ER visits/hospitalizations NNT = 100
  - ↓exacerbations requiring oral steroids NNT = 50
  - No diff serious adverse events OR 0.92 (0.74, 1.13)
- Limitations: 2 not blinded, selective reporting, all industry funded

Cochrane Database Syst Rev. 2013 Dec 16;12:CD009019.

Who's on First?

	Intervention	Comparator	NNT
First Line	ICS	LTRA	28
	LABA		C/I, non sign increase mortality Formoterol OR 4.49 Salmeterol OR 1.33
Second Line (Add to ICS)	Increase ICS (quadruple)	Placebo	4*
	LABA	Placebo	41 (17-435)**
	LABA	LTRA	62
	LABA	Increase ICS	73
Single Inhaler Therapy	Single Inhaler Therapy for Maintenance & Relief	Maintenance Combo + SABA	50

Pediatrics

	Intervention	Comparator	NNT
First Line	ICS	LTRA	28
	LABA		C/I
	LTRA		No evidence ↓exacerbations or hospitalizations
Second Line (Add to ICS)	LABA	Placebo	No sign benefit RR 0.92 (0.60 to 1.40) (Additional 3/1000 Serious a/es)[1]
	LABA	LTRA	No sign difference RR 0.84 (0.53 -1.34)
	LABA	Increase ICS	Trend for ↑ exacerbation RR 1.24 (0.58 to 2.66), hospital admission RR 2.21 (0.74 to 6.64) with LABA
	LTRA	Placebo or increase ICS*	No sign difference RR 0.8 (0.34-1.91)

Cochrane Database Syst Rev. 2012 Oct 17;10:CD010005.

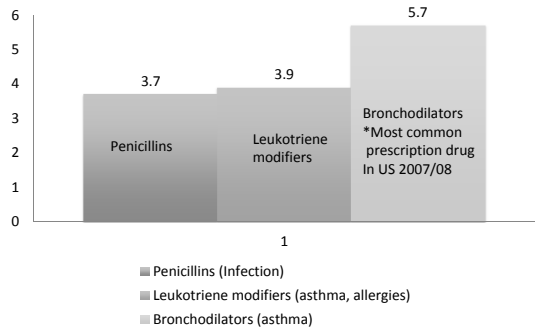
GINA GUIDELINES 2014

- For persistent symptoms/exacerbations despite low dose ICS:
- For adults and adolescents:
  - **ICS/long-acting beta2-agonist (LABA).**
- For adults and adolescents, risk of exacerbations reduced with
  - **ICS/formoterol (beclometasone or budesonide) as both maintenance and reliever**
- For children 6–11 years:
  - **Increasing ICS dose preferred over combination ICS/LABA.**

http://www.ginasthma.org/local/uploads/files/GINA_Report_2014_Aug12.pdf

Tina Korownyk

% of Prescription Drugs used most often Children aged 0-11yrs



http://www.cdc.gov/nchs/data/databriefs/db42.htm

Will I still make the basketball team?

Asthma & ICS on Growth

- CAMP RCT, 1041 children, asthma 4-7yrs duration[2]
- Mean height upon entry: 56 %ile[1]
- At follow up (24.9yrs)
  - Mean dose budesonide = 636mg/day
  - Mean adult height 1.2cm lower, similar to that after 1st 2 yrs
- Sys Rev 25 RCTs, 8471 children[3]
  - Daily ICS (vs Non-ICS) reduced change in baseline height
  - MD -0.61 cm/y
- Sys Rev, Higher dose ICS =greater decrease in growth velocity[4]
  - No diff between molecules (ciclesonide, fluticasone, mometasone)
  - lack of / incomplete reporting of growth velocity in 86% trials

1) J Pediatr 2003;142:286-91. 2) N Engl J Med 2012;367:904-12.3) Evid Based Child Health. 2014 Dec;9(4):829-930 4) Evid Based Child Health. 2014 Dec;9(4):931-1046.

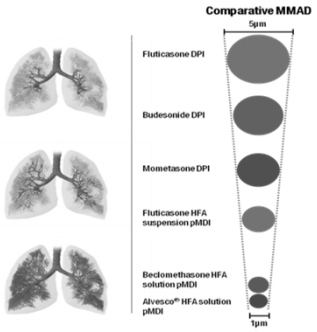
What do you think of New?

- 48 patients - usual brand of ventolin™ replaced for one week with a “new” puffer
- New was actually the same

New was Better	New was Worse	No Difference
46%	27%	27%

Journal of Generic Medicines 2005;2:201–8

Ciclesonide



- In theory – smaller particles, less systemic absorption, less adrenal and growth suppression

Ciclesonide

- Systematic Review, 6 RCTs, 3256 children (4-17 yrs)
  - vs budesonide, fluticasone but not beclomethasone
- Demonstrates “non-inferiority" of ciclesonide, no diff adverse events
- Surrogate endpoint: FEV1 at 12- 24 weeks.
- No assessment of exacerbations/hospitalizations

Kramer S, Rottier BL, Scholten RJPM, Boluyt N. Ciclesonide versus other inhaled corticosteroids for chronic asthma in children. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD010352.

Vitamin D

- RCT 408 pts with Vit D <30ng/ml, 9 US Centres
- Oral vitamin D3 (100,000 IU once, then 4000 IU/d for 28 weeks) or placebo + ciclesonide (320 µg/d).
- Outcome: NO difference in time to treatment failure or exacerbation over 28 wks (28% vs 29%) HR 0.9 CI 0.6-1.3
- Bottom Line: No benefit with Vit D supplementation, even in those with LOW vit D levels.

JAMA. 2014 May;311(20):2083-91.

Val Montessori

What if Peter Parker had been Bitten by a Tick Instead of a Spider?
Lyme Disease

Val Montessori MD, FRCPC
Division of Infectious Diseases, St. Paul's Hospital
2015

Disclosure of Commercial Support

» **Valentina Montessori**
» **Relationships with commercial interests**
– **Speakers Bureau/Honoraria: Pfizer (vaccines)**

Learning Objective

» Become familiar with the current Infectious Disease Society of America Guidelines for the Diagnosis and Treatment of Lyme Disease
» Review the epidemiology of Lyme Disease in British Columbia

Overview

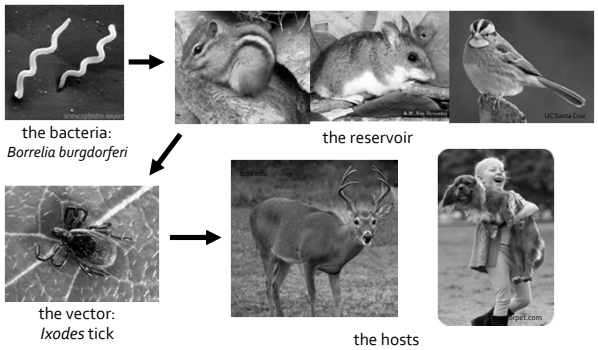
- Review the epidemiology of Lyme Disease in North America
- Review the clinical presentation of Lyme Disease
- Discuss the diagnosis and diagnostic dilemmas
- Discuss the treatment of Lyme and the role of antibiotics at each stage of disease

US CDC Press Release (August 19, 2013):

- 30,000 cases annually reported
- Three studies to enhance surveillance:
  – Medical insurance claims: 22 million people annually x 6 years
  – Survey of clinical labs
  – Survey of general public: self-reported disease
- True incidence ~ 300,000 cases per year
- 96% of cases in 13 North East and Midwest states

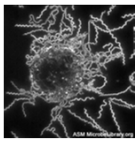
Most common vector-borne disease in Europe and North America

Lyme Disease: The main players



Val Montessori

Borrelia burgdorferi is very complex!

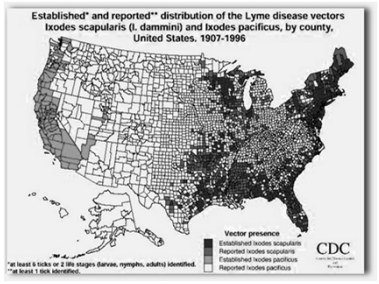


- More plasmids than any other bacteria[1]
  - many genes related to pathogenicity are on plasmids
  - 90% of genes are specific to *Borrelia*
- Genetic recombination → diverse population within the host
- Large number of lipoproteins with variable expression in response to:
  - Temperature, pH, population density, host factors[2]
- Immune system evasion and chronic infection
  - Tick saliva inhibits host phagocyte function, complement and Tcell response[1]
  - Host antibodies target the dominant phenotype while spirochetes down regulate those antigens to survive[3]
  - Can bind large host proteins in multiple tissues and immune protected sites: decorin, fibronectin, integrin[1]

[1]Pal et al, Microbes and Infect 2003;[2]Hefty et al., Infect Immunity 2002;[3]Liang et al., J Exp Med 2002

Ixodes in North America

Two main species:
- *I. scapularis* and *I. pacificus*



California Department of Public Health

Ixodes pacificus…

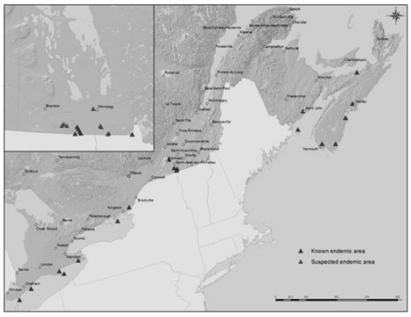
lower *Borrelia* infection rates
less abundant
feeds on reptiles > rodents

Determinants of *Ixodes* range

- Temperature: mean annual degree days > 0° C[1]
  - Affects adult mortality, larvae development and host finding
- Suitable habitat
  - Low-lying vegetation, leaf litter, water source
- Hosts: Deer mouse and White-tailed deer
  - Both abundant throughout Canada (except Newfoundland)
  - Deer populations > 7 per km² in Ontario and Quebec[2]
- Immigration
  - *Ixodes* ticks found on migratory birds, some infected with *B. burgdorferi*[3]
  - Billions of birds migrate through Canada annually

[1]Ogden N et al., Int J Parasitology 2005 ;[2]Ogden N et al., Int J Parasitology 2006;[3]Morshed M et al., J Parasitology 2005

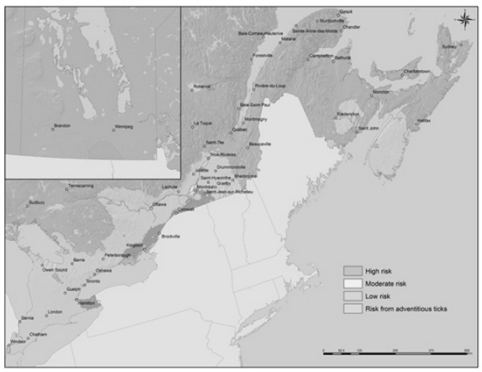
Known or Suspected Lyme endemic areas in Eastern and Central Canada



1. Endemic = all 3 stages (larvae, nymph, adult) are present on resident animals or in the environment for at least 2 years
2. Evidence that established ticks or reservoir hosts carry *B. burgdorferi*

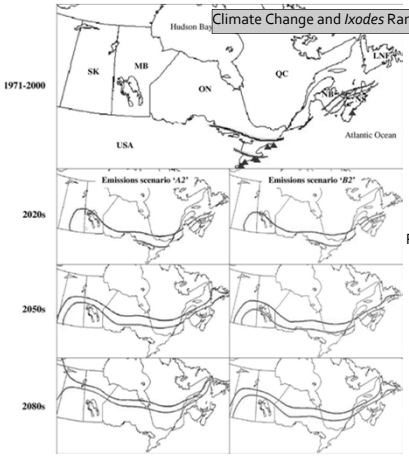
Public Health Agency of Canada, 2013

Areas at risk of becoming Lyme endemic areas in Eastern and Central Canada



Public Health Agency of Canada, 2013

Climate Change and *Ixodes* Range Expansion



▲ Current endemic *Ixodes scapularis* populations

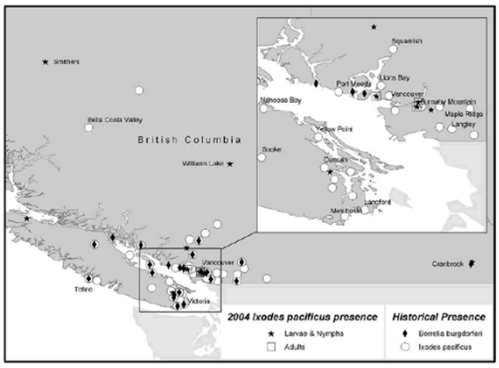
Less warming under B2

Red line = Great Lakes Cooling

Ogden N et al., Int J Parasitology 2006

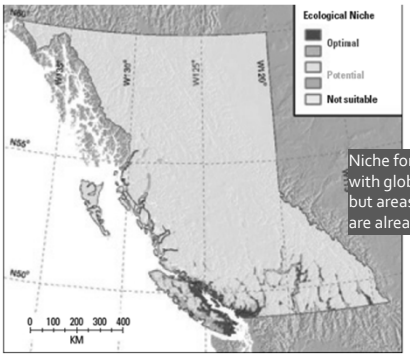
Val Montessori

What about BC?



Ecological niche modeling for areas at risk for Lyme Disease in BC

Henry B and Morshed M, BCMJ 2011



Niche for *Ixodes* may increase with global warming…
but areas with high populations are already affected

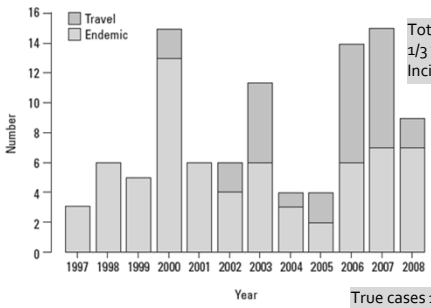
BC CDC Tick and Mouse Surveillance

- Tick density is low
  - 41 ticks found through active dragging at 17 sites on Vancouver Island → none infected
  - 115 ticks submitted from veterinarians on Vancouver and Gulf Islands → none infected
  - No *Ixodes* ticks found over 2 years in the Okanagan
- *Ixodes* infection rates are low and stable
  - 1993-1996: 10,056 ticks screened, 0.4% infected
  - 1997-2007: 8,602 tested, 0.35% infected
- Deer mouse infection rates are low
  - 164 mice tested for *B. burgdorferi* antibodies → 3.6% positive
  - 3500 mice tested by culture and PCR → 0.83% infected

Henry B and Morshed M, BCMJ 2011

BC CDC Human Surveillance

Number of endemic and travel-related cases of Lyme Disease in BC 1997-2008

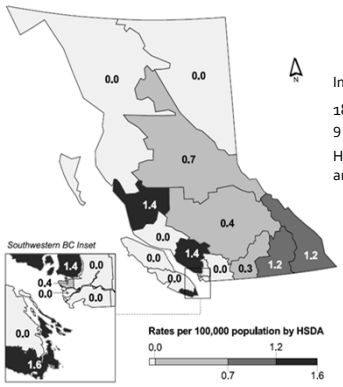


Total: 93 cases
1/3 travel-related
Incidence 0.1-0.3 per 10^5

True cases 142 (95% CI 111-224)
True incidence 0.5 per 10^5

Henry B and Morshed M, BCMJ 2011

31.2 Lyme Disease Rates by HSDA, 2012



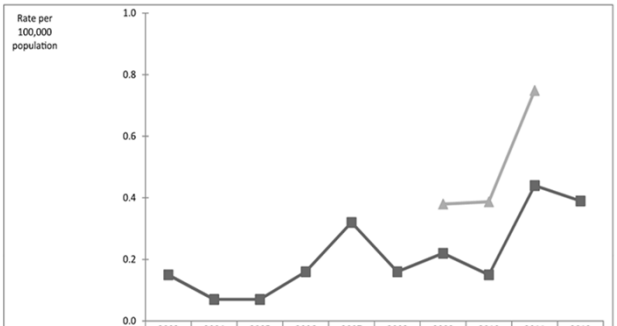
In 2012:

18 total cases (0.4 per 10^5)
9 likely travel-related

Highest rates: South Vancouver Island and North Shore/Coast Garibaldi

BC CDC Annual Summary of Reportable Diseases, 2012

31.1 Lyme Disease by Year, 2003-2012 BC CDC Annual Summary of Reportable Diseases, 2012



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
BC Lyme Reports	6	3	3	7	14	7	10	7	20	18
BC Lyme Rate	0.2	0.1	0.1	0.2	0.3	0.2	0.2	0.2	0.4	0.4
Canadian Lyme Rate							0.4	0.4	0.7	

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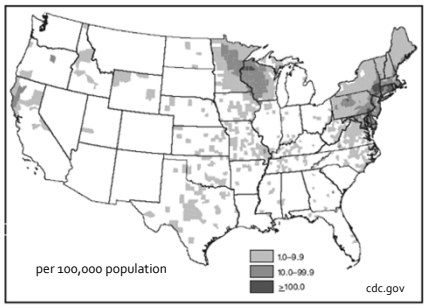
FIGURE 2. Average rate* of Lyme disease, by county of residence† — United States, 1992–2006§



In 2006…
Connecticut: 73.6 per 10^5
Columbia County, NY 962 per 10^5

Washington: 0.2 per 10^5
Oregon: 0.4 per 10^5
No change since 1992

"Acute Lyme Disease"

Stage 1: Acute
- Erythema migrans - single lesion
- Fever, chills, headache
- Migratory arthralgias
- Lymphadenopathy

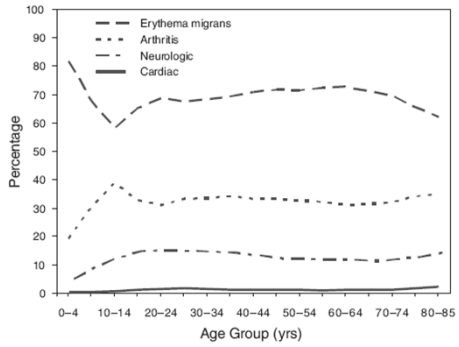
Stage 2: Early Disseminated:
1. Multiple EM
2. Neurological
   - Aseptic meningitis
   - Encephalopathy
   - Bell's palsy
   - Polyneuropathy
3. Cardiac
   - AV block
   - Acute myopericarditis

"Chronic Lyme Disease"

Months later…

Stage 3: Late Disseminated
1. Lyme arthritis
   - Chronic arthralgias
   - Joint effusion
2. Late neurological
   - Peripheral neuropathy
   - Encephalopathy

FIGURE 8. Percentage of symptoms reported among Lyme disease patients,* by age group — United States, 1992–2006



* N = 148,899.

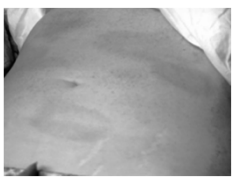
[1]MMWR 2008:Vol 57,#10

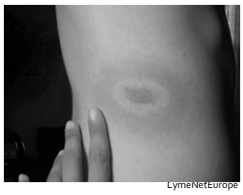
Erythema migrans

- Begins as red papule at site of tick bite
- Round or oval erythema expanding over days-weeks
  - Sensitivity of sign increases with diameter
  - At least 5 cm, can grow > 20 cm
  - Lasts up to 8 weeks
- Only 40% of lesions are classic "bulls-eye"
- Multiple lesions in 20%
- Rare: pain, vesicles, itching, swelling, scaling, ulceration
- Hypersensitivity to tick saliva
  - Erythema during tick attachment or within 48 hours of detachment
  - Lesion < 5 cm or that disappears in 24-48 hours

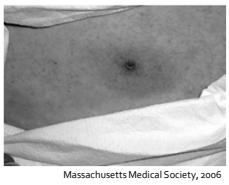
[1]US Centers for Disease Control;[2] Johns Hopkins Arthritis Center, 2012;[3]Canadian Communicable Disease Report, 2009

Erythema migrans

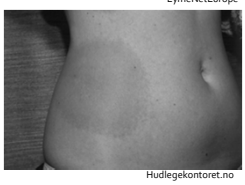




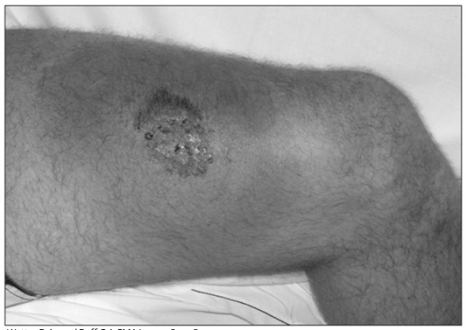
LymeNetEurope



Massachusetts Medical Society, 2006



Hudlegekontoret.no



Wetter D A , and Ruff C A CMAJ 2011;183:1281

CMAJ·JAMC

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Lyme Disease: Direct Diagnosis

- Problem: *Borrelia* few and transient in tissue and body fluids
- Culture:
  - EM skin biopsy: 60-88% sensitivity[2-4]
  - Blood culture only 40% sensitivity in early disease with EM lesion[5]
  - CSF and synovial fluid culture poorly sensitive[5,6]
- PCR
  - EM skin biopsy: 69% sensitivity[7]
  - Synovial fluid: 85% sensitivity[8]
  - Plasma: 44% sensitivity[4]
  - Combined plasma culture-PCR: 70% sensitivity[7]
  - CSF poorly sensitive[9]

Best direct tests = skin biopsy culture +/- PCR or synovial fluid PCR

[1]Berger et al., J Clin Micro 1992;[2]Iurca et al., CID 1998;[4]Liveris et al., Diag Micro ID 2012;[5]Aguero-Rosenfeld et al., ID Clinics NA 2008; [6]Karlsson et al, J Clin Micro 1990;[7]Wang et al., 2010;[8] Nocton et al., NEJM 1994 ;[9]Lebech et al. Mol Diag 2000

Lyme disease: Indirect Diagnosis

- Serology should take place *within the epidemiological and clinical context*
  - Has the patient had a tick exposure? Is Lyme disease endemic?
  - Do they have signs and symptoms consistent with Lyme Disease?

Guidelines for Serological Testing for Lyme Disease[1,2]

Lyme Disease Endemicity: incidence	Objective Clinical Signs and Symptoms	Pre-test probability	False Positive Rate	Testing
None or low: 0.01%	None	< 0.2	44%	Optional
Moderate: 0.1%	Present	0.2-0.8	16%	Yes
High: ≥ 1.0%	Present	> 0.8	5%	No

Classic EM rash is sufficient for Lyme diagnosis[3]

[1]Bunikis et al., Med Clin NA 2002;[2]Tugwell et al., Ann Int Med 1997;[3]IDSA Guidelines, CID 2006

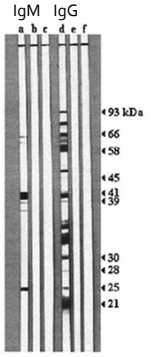
Serology

ELISA:

- Multiple tests using various whole cell or antigen combinations
- Sensitivity 40-60% in early infection → 90-100% in late disease[1-3]
- Specificity 70-90%: false positives in syphilis, EBV, lupus, *B. hermsii*[2,4]

Western Blot:

- IgM: at least 2 of 3 bands positive[5]
- IgG: at least 5 of 10 bands positive[5]
- Better sensitivity than ELISA in early infection[6,7]
  - IgG or IgM 54% in first week of EM
  - 80% by day 8-12 of antibiotic therapy
  - 59% one year post-treatment
- IgM sensitivity drops 30 days post-treatment[7]
- Specificity 92-94% but 100% if ELISA is positive first[6,7]



[1]Johnson et al., JID 1996;[2]Bunikis et al., Med Clin NA 2002;[5]Steere et al., CID 2008;[4]Henry et al., BCMJ 2011 [5]MMWR 44 (31),1995;[6]Johnson et al., JID 1996; [7]Engstrom et al., J Clin Micro 1995

Serology: Two-Step Approach

BC CDC Recommendations: Two-step approach

Step 1: ELISA → if negative repeat after 2-4 weeks
Step 2: Western Blot on ELISA + or indeterminate results

How good is the Two-Step? ➡ Sensitivity 75% and Specificity 99%[1]

Table 1. Sensitivity of two-test approach for serodiagnosis of Lyme disease: immunoblotting of samples positive or equivocal by FLA-ELISA.

Patient group	Sensitivity (%)	No. positive*/ total
Erythema migrans, all	64	37/58[†]
Culture-positive	56	24/43[†]
Localized infection (single skin lesion)	51	20/39
Disseminated infection (secondary skin lesion)	100	4/4
Culture not done	87	13/15
Localized infection (single skin lesion)	82	9/11
Disseminated infection (secondary skin lesion)	100	4/4
Early neurologic (meningitis/facial palsy)	100	3/3
Lyme arthritis[‡]	100	36/36
Late neurologic (encephalopathy/polyneuropathy)[§]	100	14/14
All specimens	81	90/111

Patient population:

- Lyme endemic areas
- EM: most culture +
- Neuro/joint: most with EM
- no previous serology

[1]Ledue et al., ASM 1996;[2]Johnson et al., JID 1996

Prospective Study of Serologic Tests for Lyme Disease

Steere et al., CID 2008

Variable	Proportion (%) of patients with positive result, by test(s)			
		Sonicate 2-test approach		
	VlsE C6 peptide ELISA	ELISA and Western blot IgM	ELISA and Western blot IgG	ELISA and Western blot IgM or IgG
Patients with Lyme disease				
Skin infection (stage 1)				
Erythema migrans without evidence of disseminated disease				
Acute	7/36 (19)	4/36 (11)[a]	2/36 (6)[b]	6/36 (17)
Convalescent, after antibiotics	17/36 (47)	14/36 (39)[a]	6/36 (17)[b]	19/36 (53)
Erythema migrans with evidence of disseminated disease[c]				
Acute phase	15/40 (38)	15/40 (38)[a]	6/40 (15)[b]	17/40 (43)
Convalescent phase (after receipt of antibiotics)	25/40 (63)	28/40 (70)[a]	8/40 (20)[b]	30/40 (75)
Disseminated infection (stage 2)				
Acute neurologic or cardiac involvement[d]	13/13 (100)	11/13 (85)	11/13 (85)	13/13 (100)
Persistent infection (stage 3)				
Arthritis or chronic neurologic involvement[e]	31/31 (100)	7/31 (23)	31/31 (100)	31/31 (100)

2013: C6 ELISA *alone* more sensitive than Two-Step in EM and early Neuro[1]

- EM: 66% sensitivity vs. 35%
- Early Neuro Disease: 88% sensitivity vs. 77%

[1]Wormser et al., Diag Micro and ID 2013

Problems with serology:

- It is imperfectly sensitive in early disease
- Antibiotic therapy may blunt the antibody response
  - 20-25% of patients with early treated disease never seroconvert[1,2]
- Serology can continue to be positive for decades[3]
  - Cannot use serology for test of cure
  - IgM in late disease more likely to be false positive[4]

Two-step serology in BC:

ELISA: VIDAS: 100% sensitivity when compared to WB+ samples[5]

Western Blot: MarDx

3000 samples per year → 90 +/indeterminate ELISA →
7-12 cases confirmed Lyme

[1]Aguero-Rosenfeld et al., J Clin Micro 1993;[2]Engstrom et al., J Clin Micro 1995;[3]Kalish et al., CID 2001; [4]Halperin et al., Am J Med 2013;[5]Jespersen et al., J Clin Epi 2002,[6]Henry et al., BCMJ 2011

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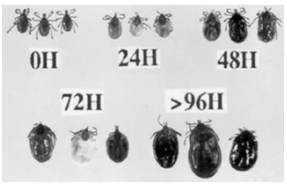
A Comparison of Lyme Disease Serologic Test Results From 4 Laboratories in Patients with Persistent Symptoms After Antibiotic Treatment

- Serum samples from 37 patients with post treatment Lyme syndrome and 40 health controls tested at 4 labs
- If standard 2 step testing used – no significant difference
- If own criteria then one private lab increased sensitivity, one decreased
- HOWEVER
- Steep decline in specificity

- 15/40 (37.5%) of normal volunteers met IgM criteria
- 11/40 (27.5%) met IgG criteria
- 23/40 (57.5%) met one or other

- Fallon et al, Clinical Infectious Diseases 2014; 59 (12): 1705-1710

IDSA Lyme Disease Practice Guidelines, 2006



R. Falco, IDSA 2006

- Prophylaxis after tick bite:
  - Doxycycline 200 mg single dose
  - Tick is *I. scapularis* that has been attached for ≥ 36 hours
  - Dose can be given within 72 hours of tick removal
  - Local rate of tick infection is ≥ 20%
- Early Lyme Disease: Erythema migrans
  - Doxycycline 100 mg BID x 14 days
  - Amoxicillin 500 mg TID x 14 days
  - Cefuroxime 500 mg BID x 14 days
  - Macrolides inferior – *use only if necessary*

IDSA Lyme Disease Practice Guidelines, 2006

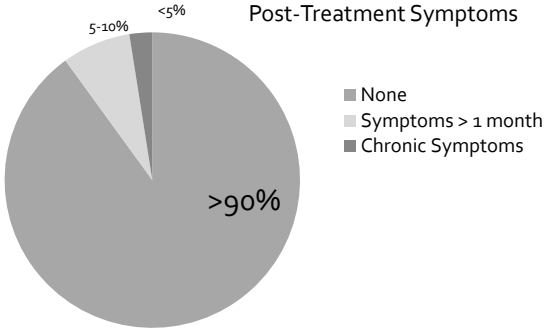
- Early Neurologic Lyme Disease
  - LP patients with suspicion of meningitis → if CSF normal treat as EM, if pleocytosis treat with:
    - Ceftriaxone 2g QD x 14 days
    - Alternatives: Cefotaxime or PCN G
    - B-lactam allergy: Doxycycline 200 mg BID x 28 days
- Early Lyme carditis
  - Admit for continuous heart monitoring
    - Symptomatic (dyspnea, chest pain, syncope)
    - 1st degree AVB with PR ≥ 30 msecs
    - 2nd or 3rd degree AVB → possible temporary pacemaker
  - Parenteral antibiotic with oral step-down to complete 14 days

IDSA Lyme Disease Practice Guidelines, 2006

- Late Lyme Arthritis
  - Oral antibiotics x 28 days
  - If persistent joint swelling → re-treat x 4 weeks with oral or IV
  - If no resolution and synovial fluid PCR negative → symptomatic management (NSAIDs, intra-articular steroids, rheum consult)
- Late Lyme Neurologic Disease
  - IV antibiotics x 4 weeks
- Post-Lyme Disease Syndrome: Symptoms persist after treatment
  - EM recurrence is extremely rare[1]
  - If meningitis recurs → re-treat with IV x 4 weeks
  - Extracutaneous Lyme Disease can resolve slowly
  - 10% of Lyme arthritis joint effusions can persist up to 4 years[2]

[1]Smith et al., Ann Int Med 2002;[2]Malawista, Inflammation 2000

Early Lyme Treatment is Very Successful!



Smith et al., Ann Int Med 2002;Steere et al., Ann Int Med 1983;Dattwyler et al., NEJM 1997;Massarotti et al., Am J Med 1992

Why do some patients with treated Lyme Disease still have symptoms?

- Dead antigen still produces an inflammatory response[1]
- Post-infectious immune phenomenon[2]
- There is a unrecognized co-infection
  - Babesiosis
  - Human Granulocytic Anaplasmosis
  - *B. miyamotoi*
- There is not a higher rate of complaints than in the general population[4]
- Borrelia is still alive but has down-regulated antigens or cloaked itself in biofilm or host antigens
  - Symptoms occur with new antigen expression or through dissociation from immune protected sites → clearance without need for antibiotics[1,2]

[1]Malawista, Inflammation 2000;[2]Craft et al., J Clin Invest 1986;[3]Steere et al., Nat Reviews 2004;[4]Wormser et al., CID 2006

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Does Borrelia persist after treatment?

PRO:

- Relapses occur rarely[1,2]
- New specific IgM and IgG responses late in disease[3]
- Biological evidence in animals[4-6]
- Embers et al, PLoS One 2012
  - Rhesus macques infected and treated post-dissemination
  - DNA and RNA recovered in brain and cardiac tissue
  - Positive xenodiagnosis

AGAINST:

- Synovial fluid and tissue is PCR negative and patients treated with immune modulators do not become PCR positive[7,8]
- No *Borrelia* has been detected by culture or PCR in 843 samples of humans with persistent symptoms after antibiotics[9,10]

[1]Steere et al., Arth and Rheum 1994;[2] Wormser et al., CID 2006;[3]Craft et al., J Clin Invest 1986;[4]Barthold et al., Antimicrob Agents Chemo 2010;
[5]Embers et al., PLoS One 2012;[6] Yrjanainen et al., Microbes Infect 2006; [7]Steere et al., Nat Reviews 2004;[8]Nocton et al., NEJM 1994;
[9]Klempner et al., NEJM 2001;[10]Klempre et al., Vector Bourne Zoo Dis 2002

Do antibiotics help with persistent symptoms?

- Longer courses of antibiotics *up front* do not improve response rates[1]

Randomized Double-blind Placebo Controlled Trials

	Patients	Intervention	Outcome	Adverse Event
Klempner et al., NEJM 2001	78 IgG + 51 IgG -	Ceftriaxone x 4 wks Doxycycline x 8 wks	Quality of life	25% treatment 17% placebo
Krupp et al., Neurology 2003	55	Ceftriaxone x 4 wks	Fatigue Cognition CSF OspA	2% treatment 5% placebo
Fallon et al., Neurology 2008	37 patients 20 controls	Ceftriaxone x 10 wks	Memory at wks 12 and 24	26% treatment 7% placebo

Conclusions:
•There is no strong evidence for antibiotic treatment
•Disability of patients with post-Lyme symptoms is significant

[1]Wormser et al., CID 2006

How can we manage patients with persistent symptoms?

Complex Chronic Diseases Program
BC Women's Health Centre

- Myalgic Encephalomyelitis
- Chronic Fatigue Syndrome
- Fibromyalgia Syndrome
- Lyme disease

Please use referral form on website!

Fax: 604-875-3738

www.bcwomens.ca/Services/HealthServices/complex-chronic-disease-program

Summary

- Rates of *B. burgdorferi* infection in tick and mouse populations are low in BC…but annual reporting likely *underestimates* the true number of cases
- *Ixodes* and *B. burgdorferi* surveillance is essential to identify endemic areas → supports clinical diagnosis and interpretation of serology
- Lyme disease in Canada is likely to increase with global warming, particularly in Eastern and Central Canada
- *B. burgdorferi* has adapted many mechanisms for host immune system evasion and may be able to survive antibiotics
- Antibiotics are very effective for treating early Lyme Disease… *but not for persistent symptoms*

A few more thoughts…

- We do not know why some patients have chronic symptoms post-treatment…but there is significant associated disability
- Serological diagnosis is imperfect, especially in acute disease
- Less than half of EM lesions will be "classic"…but if you see it treat it!

Thank You!

Mike Kolber

STI, HPV, GC, STD, BV – shielding us from the genital villains

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University of Alberta
Department of Family Medicine
Family Physician Peace River
DTC April 2015

Faculty/Presenter Disclosure

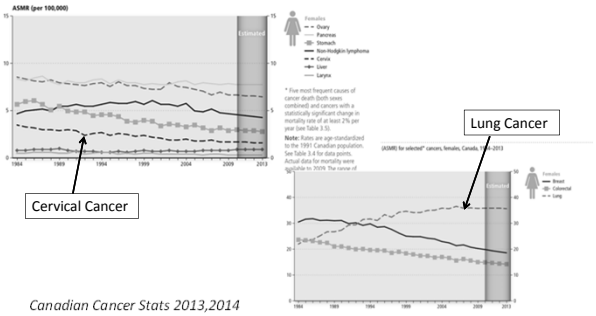
- **Faculty/Presenter(s): Michael R. Kolber**
- **Relationships with commercial interests:**
  - Pay from University of Alberta and Alberta Health
- Research and Speaking Fees
  - **Non-Profit Sources** (Alberta College of Family Physicians, Towards Optimized Practice)
  - **No funding from industry**

Objectives

- HPV vaccine evidence:
  - Benefits (warts and CIN)
  - Risks
- STI diagnosis
- Bacterial vaginosis: **3 Ds:**
  - **D**rugs
  - **D**uration
  - **D**e route: "mouth or south"

Cervical Cancer in Canada

- 1450 cases, 380 deaths / year



Canadian Cancer Stats 2013,2014

HPV and Cervical Neoplasia

- > 90% of cervical cancer have HPV (99% SCC)
  - 90% having 1 subtype (**~ 70%: 16 or 18**)

Table 1
Results from meta-analysis showing number of women tested for HPV and HPV16, number and percentage positive by cervical disease grade.

Grade of cervical disease	Number of women tested	Number of women HPV-positive	Percentage HPV-positive	Percentage HPV16-positive[a]
Normal cytology	266611	33154	12	20
ASCUS	12983	6810	52	23
LSIL	17805	13480	76	25
HSIL	7743	6616	85	48
CIN1	11043	8108	73	28
CIN2	4754	4068	86	40
CIN3	11618	10753	93	58
ICC	40679	36374	89	63

[a] Among HPV-positives.

Int. J. Cancer 2012: 131, 2349, NEJM 2003;348:518, Vaccine 2012; 30S: F12

Ano-Genital Warts (AGW)

- **~3-5% young adults**
- 90% associated **HPV 6,11**

BMC Infectious Diseases 2013, 13:39

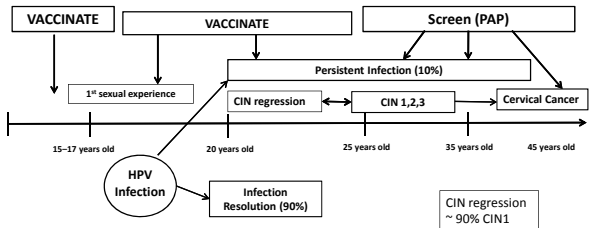
Mike Kolber

How quickly is HPV Transmitted?

- 444 HPV NEG US College ♀ q 4 months x ~ 3.5 yrs[1]
- Risk of getting HPV:
  - Sexually active → **50% become HPV POS @ 3 yrs**
- Always using condoms ↓ risk of trans (NSS)
  - Other studies: condom use inconsistently ↓ risk[2,3]

[1]*Winer, Am J Epidemiol* 2003;157:218, [2]J Inf Dis 2013;208:373, J Inf Dis 2012;205:1287

HPV to Cervical Cancer: Kolber simplified



Lancet 2007; 370: 890, Lancet 2004; 364: 1678, Int J Gyne Path 1993; 186, *Obstet Gynecol 2009;113:18–25*

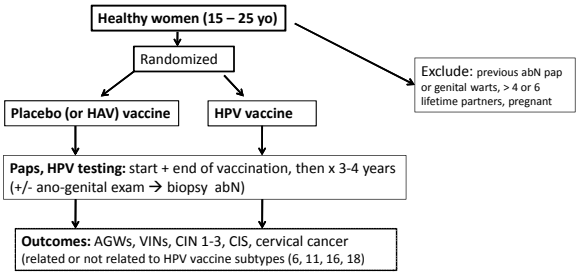
HPV vaccine recommendations

- Health Canada[1]:
  - Gardisil (6,11,16,18)
    - 2006: females 9 – 26 years old
    - 2010: **males 9 – 26 years old**
    - 2011**: females up to 45 years old**
  - Cervarix (16,18)
    - 2010: **females 10 – 25 years old**
- AHS: Sept. 2014: Grade 5 boys (Grade 9 catch up)[2]

Alberta Health Services

[1]NACI 2012 Update on HPV Vaccines; ISSN 1481: 8531
[2]www.immunizealberta.ca accessed Sept. 3, 2014

HPV Vaccine RCTs: study design



Per protocol analysis: **HPV NEG women**	**Intention to Treat: All COMERS (HPV POS or NEG)**
HPV NEG at start (+/- end), Received 3 doses	Women vaccinated ≥ 1
May only look at HPV vaccine subtypes	irrespective of baseline HPV status
= IDEAL CASE (Mimics vaccine programs)	**= CLINICAL PRACTICE (women not in vaccine program)**

3 large RCTs – 36,000 ♀15-26 years

Study	Vaccine	Patients	Primary Outcomes	Follow Up
FUTURE 1[1] 2007	HPV-4	5455 ♀, 16- 24 yo S. America: 40% N. America 30% Europe 20%, Asia Pacific 10%	AGWs and vulvar lesions Cervical lesions ≥ CIN 1	4 years
FUTURE 2[2] 2007	HPV-4	12,167 ♀ 15-25 yo Europe 65%, S. America 25% N. America 8%	Cervical lesions ≥ CIN 2	3 years
FUTURE 1 + 2[3] 2010	HPV-4	17,622 ♀ 15-25 yo	AGWs and low grade CINs	4 years
PATRICIA[4] 2012	**HPV-2**	18,644 ♀ 15-25 yo Asia-Pac 40%, Europe 40% S. America 10% N. America 10%	Cervical lesion ≥ CIN 2	4 years

AGW = Anal Genital Warts

[1]*NEJM 2007;356:1928* [2]*NEJM 2007;356:1915* [3]*BMJ 2010;340:c3493* [4]*Lancet Oncol 2012;13: 89*

Results: RCTs 15 - 26 years ♀

	AGWs (or VINs) Per protocol	AGWs (or VINs) Intention to Treat	Cervical Lesions ≥ CIN 2 Per protocol	Cervical Lesions ≥ CIN 2 Intention to Treat
FUTURE 1	Only HPV lesions in vaccine 0 vs 2.6%, ARD = 2.6% NNT = 40	All HPV lesions 3.8 vs 5.7%, ARD = 1.9% **NNT = 53**	Only HPV lesions in vaccine 0 vs 1.9%, ARD = 1.9% **NNT = 50**	All HPV lesions 6.6 vs 7.1% ARD = 0.5% **NNT = 200***
FUTURE 2	NR	NR	Only HPV lesions in vaccine 0.02% vs 0.8%, ARD =0.78% **NNT = 125**	All HPV lesions 3.6 vs 4.4%, ARD = 0.8% **NNT = 125**
FUTURE 1+2	0.2% vs 2.5% ARD = 2.3% NNT = 44	All HPV lesions 1.5 vs 4% ARD = 2.5% **NNT = 40**	Reported CIN 1 Only HPV types in vax 0.1 vs 2.2% ARD = 2.1% NNT = 48	Reported CIN 1 Only HPV types in vax 1.3 vs 4.2% ARD = 2.9% NNT = 36
PATRICIA	NR (only 16,18)	NR (only 16,18)	All HPV lesions 1.1 vs 3.2%, ARD = 2.1% **NNT = 50**	All HPV lesions 3.3 vs 4.9%, ARD = 1.6% **NNT = 60**

NR = not reported, VIN = vaginal / vulvar intraepithelial lesions

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What about Older females 25-45 years?

- Multi-country placebo controlled RCT HPV-4 of 3819 ♀, followed x 4 years
  - 33% baseline HPV POS
- 1' outcome: External genital lesions or CIN *or persistent HPV 6,11,16,18 infection:*
  - CIN 2/3: 1.1% vs 1.4%: (ITT) [NSS]
  - EGL: 0.6% in both (ITT)

Br J Cancer 2011; 105: 28, Lancet 2009; 373: 1949 (interim)

What about Men?

- Multi-country placebo controlled RCT HPV-4
- > 4000 16 – 26 years olds, 65% S or N. America
- AGWs at 3 years, all HPV subtypes: (ITT)
  - Vaccine = 1.8%, placebo = 4.4%, ARD = 2.6%
  - **NNT = 40**

Efficacy of Quadrivalent HPV Vaccine against HPV Infection and Disease in Males

NEJM 2011; 364: 401

Cohort Data: Genital Warts STI clinics

> 50% RRR @ 5 year follow up

-♀ < 30 yo: 12% to 4%, ♂16% → 8%

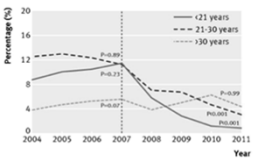


Fig 1 Proportion of Australian born women diagnosed

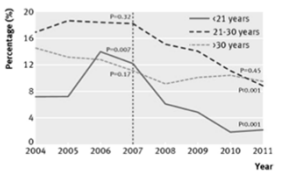
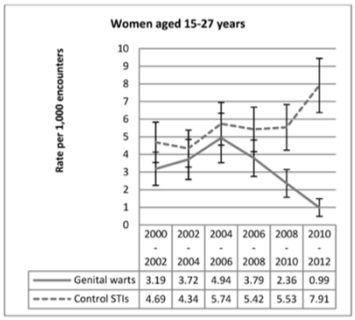


Fig 3 Proportion of Australian born heterosexual men

BMJ 2013;346:f2032 *Lancet Infect Dis* 2011; 11: 39 Sex Transm Infect 2011, [4]*JAMA* 2014;311(6):597

Cohort Data: Genital Warts Primary Care Aussie



	2000 - 2002	2002 - 2004	2004 - 2006	2006 - 2008	2008 - 2010	2010 - 2012
Genital warts	3.19	3.72	4.94	3.79	2.36	0.99
Control STIs	4.69	4.34	5.74	5.42	5.53	7.91

BEACH program, Harrison et al. PLoS ONE 2014: e105967. doi:10.1371/

HPV Adverse Event Rates

Study	Number of doses	Serious Aes # (per 100,000)	Syncope	Anaphylaxis
Randomized Controlled Trials				
FUTURE 1 2007	~8000	10	NR	NR
FUTURE 2 2007	~18,000	30	0	0
PATRICIA 2012	~28,000	30	NR	NR
Post Marketing Surveillance				
AUSSIE 2008[9]*	380 000	35 anaphylaxis	NR	Re-challenged 25 2 anaphylaxis
US JAMA 2009[8]	23 million	~4	1847	28 Confirm RR: 1/100K
CAN 2014[7]	~ 700,000	~ 2	NR	2 (0 confirmed)

* Specifically reported on anaphylaxsis

[7]Vaccine 2014; (9):1061 [8]JAMA 2009;302(7):750 [9]CMAJ. 2008;179(6):525

HPV Vax Not Recommended in Pregnancy

- FUTURE 1+2: pregnancies
  - 1,396/10,418 (13.4) vaccine arm
  - 1,436/9,120 (15.7) placebo
- HPV-4: ~ congenital Abn, spont. abortion[1,5]
- HPV-2: overall ~ rates of congenital Abn, SA[3]
  - ↑congenital Abn (13.6% vs 9.4%):[6] if received vaccine between 45 day before - 30 day after DLMP

[1]NEJM 2007;356:1928, [2]NEJM 2007;356:1915, [3]Lancet Oncol 2012; 13: 89, [4]NEJM 2011; 364:401,
[5]Gardasil Product Monograph 2013, [6]Cervarix Product Monograph 2014,
[7]Vaccine 2014; (9):1061 [8]JAMA 2009;302(7):750 [9]CMAJ. 2008 Sep 9;179(6):525

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HPV Vaccine summary

Patient Group	Number needed to Vaccinate over 3-4 years (ITT)
Females 15-26 years: AGWs	~ 40 – 50
Females 15- 26 years: ≥ CIN 2	60 – 125
Females 25-45 years: AGWs OR CIN	No diff CIN 2/3 or EGLs
Males 16-26 years: AGW	40
Women with AGW or CIN already	Unsure

Future HPV Vaccine Goals

Developing Countries:

- Non-refrigerated

Developed Countries:

- Delay paps to 25 years and ↓ intervals
  - Automatic Flex test for HPV

Both countries:

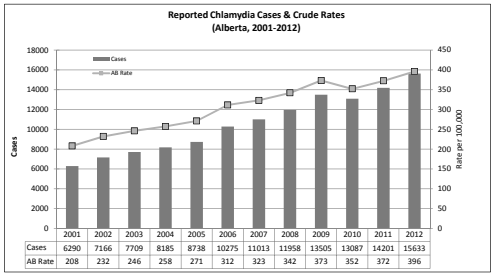
- Actual cervical cancer rates from LT studies
- Need for booster
- 1, 2 or 3 shots?

Sexually Transmitted Infections (STIs) Chlamydia (CT) / Gonorrhea (NG)

- Chlamydia: 1.4 M / yr US
  - 10xs ↑ common than Gonorrhea[1]
- 5% of women < 24 years (15 -19 yo highest)[2]
  - ~ 50% asymptomatic[1,3]
- RFs: new or > 1 sex partner, inconsistent condom use, previous STI[1]
- ~ 20% re-infected with CT in 1 year[4]
  → re-test in 3-6 months[5]

[1]Ann Int Med 2014: doi:10.7326, [2]MMWR 2014; 38: 830 [3]*BMJ 2012;345:e8013*
[4]*Sex Trans Dis 2009;* 8: 478 Clin Inf Diseases 2011;53(S3):S92–8

Number & Crude Rates of Chlamydia in Alberta, 2001- 2012



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Cases	6290	7166	7709	8185	8738	10275	11013	11958	13505	13087	14201	15633
AB Rate	208	232	246	258	271	312	323	342	373	352	372	396

2012 rate is nearly 2 times higher than in 2001.

(Communicable Disease Registry System STI Module, July 22, 2013)

Slide courtesy Dr. A. Singh

Case #1: 23 yo Cowboy Mr. G. Slinger

Kolber: "I am Dr. Kolber, it says here your chief complaint is 'personal.' How may I help you?"

Cowboy: "Well, you see – I was at the rodeo this weekend and met this nice girl…"

Kolber: "OK, nurse, please bring me the extra large urethral swab"

…2 minutes later…

Nurse: "Where did the patient in exam 4 go"

Diagnosing STIs Urine vs Cervical or Urethral Swabs

- Systematic Rev: 29 studies, mostly STI clinics
  - Chlamydia (CT) 3-22%, Gonorrhea (NG) 1-24%
- Compared urine Nucleic acid amplification (NAAT) to ♀cervical or ♂urethra swabs
- Genprobe Combo 2: detects CT and NG (Alberta)
  - Urine = cervical / urethral: sensitivities ~90%, specificities >98%
  - LR + > 100, LR - < 0.1

Cook, Ann Intern Med. 2005;142:914,

Mike Kolber

Really need First Void Urines (FVU)?

1. 222 Danish♀: gyne exam for any reason, also mailed in FVU and MSU
   – CT rate 11%
- MSU ~ FVU confirmation of CT (sens ~ 80%)

2. 108 ♀ CT POS: before treatment → MSU+FVU
- MSU sensitivity = 96%, specificity = 100
  – LR+ = ∞ LR - = 0.04
- Limitations: all patients had CT

[1]BMJ 1996; 313:1186, [2]Ann Fam Med 2012;10:50-53

Current Guidelines STI Screening

Who Should we Screen? (Women)[1]

All < 25 yo or > 25 yo with new / multiple partners

How Screen?: Urine, vaginal or cervical swab*

- **Delay paps to 25 yo → urine and vag swab*

Why screen?: ↓ STIs, ? ↓ PID and complications

Men: screen higher risk (STI clinic), high local rates with urine or urethral swab

Annals Int Med 2014: USPSTF [2]JAMA 2002; 288: 2846

Bacterial Vaginosis Treatment: Mouth or South?

- MTZ = CLIN for clinical cure[1]
  – 90% @ 2-3 weeks and ~85% @ 4 weeks
    - Irrespective of mode of administration, duration
  – ↓ AEs with clinda (13% vs 17%): NSS
- Oral MTZ: 2 gr vs 500 mg bid x 7d[2]
  – Clinical cure: 2 weeks: 86 vs 97%
    - ↑ recurrence (54% vs 14%) @ 3-4 weeks
- Alberta Guidelines[3]
  – MTZ oral 7d or vaginal 5d; clinda vaginal 7d
  – Alternative: clinda oral 7d, MTZ 1 dose

Cochrane 2009: CD006055, JAMA 1985: 1046, Alberta Treatment Guidelines for STIs (2012)

Summary Genital Villains

- **HPV**: Grade 5 girls and boys
  – NNV: AGWs ~ 40 -50, ≥CIN 2 ~ 60-125
  – Works better if given prior to sexual debut
- **STI**: chlamydia 5% in ♀< 24 yo
  – Urine (any urine will do), self vag swab
  – re-check after CT treated
- **BV**: Mouth OR south

Adil Virani and Alnoor Ramji

Hepatitis C: Unmasking the new agents

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Disclosures: Alnoor

Company Name	Relationship
Abbvie	Investigator, consultant
BI	Investigator, Consultant
BMS	Investigator, Consultant, Speaker
Gilead Sci. Inc	Investigator, Consultant, Speaker
Hoffman LaRoche	Investigator, Consultant, Speaker Nursing Support
Janssen (J. & J.)	Investigator, Consultant, Speaker
Novartis	Investigator
Merck & Co.	Investigator, Consultant, Speaker Nursing Support
Vertex Pharmaceuticals	Investigator, Consultant, Speaker

Disclosure: Adil

NO financial relationships or conflicts of interest with any pharmaceutical companies.

Adil has received honoraria for work related to providing advice about rational drug use from:

- ❑Canadian Agency for Drugs and Technologies in Health
- ❑PMPRB
- ❑Therapeutics Initiative

Outline

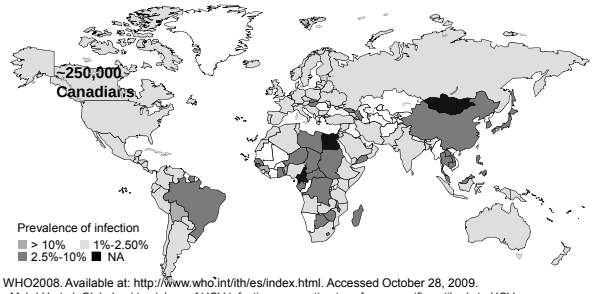
- Epidemiology/genotypes — Dr. Ramji
- Screening — Dr. Ramji
- Treatment options — Dr. Virani
- Outcomes — Dr. Virani
- Clinical Applications — Dr. Ramji

Objectives

- At the conclusion of this presentation, participants will be able to describe:
  - ➢ the prevalence and different genotypes of HCV in Canada
  - ➢ the prognosis in those presenting with acute HCV infection
  - ➢ new treatment options available in Canada
  - ➢ the efficacy rates of new agents on sustained virologic response
  - ➢ the clinical application of these agents in BC

Estimated 185 Million Persons With HCV Infection Worldwide

- 3-4 million newly infected each yr worldwide



WHO2008. Available at: http://www.who.int/ith/es/index.html. Accessed October 28, 2009.
Mohd H et al. Global epidemiology of HCV infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013; 57(4):1333-1342.

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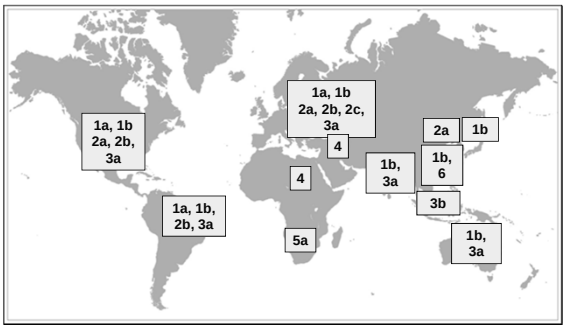
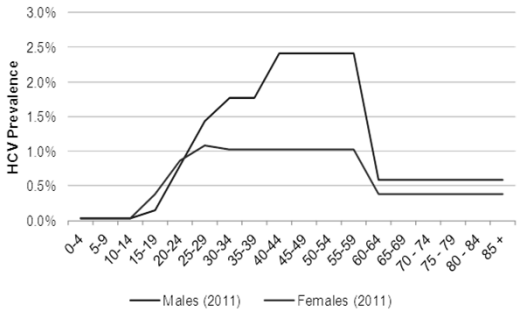
HCV Infection: Worldwide Genotype Distribution



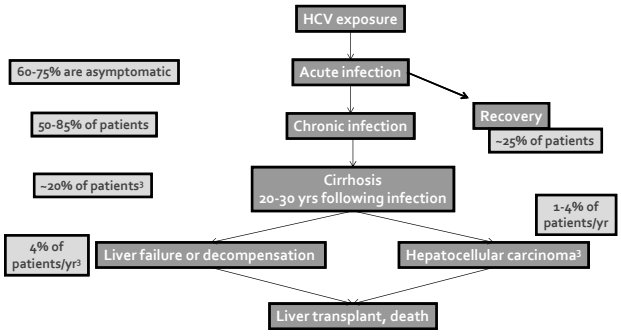
Fang et al. *Clin Liver Dis*. 1997.

Age and gender distribution of anti-HCV positive cases in Canada (2011).



Myers R. et al.. Can J Gastroenterol Hepatol. 2014 May;28(5):243-50.

Prognosis of HCV infection



1. Seeff LB. Hepatology 2002;36(Suppl 1):S35-46; 2. Sherman et al. Curr Oncol. 2011;18:228-40; 3. Consensus recommendations of the Steering Committee.

Criteria for Screening: Symptoms

•Fatigue •Nausea, loss of appetite • Arthralgia

•Abdominal pain • Hepatosplenomegaly

60-75% of patients are asymptomatic[4]

Possible dermatological signs:

- Mixed essential cryoglobulinemia
- Lichen planus
- Porphyria cutanea tarda
- Maculopapular rash
- Jaundice (past or present)

Other possible extrahepatic manifestations:

- Membranous or membranoproliferative glomerulonephritis
- Non-Hodgkin's lymphoma
- Sjögren's syndrome

*Symptoms described are non-specific and not strongly associated with hepatitis C.
1. Wong and Lee. CMAJ. 2006;174:649-59; 2. Centers for Disease Control and Prevention. Available from: www.cdc.gov/hepatitis/resources/professionals/pdfs/abctable.pdf; 3. Consensus recommendations of the Steering Committee; 4. Seeff LB. Hepatology 2002;36(Suppl 1):S35-46.

Screening: Risk Factors

High risk factors[1,2]

- Injection drug use (IDU) (58% of chronic infections)
- Receipt of healthcare where there is a lack of universal safety precautions or higher HCV incidence
- Blood transfusion or organ transplant prior to 1992

High-risk populations[3]

Refugees and immigrants	21%
Prisoners	18.7%
Baby boomers (1943-1967)	~5.98%

Intermediate risk factors[2]

- Incarceration
- Hemodialysis
- Infant born to infected mother
- Needle stick injuries

IDU: injection drug use.
1. Cornberg et al. Liver Int. 2011;31(Suppl 2):S30-60;
2. Pinette et al. Public Health Agency of Canada. Available from: http://www.phac-aspc.gc.ca/hepc/pubs/pdf/hepc_guide-eng.pdf;
3. Remis RS. Final Report. Public Health Agency of Canada. 2007. Available from: http://www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/model07-eng.pdf.

CDC Recommendations (August 2012)

Screening of those born between 1945-1965[1,2]

*** In Canada : CLF suggests 1945-1975

→ One-time testing during a yearly checkup or as a part of insurance blood work

In the US, >75% of adults with chronic hepatitis C are baby boomers

- 73.4% of HCV-related deaths were in persons 45-64 years of age

CDC: Centers for Disease Control and Prevention
1. Hepatitis C: Proposed Expansion of Testing Recommendations, 2012. Available from: http://www.cdc.gov/nchhstp/newsroom/docs/HCV-TestingFactSheetNoEmbargo508.pdf;
2. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6104a1.htm?s_cid=rr6104a1_w.

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Evaluation:

Laboratory Testing[1,2]

Virological tests to confirm HCV infection

- Anti-HCV
- HCV-RNA
- HCV genotype

Bloodwork

- CBC
- Liver enzyme & function tests:
  - ALT, AST, GGT, alkaline phosphatase, bilirubin, INR (or PT), albumin
  - Normal ALT is not a contraindication to treatment (⅓ have normal test results)[2]
- Creatinine

Abdominal ultrasound

- Test for cirrhosis and exclude hepatocellular carcinoma

Tests to rule out coinfections

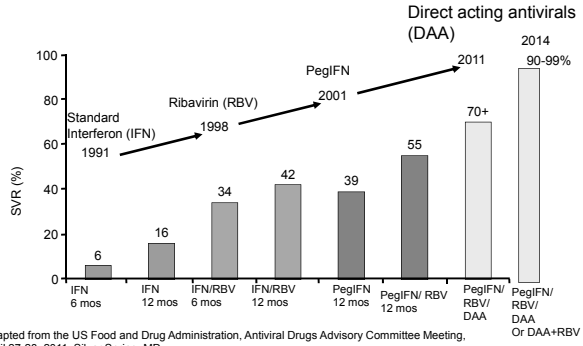
- Hepatitis A (HAV-Ab)
- Hepatitis B (HBsAg, HBsAb)
- HIV (Anti-HIV)

Tests to exclude other causes of liver disease

ALT : alanine aminotransferase; AST : aspartate transaminase; CBC: complete blood count; GGT: gamma-glutamyl transferase; HAV: hepatitis A virus; HAV-AB: hepatitis A antibody; HB: hepatitis B; HBsAG: hepatitis B surface antigen; HBsAb: hepatitis B surface antibody; HIV: human immunodeficiency virus; INR: International normalized ratio; PT: Prothrombin time

1. Myers et al. Can Gastroenterol. 2012;26(6):359-75; 2. Pinette et al. Public Health Agency of Canada. Available from: http://www.phac-aspc.gc.ca/hepc/pubs/pdf/hepc_guide-eng.pdf.

The Evolution of HCV treatments on Sustained Virologic Response (SVR)

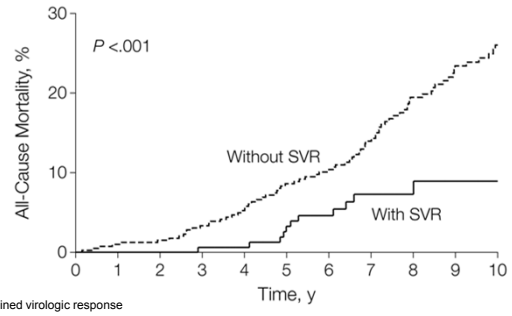


Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.

Definitions used in HCV trials

- **Sustained Virologic Response (SVR)**: undetectable HCV RNA 12 or 24 weeks AFTER stopping therapy
- **Relapse:** undetectable HCV RNA on therapy with detectable HCV RNA after stopping therapy.
- **Partial response:** > 2 log decline in HCV RNA but detectable HDV RNA after 12 weeks of HCV therapy
- **Non-response:** detectable HCV RNA after 12 weeks of HCV therapy

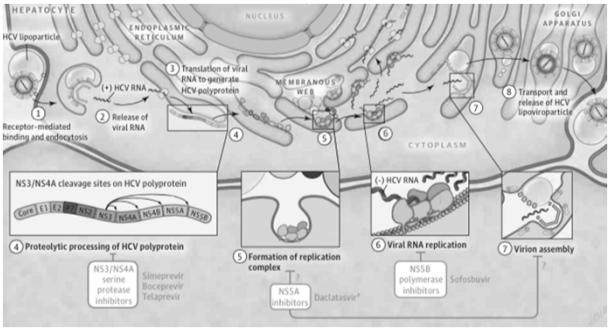
Viral Eradication Significantly Reduces All-cause Mortality in HCV



SVR: sustained virologic response

Adapted from van der Meer AJ, *et al. JAMA* 2012; 308(24):2584-93

HCV Lifecycle and DAA Targets



Kohli A, et al. JAMA Aug 2014

Treatment options

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Duration	Cost for One Course of Therapy ($)
HCV Protease Inhibitor						
Boceprevir (VICTRELIS)	200 mg	Cap	12.5000	4 × 200 mg 3 times daily	24 to 44 wks	25,200 to 46,200[d]
Simeprevir (GALEXOS)	150 mg	Cap	434.55[a]	150 mg once daily	12 wks	36,502[e]
Telaprevir (INCIVEK)	375 mg	Tab	69.3810	3 × 375 mg 2 times daily	12 wks	34,968[e]
Nucleotide Polymerase Inhibitor						
Sofosbuvir (Sovaldi)	400 mg	Tab	654.76[a]	400 mg once daily	12 wks	55,000[f]
Combination Peginterferon alfa + Ribavirin Therapy						
Peginterferon alfa-2a + RBV (Pegasys RBV)	180 mcg/200 mg	Vial or syringe/ 28, 35, or 42 tabs	Per wk 395.8400[c]	Peginterferon 180 mcg/wk; RBV 800 to 1,200 mg/day[b]	24 to 48 wks	9,500 to 19,000
Peginterferon alfa-2b + RBV (PEGETRON)	50 mcg/200 mg	2 vials + 56 caps	774.7700[c]	Peginterferon 1.5 mcg/kg/wk; RBV 800 to 1,400 mg/day[b]	24 to 48 wks	9,297 to 18,594
	150 mcg/200 mg	2 vials + 84 or 98 caps	856.1200[c]			10,273 to 20,547

https://www.cadth.ca/sites/default/files/pdf/TR0007_HepC_ScienceReport_e.pdf

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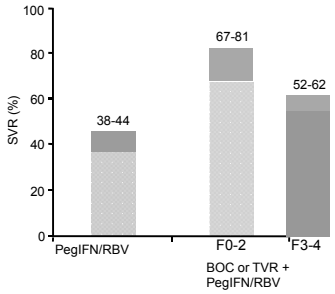
Treatment Options (all oral)

Drug	Strength	Dosage Form	Recommended dose and duration	Treatment Cost
Ledipasvir (NS5A inhibitor)+ **Sofosbuvir** Nucleotide analog inhibitor (**Harvoni**)	90 mg/400 mg	Fixed Dose Tablet	Once Daily x 12-24 wks (possibility of 8 wks in treatment naïve, non-cirrhotic)	12 wks – ~$67,000
Paritaprevir/ritonavir + ombitasvir + dasabuvir (Holkira Pak)	150mg/100 mg + 25 mg + 250 mg	Oral Tablets	Ombitasvir/Paritaprevir/ritonavir (2 q AM) + Dasabuvir 1 tablet BID	12 weeks - $55,860

SVR Rates of Boceprevir or Telaprevir in Genotype 1 Treatment-Naive Patients Triple Therapy for up to 48 Wks



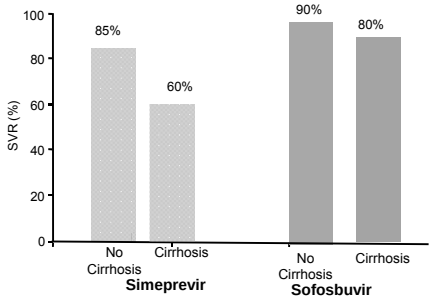
Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416.

Most Common Treatment-Related Adverse Events*

Adverse Event	Arm 1 (PR48); n=363 (%)	Arm 2 (RGT); n=368 (%)	Arm 3 (BOC/PR48); n=366 (%)
Fatigue	59	52	57
Headache	42	45	43
Nausea	40	46	42
Anemia	29	49	49
Dysgeusia	18	37	43
Chills	28	36	33
Pyrexia	32	33	30
Insomnia	32	31	32
Alopecia	27	20	28
Decreased Appetite	25	26	24
Pruritis	26	23	25
Neutropenia	21	25	25
Influenza Like Illness	25	23	22
Myalgia	26	21	24
Rash	22	24	23
Irritability	24	22	22
Depression	21	23	19
Diarrhea	19	19	23
Dry Skin	18	18	22
Dyspnea	16	18	22
Dizziness	15	21	17

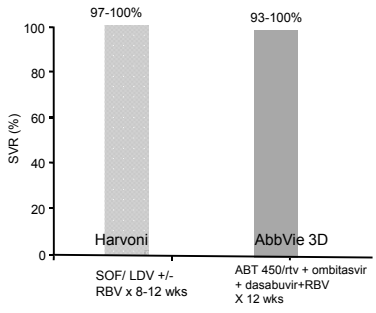
*Reported in ≥20% of patients in any treatment arm and listed by decreasing overall frequency

2014 /2015 :Virologic Response to PEG-INF + RBV + Simeprevir or Sofosbuvir in Genotype 1 Treatment-Naive Patients



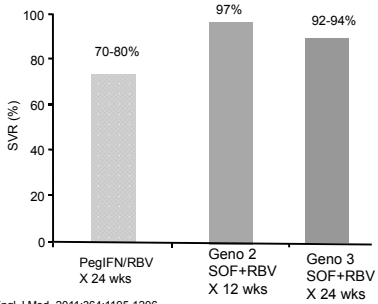
Jacobson I, et al. EASL 2013. Abstract 1425. Reproduced with permission.
Lawitz E, et al. EASL 2013. Abstract 1411. Reproduced with permission.

2015 /2016 :Virologic Response to Non-interferon based therapy: Genotype 1 :Treatment-Naive Patients: Non-cirrhotic and cirrhotic sub-groups



Feld JJ, et al. N Engl J Med. 2014;370:1594-1603. Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr 12
Poordad F, et al. EASL 2014. Abstract O163

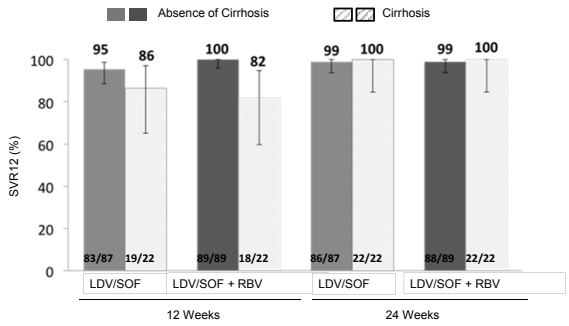
2014 /2015 :Virologic Response to PEG-INF + RBV vs. Sofosbuvir + RBV (all-oral) in Genotype 2 and 3 Treatment-Naive Patients



Poordad F, et al. N Engl J Med. 2011;364:1195-1206.
Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416.
Gane E, et al. *J Hepatol.* 2013;58(suppl 1):S3. Abstract 5.
Lawitz E, et al. *N Engl J Med.* 2013;368:1878-1887.

Adil Virani and Alnoor Ramji

ION 2: SOF/LDV FDC ± RBV for 12 or 24 Wks in Treatment-Experienced GT1 Pts: Based on cirrhosis



Afdhal N, EASL, 2014
Afdhal N, et al. *N Engl J Med* 2014; 2014 Apr

Error bars represent 95% confidence intervals

SAPPHIRE I & II: ABT-450/RTV/Ombitasvir + Dasabuvir + RBV in Noncirrhotic GT1 Pts: AE's

AEs	SAPPHIRE I		SAPPHIRE II	
	3 DAA + RBV (n = 473)	Placebo (n = 158)	3 DAA + RBV (n = 297)	Placebo (n = 97)
Any AE, n (%)	414 (87.5)	116 (73.4)	271 (91.2)	80 (82.5)
AE leading to D/C, n (%)	3 (0.6)	1 (0.6)	3 (1.0)	0
Any serious AE, n (%)	10 (2.1)	0	6 (2.0)	1 (1.0)
Grade 3/4 lab events, n/N (%)				
▪ ALT	4/469 (0.9)	7/158 (4.4)	5/296 (1.7)	3/96 (3.1)
▪ AST	3/469 (0.6)	3/158 (1.9)	3/296 (1.0)	1/96 (1.0)
▪ Alkaline phosphatase	0	0	0	0
▪ Creatinine	–	–	2/297 (0.7)	0
▪ Total bilirubin	13/469 (2.8)	0	7/296 (2.4)	0
▪ Hemoglobin < 8 g/dL	0	0	1/296 (0.3)	0
Hemoglobin < 10 to 8 g/dL, %	5.8	0	4.7	0

Feld JJ, et al. N Engl J Med. 2014;370:1594-1603. Zeuzem S, et al. N Engl J Med. 2014;370:1604-1614.

CADTH 2014 recommendations

- Triple therapy with a DAA plus PegINF and RBV treatment should be offered *only* to patients who:
  - are treatment-naive *or* have relapsed
  - have moderate to severe fibrosis (Metavir score F2, F3, or F4).
- People who have been previously treated with DAA plus PR triple therapy and had a partial or no response should not be re-treated with another DAA plus PR regimen.
- Simeprevir is the drug of choice among the protease inhibitors (boceprevir, telaprevir, and simeprevir).
- No recommendation can be made regarding the place in therapy for sofosbuvir (not reviewed sufficiently in the initial CADTH review).

- CADTH Recommendations did not include at Harvoni or Halkori Pak.
- New Hep C Treatment Recommendations coming for 2015

https://www.cadth.ca/node/84131

BC Pharmacare: Mar. 24 2015

- All persons must have >/= Stage 2 fibrosis

- Genotype 1
  - Treatment naïve or experienced / cirrhosis or non-cirrhotic:

  Harvoni (sofosbuvir+ ledipsavir) 8-24 weeks: SVR 95-99%

- Genotype 2 or 3
  - Naïve -24-48 weeks Peg-Inf + ribavirin SVR 70-90%
  - Treatment failures – Sofosbuvir + ribavirin 12- 24 weeks: SVR 70-90%
  - Interferon intolerant /in-eligible – sofosbuvir + ribavirin

British Columbia: (Purely My Opinion)

- The drugs are effective and here.
- Treating (and curing) HCV has mortality benefit…. So we should

- Requires:
  - Identification of patients – screening with linkage to care model
    ? Thru GP / public education, formal screening program ($$)

British Columbia: (Purely My Opinion)

Treatment strategy:

•Greatest impact on those with advanced disease.
  - Need to consider morbidity / mortality benefit
  - Costs

•Firstly: Treat Stage 2 fibrosis and greater reasonable ??

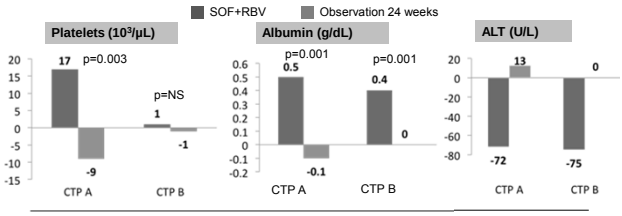
•Later (? 3-5 yrs.) :Treatment as prevention (open access) … eventually to eliminate HCV

Adil Virani and Alnoor Ramji

HCV Pipeline

- Holkira-pak – Health Canada approved not reimbursed by province –undergoing CDR (list price $45,000 per course-12 wks.)
- Greatest needs:
  - (Decompensated liver disease)
  - Genotype 3 – approx. 25-30% in BC
  - Renal failure patients

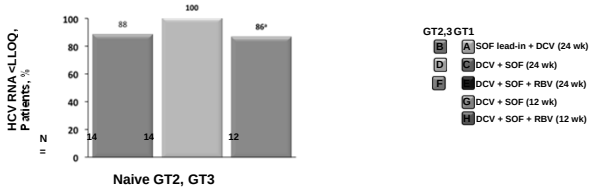
SOF+RBV for Treatment of Chronic HCV with Cirrhosis and Portal HTN ± Decompensation: Week 24 Interim Results



	Ascites		Hepatic Encephalopathy	
Patients, n	SOF + RBV n=25	Observation n=25	SOF + RBV n=25	Observation n=25
Baseline	6	9	5	2
Week 12	5	8	3	3
Week 24	0	7	0	4

Afdhal N, EASL, 2014, O68

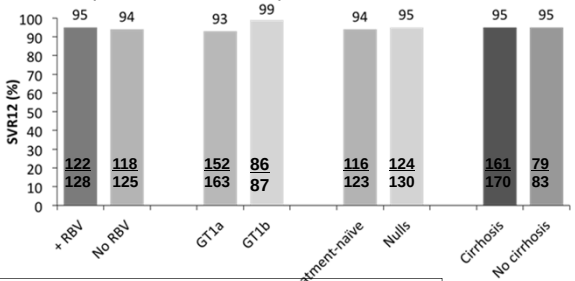
Genotype 3: Sofosbuvir and Daclatasvir x 12 weeks (? May 2015): SVR



- SVR12 rates were similar in subgroups defined by viral subtype
  - 92% (24/26) GT2
  - 89% (16/18) GT3

Sulkowski et al. *N Engl J Med.* 2014;370:211.

grazoprevir and elbasvir ± RBV: 12 or 18 weeks: Hcv Gt1 Infected Patients with cirrhosis or previous null response: C-WORTHY



SVR12 was 92% (23/25) in null responders with cirrhosis treated for 12 weeks with grazoprevir + elbasvir ± RBV

34

* Includes all patients treated with 12 or 18 weeks of grazoprevir + elbasvir ± RBV

Hepatitis C: Summary

- HCV occurs in about 250,000 Canadians
- ~ 20% of those with HCV progress to cirrhosis (in 20 yr. follow-up).
- Viral eradication with DAAs occur in 70-99%
- New all oral DAA regimens are well tolerated, and have a shorter course of therapy
- Viral eradication is associated with a mortality benefit
- New DAAs regimens costs are ~ $
- Many new drugs in the pipeline

Hepatitis C: Unmasking the new agents

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Mike Kolber

Constipated in 2015
The Poop on Hard, Infrequent or Painful Poop

DTC April 2015

Mike Kolber BSc, MD, CCFP, MSc

Faculty/Presenter Disclosure

- **Faculty/Presenter(s): Michael R. Kolber**
- **Relationships with commercial interests:**
  - Pay from University of Alberta and Alberta Health
- Research and Speaking Fees
  - **Non-Profit Sources** (Alberta College of Family Physicians, Towards Optimized Practice)
  - **No funding from industry**

Objectives

After this session you should be able to:

- Understand the limitations of evidence pertaining to constipation
- Understand appropriate diagnostic work up for new onset constipation
- Understand which therapies have reasonable evidence to use in your practice
  - And which products you should likely avoid
- Relative costs of different products

Definition

- *unsatisfactory defecation characterized by **infrequent stools** or difficult stool passage.*
- Difficult stool passage: ***straining, incomplete evacuation, hard** stools, prolonged time to stool, or need for **manual maneuvers** to pass stool*

Am J Gastro 2005 Am College of Gastro Chronic Constipation Task Force

Constipation
Common and Chronic

- 12-19% of N. Am adults[1,4]
- More common:[1,3,4]
  - Females
  - older adults, kids
  - ↓SES or education
- Chronic: 89% similar symptoms 1.5 years later[1]
- ↓ Quality of life (Peds: parents > kids)[5]

[1]*Am J Gastro 2004; 99:750,* [2]Aliment Pharmacol Ther. 2010; 31: 938
[3]*Am J Gastro* 2011; 106:1582 , [4]Gastroenterology 2013; 144(1): 218
[5]Aliment Pharmacol Ther. 2010; 31: 938

Who Can you Trust…
… Not the Reviews!

- Most Authors appear to be:
  - Industry affiliated
  - Early adaptors: remember Tegaserod?
  - Re-quote other work without analyzing primary papers
- Most guidelines are:
  - Incomplete, experience based
  - Written by specialists
- Most Studies are:
  - Small n's, days to weeks, placebo controlled
  - some meaningless outcomes
  - No great primary care RCT

Mike Kolber

STOOL Trial

- Pragmatic, multi-step trial, UK primary care
- Mimic what occurs in clinical practice

TABLE 1 Individual laxative treatment strategies

Strategy	Step 1	Step 2
1	Bulk laxative	Combination of bulk + stimulant laxative
2	Bulk laxative	Combination of bulk + osmotic laxative
3	Stimulant laxative	Combination of stimulant + bulk laxative
4	Stimulant laxative	Combination of stimulant + osmotic laxative
5	Osmotic laxative	Combination of osmotic + bulk laxative
6	Osmotic laxative	Combination of osmotic + stimulant laxative

- Multi-level approval delays
- Minimal buy in from practices: too busy, no space, inadequate compensation
  - Amendments: minimize effort, more practices

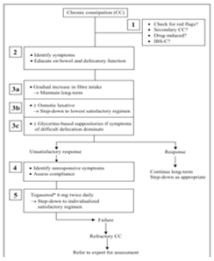
Health Technology Assessment 2008; Vol. 12: No. 13

Canadian Guidelines 2007
9 Gastros, 1 GP

- Recommend: CBC, TSH, calcium, albumin
- Don't support exercise

IMPORTANT NOTE: At Health Canada's request, as of March 30, 2007, Novartis Pharmaceuticals Canada Inc has suspended the marketing and sales of Zelnorm® (tegaserod hydrogen maleate) in Canada. ®Zelnorm is a registered trademark.

CONFLICTS OF INTEREST: The following authors have an affiliation with a company or receive remuneration or royalties from a commerical organization: Dr P Paré – Axcan Pharma (speaker and research), Dynogen (research) and Novartis (speaker, advisory board and research); Dr SC Ganguli – Novartis (consensus development, speaker and research); Dr SM Collins – AstraZeneca (advisory board and research), Nestle (research) and Novartis (speaker); and Dr G Turnbull – Novartis (advisory board and research).



Can J Gastroenterol 2007;21(Suppl B):3B-22B.

Constipation PLUS
Alarm symptoms = investigations

Bleeding

Weight loss

Obstruction

Which symptoms correlate with CRC?

Symptom	BJGP 2010[1]	BMC Gastro 2011[2]	BMJ 2010[3]
Anemia	4	NR	
Abdominal Pain	2.5	1	~1
Constipation	1.7	1.1	< 1

FIT / FOBT+ (75mcg) ~ $10^{4,5}$

[1]British J Gen Pract 2011, [2]BMC Gastro 2011, 11:65, [3]BMJ 2010;340:c1269
[4]*Am J Gastro* 2012; 107:1570 [5] *Ann Intern Med.* 2014;160:171

'Causes' of Constipation

- **Idiopathic / Functional**:
  - Dietary Fibre, Exercise
- **Secondary**: "A LEMON"
  - **A**nal Fissure → withholding
  - **L**esion: colorectal cancer
  - **E**ndocrine**:** DM, hypothyroid, calcium
  - **M**edications:
    - **O**piods / **O**thers: TCAs, iron, anti-cholinergics (anti-histamines), CCBs
  - **N**eurological: MS, Parkinsons, spinal cord injury
- **Defacatory Dysfunction: pelvic floor**
  - rectocoele, prolapse (++ straining or manual help)

Kolber 2015, McCallum BMJ 2009;338:b831

No good studies evaluating investigations…

- No adult studies looking at evidence / yield of tests for secondary causes[1-3]
  - CBC, TSH, FBS, calcium
  - Celiac ~1% of population (2-5% of IBS)
  - No adult study directly looking at abd xray[1]
- Majority treat without investigating

[1]*Rao, Am J Gastro 2005;100:1605,* [2]*Am J Gastro 2005 - Vol. 100, No. S1*
[3]*Gastro 2013;144(1): 218*

Mike Kolber

Primary Care Fibre study
Dutch IBS patients

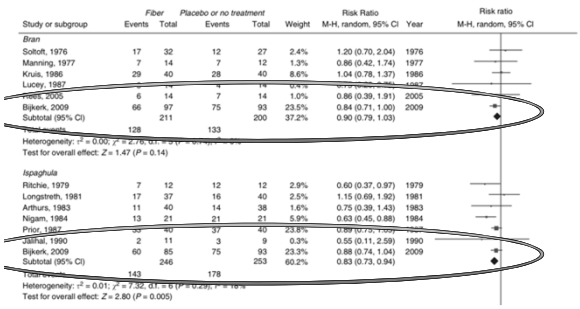
- 275 primary care IBS patients, 78% ♀, 34 years, 56% IBS-C
- Randomized: psyllium (10g), bran (10g) or placebo x 12 weeks
- Outcome: Adequate pain relief in 2/4 preceding weeks (%)

Time	Psyllium	Bran	Placebo	NNT
1 month	57*	40	35	*Psyllim vs placebo = 4
3 months	47	56^	32	^Bran vs placebo = 4

- *Conclusion: Psyllium offers benefits in patients with irritable bowel syndrome in primary care.*

Bijkerk BMJ 2009; 339:b3154

Fibre in IBS: Systematic Review
Global Symptoms / Abdominal Pain



Am J Gastroenterol 2014; 109:1367

Fibre Handouts

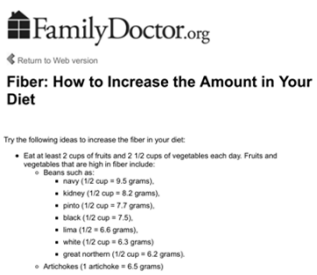

Fibre scoreboard for adults

Healthy eating, which includes eating plenty of fibre, is one of the best defences against many types of cancer. What does fibre do? Fibre is a part of plant-based foods that is not digested by the human body. Fibre works to keep your digestive system healthy.

Foods with the most fibre
- vegetables and fruit
- whole grain foods
- legumes (beans, peas and lentils) and nuts

Foods with little or no fibre
- milk and milk products
- fats (oils) or sugars
- snack foods such as tortilla chips
- meats

Vegetable	Fibre	Fruit	Fibre
Asparagus, boiled, 5 spears	1 g	Apple, with skin, 1 medium-sized	3 g
Beans, green or yellow, steamed, 125 mL (½ cup)	2 g	Applesauce, 125 mL (½ cup)	2 g
Broccoli, raw or steamed, 125 mL (½ cup)	2 g	Apricots, dried, 60 mL (¼ cup)	3 g
Brussels sprouts, steamed, 125 mL (½ cup)	3 g	Banana, 1 medium-sized	2 g
Cabbage, cooked, 125 mL (½ cup)	1 g	Blueberries, 125 mL (½ cup)	2 g
Carrots, raw or steamed, 125 mL (½ cup)	2 g	Cantaloupe, ¼ of a small fruit	2 g
Cauliflower, raw, 125 mL (½ cup)	1 g	Dates, 5	4 g
Celery, raw, 1 stalk	1 g	Grapefruit, white or pink, ½	2 g
Lettuce, 250 mL (1 cup)	1 g	Grapes, with skin, 20	1 g
Mushrooms, cooked, 125 mL (½ cup)	2 g	Fruit juice, 100%, 125 mL (½ cup)	traces
		Mango, ½	2 g
		Orange, 1 medium-sized	3 g
Vegetable	**Fibre**	**Fruit**	**Fibre**


FamilyDoctor.org

Return to Web version

Fiber: How to Increase the Amount in Your Diet

Try the following ideas to increase the fiber in your diet:

- Eat at least 2 cups of fruits and 2 1/2 cups of vegetables each day. Fruits and vegetables that are high in fiber include:
  - Beans such as:
    - navy (1/2 cup = 9.5 grams),
    - kidney (1/2 cup = 8.2 grams),
    - pinto (1/2 cup = 7.7 grams),
    - black (1/2 cup = 7.5),
    - lima (1/2 = 6.6 grams),
    - white (1/2 cup = 6.3 grams)
    - great northern (1/2 cup = 6.2 grams).
  - Artichokes (1 artichoke = 6.5 grams)

Prunes vs Psyllium RCT

- 40 constipates, 95%♀, 38 yrs
- Prunes vs psyllium x 8 weeks (single blinded)

CSBMs / week

	Baseline	Treatment	Change
Prunes	1.8	3.5	1.7
Psyllium	1.6	2.8	1.2

- Global symptoms, straining: no diff
- Conclusion; *prunes more effective*
- Sponsor: California Dried Plum Board

Aliment Pharmacol Ther 2011; 33: 822
Aliment Pharmacol Ther 2014; 40: 750

Psyllium is superior to docusate sodium for treatment of chronic constipation

J. W. McRORIE, B. P. DAGGY, J. G. MOREL, P. S. DIERSING, P. B. MINER* & M. ROBINSON*
*The Procter & Gamble Company, Cincinnati, Ohio; and *The Oklahoma Foundation for Digestive Research, Oklahoma City, Oklahoma, USA*

- 170 constipates: blinded RCT x **2 weeks**
- Outcomes: multiple
- Issues: 1 sided p-values, lead author = industry
- Outcomes:
  - BMs: 3 vs 2.5 / week (diff = 0.5 / week)
  - Rest of outcomes same
- *Conclusion: psyllium better than docusate*

Aliment Pharmacol Ther 1998; 12: 491

Ducosate RCTs

- Edmonton Hospice: prevention trial
- RCT of senna + ducosate vs senna + placebo
  - 74 hospice patients (91 -100% of arms on opiods)
  - RCT x 10 days
- No difference in: stool frequency, volume, or consistency or completeness of evacuation
- No kidding!

Tarumi, J Pain Symptom Manage 2012

Mike Kolber

Stool Softners:

Ducosate sodium (Colace) or calcium (Surfak)

- CADTH 2014: paucity of good quality evidence
- 1 RCTs, 2 non-RCTs, 2 SRs
- Colace similar to placebo in:
  - stool frequency
  - Constipation symptoms (i.e. abdominal cramps)
  - Incomplete evacuation

CADTH 2014 Dioctyl Sulfosuccinate or Docusate (Calcium or Sodium) for the Prevention or Management of Constipation

Bisacodyl primary Care RCT

- Bisacodyl (Dulcolax): multi-centre placebo control RCT, UK primary care
- 368 pts, 80% ♀, 20 yrs constipated, 1 BM /wk
- BIS vs PLAC daily x 4 weeks, blinded, mITT
- BMs / week: BIS = 5 PLAC = 2
- Global efficacy: "Good/satisfactory":
  - 80% vs 50%, ARD = 30%, NNT = 4
- High quality study, funded by….

CLINICAL GASTRO HEPATOLOGY 2011;9:577

Bisacodyl for Acute constipation

- Primary care RCT: Bisacodyl 10 mg po vs placebo
- Patients PHx of constipation, BM 4-5 / week
  → treated if no BM in 3 days
  - Excluded those taking laxatives, previous surgery
  - **n = 22, 9 day study**
  - Industry funded
- Outcomes:
  - ↑ BMs (1/ day greater than placebo)
  - ↓ Investigator reported symptoms

Aliment Pharmacol Ther 2006: 23, 1479

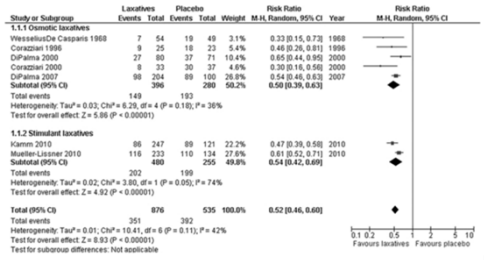
Ducosate + Senna vs PEG Post op Ortho

NORGINE

- Prevention RCT
- RCT: colace + senna (+ enemas) vs PEG 3350
- Limitations:
  - 31 patients (- 3 protocol violations) = 28 analyzed
  - Not RCT: Randomized by who is working
  - PEG funded
- Outcome: time to first BM:
  - PEG 3350: 1-2 days faster (~3 vs ~5 days)
  - NSS ↑ AEs (PEG): abd cramps, flatus

Inter J of Orthopaedic and Trauma Nursing; 2010: 14, 75

Stimulants ~ Osmotics?



Global symptom improvement: NNT = 3 (both osmotics, stimulants)

Ford, Gut 2011;60:209

Do Stimulants lead to Dependence or GI nerve abnormalities?

- 1968: surgery for refractory constipation = altered myenteric plexus – conclude due to senna[1]
- Chronic laxative users (18Xs recommended)
  - Colonic biopsy = altered myenteric plexus
- Association vs causation?
- Stimulants and 'tolerance'?[2]
  - Some ↑ dose over time
- Stimulants and dependence?
  - Able to switch between stimulants and other agents

Gut 1968;9:139, Am J Gastro 2005;100:232

Mike Kolber

PEG vs Placebo
Systematic review - Adults

- 5 trials, 604 pts, 77% female, FU 1 – 24 weeks[1]
- Treatment failures:
  - # stools, tools (rescue), or staining or other symptoms
  - PEG 38% vs 70%: ARD = 32%, NNT = 3
- ↑ stool frequency: ~2.5 / week

[1] *Ford Gut 2011; 60: 209-218*

PEG vs Placebo
Best Adult RCT

- 304 US patients, X = 55 yrs, ♀, 23 yrs constipated
  - Excluded IBS, narcotic users
- 1 'outcome: achieving 50% 'successful' weeks:
  - Successful = > 3 BMs, no rescue meds, < 1 of straining / incomplete / hard stools (25% of time)
- PEG 52% vs 11% placebo: ARD = 41% NNT = 3
- Super efficacy: above + no symptoms: 47 vs 14%, ARD = 33%, NNT = 3
- ↑GI Aes: diarrhea, gas, nausea: 40% vs 25%
  - Med DC: placebo 2xs greater (no #s given)
- Funded by PEG

Dipalma, Am J Gastroenterol 2007;102:1436–1441

PEG 3350 vs Lactulose
Systematic Review

- Adults: PEG superior to Lactulose[1]:
  - Stool frequency↑ (~ 0.3/ week)
  - Fewer rescue laxatives
  - No diff in abdo pain
- Peds: PEG[1,2]:
  - Stool frequency ↑ (~ 1.5 more per week)
  - Superior abdo pain relief: PEG 76%, Lact 55%, NNT = 5
  - ↓rescue medications

[1]*Lee-Robichaud H, Cochrane Reviews 2010, CD007570*
[2]*Candy, Arch Dis Child 2009;94:156–160*

Prucalopride (Resotran)
5-HT_4 AGO

Chronic constipation adult ♀

	Health Canada	Europe	FDA
Approval	✓?	✓?	✖
Dose	2mg (1mg elderly)		

RCTS Prucalopride vs placebo

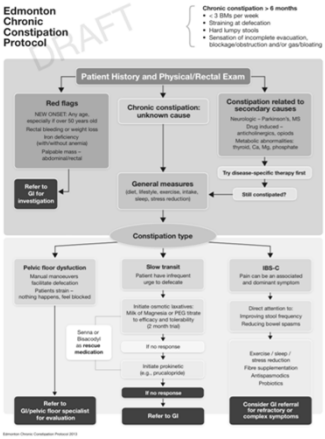
- ↑ weekly BMs: 0.5 → 1.5 / week (PLAC ↑ to 1)
- 15% ↑ self rated 'effectiveness' (NNT = 7- 8)
- 4 mg NOT superior to 2 mg in most outcomes
- Withdrawal due to Aes (headache): 8% vs2%

[1]NEJM 2008; 358;22: 2344; [2]Alim Phar Ther 2009; 29: 315,[3]Gut 2009;58:357

Fool me once; shame on you
Fool me twice; shame on me!

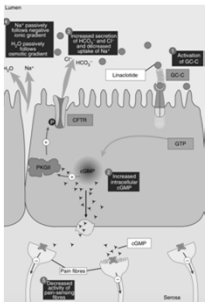
- 5-HT_3 AGO: Alostron (Lotronex): Ischemic colitis
- 5-HT_4 AGO: Cisapride (Prepulsid), Tegaserod (Zelnorm): CV events

Mike Kolber



Linaclotide (Constella)

- Heat stable enterotoxins that cause diarrhea



Linaclotide RCTs: Constipation

- Multi-site (N. Am), placebo controlled RCTs, industry support
- Linaclotide 145, 290 mcg or placebo x 12 weeks
  - 1 RCT: 4 week withdrawal RCT
- 1276 pts. 90% ♀, 49yo, ~2 BMs / week, abd. pain: 2.5/5 Likert

Outcomes: no diff between 145 and 290mcg

- ↑BMs / week: Lina (3) > placebo (1)
- Abdo pain: Lina = placebo ~ 0.5 ↓ Likert
- Satisfied: 40-55% vs 15-23%: ARD 18%, NNT = 6

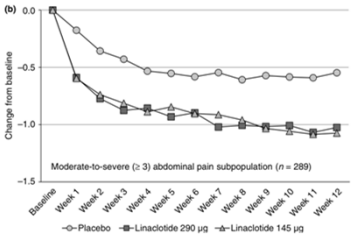
Withdrawal → BMs went back to baseline

- Aes = diarhea

N Engl J Med 2011;365:527

Linaclotide Post Hoc Analysis CC with Mod-Severe Abdominal pain

- Sub-group: mod-sev abd pain: n = 289



Aliment Pharmacol Ther 2014; 40: 1302

Linaclotide for IBS-C: RCTs

- 2 RCTs: N. American IBS-C 1600 patients, 90% ♀, 40s
- Placebo or 290 mcg x 12 weeks (+ 4 weeks WD) or 26 weeks

Outcome	Study 1 (12 weeks)	Study 2 (26 weeks)
30% ↓daily worse abdo pain	34 vs 27% NNT = 15	37 vs 17% NNT = 5
Adequate symptom relief	37 vs 21% NNT = 7	36 vs 15% NNT = 5

- Aes: ~ placebo (diarhea more common) → more DC

Rao, Am J Gastroenterol 2012; 107:1714, *Chey, Am J Gastroenterol* 2012; 107:1702
Aliment Pharmacol Ther 2013; 37: 49 (European Outcomes)

Opiod Induced Constipation Methylnaltrexone (Relistor)

- N. AM hospice / nursing home or palliative center
- 70 years, 60% cancer, 60% bothered by constipation, most ≥ 2 laxatives, 1/3 on osmotics
- 133 patients RCT: MN SQ vs PLAC q2d x 2 weeks
- BMs < 4 hours after injection
  - 52% vs 8% placebo (ARD = 44%, NNT = 3)
- Aes: placebo > MN, no ↑ pain scores

NEJM 2008;358:2332

Mike Kolber

Cadilliac or Corrolla
What's the Cost?

Product	Dose / day	90 day cost ($)
Senna	7.5 mg	11
Bisacodyl	5mg	15
Lactulose	15 mg	35
PEG 3350	17 gr	60
Linaclotide	140mcg	350
Prucalopride	2 mg	365
Linaclotide	290mcg	555

Comparative Shopping

- **Lactulose*:** 15ml qd = $12 / month
  - ↑ 3 BMs / week = **$1.00 / poop**
- **PEG 3350**: 17g qd = $20 / month
  - ↑ 3 BMs / week = **$1.70 / poop**
- **Linaclotide:** 145ug qd = $120 / month
  - ↑ 2 BM / week = **$15 / poop**
- **Prucalopride**: 2mg qd = $82 / month
  - ↑ 1 BM / week = **$20 / poop**

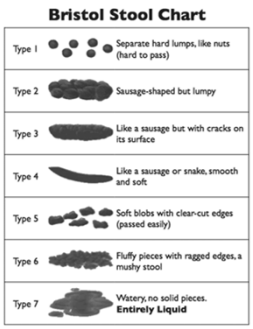
*covered by Alberta Blue Cross

Constipation Summary

- Common: look at meds, ? defacatory disorder
- Fibre and exercise
- Many 'crappy' studies; small and short, few POOs, funding bias
- Things that work: fibre, exercise, stimulants, osmotics, Linaclotide
- Prucalopride → ? safety issues
- If not working: define 'failure', compliance, ? defacatory dysfunction
- If pain +++ and ? IBS → consider anti-depressants

Extra

What do they mean?
What bothers them the most?



Lower Bristol scores correlate with slower colonic transit in constipated patients (r = 0.6)

Straining/digital manipulation → defacatory dysfunction

Am J Gastro 2010; 105:403

DRE pick up for constipated patients?

- "Feed a cold, starve a lawyer"[1]
- Defacatory Dysfunction / pelvic floor abnormality[2]
  - Tone, anal wink (for CNS cases)
  - Perineal elevation with expulsion
- Rectal Bleeding: fissure or hemmeroid?[3]

Kill as Few Patients as Possible, Gastro 2013 Review, Kolber 2015 communication

Mike Kolber

Exercise and IBS RCT

- 102 IBS patients: 79% women, 39 years old
  - Exercise: physical activity advice 2xs / month (PT) with diary and cycling test at 6 weeks
  - Control: current lifestyle, monthly call from physio
- Outcomes at 3 months:
  - IBS-SSS change: PA ↓ 51 points (pp) and 37 points (mod ITT)
  - IBS QOL: sleep, energy, fatigue, physical function improved (pp)
- Gut physiologist review of the paper:
  - "Begs the question… how it works"

Am J Gastro 2011; 106:915
Gastro 2011; 5: 1941
Am J Gastro 2005;100:232 (cohorts)

Keyvan Hadad

Jaundice and Reflux in Your Superbaby

Keyvan Hadad, MD, MHSc, FRCPC
26th Annual Best Medicine Course
April 17, 2015

Disclosure

* No relationship with commercial interests
* No conflict of interest
* No mitigating potential bias

Objectives

* Review of risk factors and management of neonatal jaundice
* Review of gastro-esophageal reflux in otherwise healthy newborns

Baby Peter Parker

* Jaundice noted at 10 hours of age
* Total serum bilirubin (TSB) 240 umol/L
* Term delivery, 3000 grams
* O+ mother
* No other risk factors

Baby Clark Kent

* Day 4 of life
* Jaundice noted on day 2 and progressively worse, TSB 240 umol/L
* Weight loss of 10.8%
* 36 week delivery, Asian male
* Post c/section, struggling with breast feeding

Baby Bruce Wayne

* Day 24 of life
* TSB 240 umol/L
* Term delivery, 3500 grams at birth
* Now 4500 grams, exclusively breast fed
* No other risk factors

Keyvan Hadad

What is the risk?

* Major risk: bilirubin encephalopathy, relatively high rate in Canada: 1/55500, largely preventable by picking up risk factors
* Minor risk: interference with establishment of breast feeding, contribution to weight loss

Who is at risk?

* Hemolysis due to ABO incompatibility or other incompatibility
* Gestational age <36 weeks
* East Asian ancestry
* Male gender
* G6PD risk

Who is at risk?

* Jaundice in the first 24 hours
* Cephalohematoma / other bruising
* Sibling receiving phototherapy
* Excessive weight loss in breastfeeding infants

How to monitor? Traditional

* Present approach in BC is TSB measurement based on clinical observation or risk factors, leading to therapy or ongoing observation, in or out of the hospital

How to monitor? Screening

* Universal screening at 24 hours of age significantly reduces subsequent development of bilirubin levels associated with risk of encephalopathy
* Endorsed by the Canadian Pediatric Society with follow-up (if treatment deemed not necessary) TSB individualized based on risk factors
* Higher levels would require treatment, earlier follow-up or repeat measurements

How to monitor? Screening

* Challenges include delay in hospital discharge, arranging post discharge follow-up, overtesting and overtreating, ensuring appropriate post-hospital care

Keyvan Hadad

Gastro-oesophageal Reflux

* GOR is very common, affecting up to 50% of neonates less than three months of age
* Natural history is self-limiting and improvement is expected with time
* Most infants do not need treatment, other than education for the parents

Gastro-oesophageal Reflux Disease

* GORD is present in a small percentage of babies with significant pain with feeds, arching of the back, association with laryngomalacia, recurrent apneas, or failure to thrive

GORD Treatment

* The overall evidence for pharmacological treatment is of low quality, with generally small number of babies per study, little correlation between parental reported symptoms and endoscopic/pH findings, short follow-up, and the generally positive natural history of the condition

GORD Treatment: PPI

* Omeprazole (Moore 2003): poor quality evidence showing symptomatic improvement of infants with likely GORD
* Lansoprazole (Orenstein 2008): no difference with placebo in terms of observer assessments or symptom diaries, no investigation to differentiate GORD from GOR

GORD Treatment: H2-receptor antagonists

* No RCT and no appropriate head to head comparison versus PPI in infants
* Limited RCT in children over age one suggests safe in that age group

GORD Treatment: Gaviscon Infant

* Antacid + alginate
* Weak evidence (short trials, limited follow-up) suggests minimal symptom improvement as assessed by parents' scoring

Peter Loewen

Thanks for your questions and discussion.

Thanks for completing your course evaluations.