24th ANNUAL DRUG THERAPY DECISION MAKING COURSE

An Evidence-Based Thriller

April 12th and 13th, 2013

Fairmont Waterfront Hotel
Vancouver, B.C.

Friday Syllabus

Sponsored by

The THERAPEUTICS EDUCATION COLLABORATION
In Cooperation with the
DEPARTMENT OF FAMILY MEDICINE and
FACULTY OF PHARMACEUTICAL SCIENCES
UNIVERSITY OF BRITISH COLUMBIA

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

The New Therapeutics: Ten Commandments

Thou shalt treat according to level of risk rather than level of risk factor.

Thou shalt exercise caution when adding drugs to existing polypharmacy.

Thou shalt consider benefits of drugs as proven only by hard endpoint studies.

Thou shalt not bow down to surrogate endpoints, for these are but graven images.

Thou shalt not worship Treatment Targets, for these are but the creations of Committees.

Thou shalt apply a pinch of salt to Relative Risk Reductions, regardless of P values, for the population of their provenance may bear little relationship to thy daily clientele.

Thou shalt honour the Numbers Needed to Treat, for therein rest the clues to patient-relevant information and to treatment costs.

Thou shalt not see detailmen, nor covet an Educational Symposium in a luxury setting.

Thou shalt share decisions on treatment options with the patient in the light of estimates of the individual's likely risks and benefits.

Honour the elderly patient, for although this is where the greatest levels of risk reside, so do the greatest hazards of many treatments.

Course Directors

Bob Rangno, Emeritus Prof., Medicine, Pharmacology, UBC & PHC
James McCormack, Prof., Pharmaceutical Sciences, UBC

Guest Faculty

G. Michael Allan, Assoc. Prof., Family Practice, University of Alberta
& Director, Evidence and CPD Program, Alberta College of Family Physicians
Mike Kolber, Assoc. Prof., Family Medicine, University of Alberta
Tina Korownyk, Asst. Prof., Family Medicine, University of Alberta

Local Faculty

Gillian de Gannes, Clin. Instr., Dermatology, Dept. of Skin Sciences, UBC
Tom Elliott, Clin. Assoc. Prof., Medicine, Endocrinology, VGH
Ken Gin, Clin. Prof., Medicine, Cardiology, UBC & VGH
Barry Koehler, Clin. Prof. Emeritus, Medicine, Rheumatology, UBC
Mark McLean, Public Health Consultant, Adj. Faculty, School of Population and Public Health, UBC
Andrew Merkur, Clin. Asst. Prof., Dept. of Ophthalmology and Visual Sciences, UBC & VGH
Natasha Press, Clin. Assoc. Prof., Medicine, Infectious Diseases, UBC & PHC
Jeremy Road, Prof., Medicine, Respiratory, UBC & VGH
Kam Shojania, Clin. Prof., Medicine, Head, Rheumatology, UBC & PHC
Adil Virani, Assoc. Prof, Pharmaceutical Sciences, UBC, & Director, LMPS
Pearce Wilcox, Assoc. Prof., Medicine, Respiratory, UBC & PHC

FHA – Fraser Health Authority
PHC – Providence Health Care
PHSA – Provincial Health Services Authority
UBC – University of British Columbia
VCHA – Vancouver Coastal Health Authority
VGH – Vancouver General Hospital
LMPS – Lower Mainland Pharmacy Services, FHA, PHSA, PHC, VCHA

24th Annual

DRUG THERAPY DECISION MAKING COURSE

Friday, April 12, 2013

An Evidence-Based Thriller

(almost Friday the 13th and 2013 "Triskaidekaphobia")

07:00 Registration (Muffins & Coffee)

Chairs - Bob Rangno and James McCormack

"A SPOOKTACULAR BEGINNING"

08:00	Welcome and Introduction	Bob Rangno
08:10	A Sixth Sense – how to make numbers less frightening	Mike Allan and James McCormack

"SQUELCHING THE TORTURE OF PAIN"

08:50	Loosening the rack on chronic neuropathic pain	Mike Allan
09:10	Questions	
09:20	Fibromyalgia, chronic fatigue and other scary F words – the deBates "motel"	Barry Koehler, Kam Shojania
09:45	Osteoporosis – gimme a break will yah	Kam and Barry again
10:10	Questions	
10:20	Refreshment Break	

"HAPPY HORMONES"

10:40	Myxedema madness and other thyroid fears	Tom Elliott
11:00	The Fear Factor of Type-2 diabetes	Tom Elliott
11:20	Questions	
11:30	Acute headache treatment – first remove axe	Tina Korownyk
11:50	Questions	
12:00	Lunch	

"CAUSTICS AND CREEPY CRAWLIES"

13:00	PPI's – how best to prevent acid spills	Mike Kolber
13:20	Fighting the "Common Cold War"	Mike Allan
13:40	MRSA & C. difficile – Double Trouble, Boil and Bubble	Natasha Press
14:00	Questions	
14:20	Refreshment Break	

"THE BUBBLING CAULDRON"

14:40	Chronic hand eczema – the non-Captain Hook approach	Gillian de Gannes
15:00	Going psycho about low dose antipsychotics	Adil Virani
15:20	Getting rid of the Bogeyman around drug withdrawal	Mark McLean
15:40	Questions	
16:00	Adjourn	

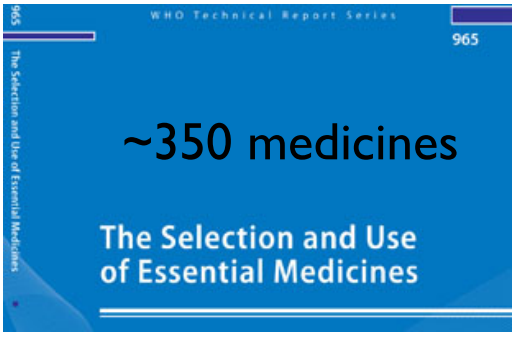
James McCormack and G. Michael Allan

A Sixth Sense - how to make numbers less frightening

Medication Use

Canada - 2008 data
Patients over the age of 65
- 5 or more drug classes - 62%
- 10 or more - 21%
- 15 or more - 6%

BC - 2010 data
- 10-25% use 5 or more Rx drugs



Health Canada
www.hc-sc.gc.ca

Drug Product Database
- includes human pharmaceutical and biological drugs, veterinary drugs and disinfectant products

~15,000 products

Medication Issues

"25% of general medicine admissions and 12% of visits by adults to the emergency department in this country are directly related to adverse drug events - 70% are deemed preventable"

"23% of patients experienced an adverse event within 30 days after hospital discharge - 72% of the events were associated with drugs, and 50% of the events were preventable" - Can J Hosp Pharm.2011;64:305–6

18,623 patients in Alberta - average of 2.12 drug therapy problems/patient - Alberta PPMI 2010

- 95.1% -1 or more
- 20.8% - 3-4
- 8.9% - 5-9
- 2.7% - ≥10

We need minimally disruptive medicine

The burden of treatment for many people with complex, chronic, comorbidities reduces their capacity to collaborate in their care. **Carl May, Victor Montori**, and **Frances Mair** argue that to be effective, care must be less disruptive

BMJ 2009;339:b2803

15 "NEGATIVE" TRIALS IN A ROW

LIPIDS
AIM-HIGH, HPS2-THRIVE (niacin)
ACCORD (fibrates)
dalOUTCOMES (dalcetrapib)

BLOOD PRESSURE
ALTITUDE (aliskiren)
VALISH, AASK, ACCORD (aggressive BP lowering)

DIABETES
ACCORD, ADVANCE, VADT (aggressive A1c lowering)
ROADMAP (olmesartan)
ORIGIN (insulin)

GENERAL
ACTIVE (irbesartan/afib)
CRESCENDO (rimonabant)

James McCormack and G. Michael Allan

Issues to Consider

~ 25-50% of people on drugs for HTN may not have elevated blood pressure on re???- BMJ 2002;325:815–7

~ 1/3 of patients diagnosed with asthma don't have asthma - CMAJ 2008;179:1121-31

~ 90% of COPD patients don't get a clinically important benefit from their inhalers - N Engl J Med 2008;359:1543-54

~ 85% of depressed patients don't get a benefit from their antidepressant - Cochrane Library CD007954

~ 50% of type 2 diabetics have an A1c level that if treated has been shown to NOT benefit or maybe even cause harm - Diabetes Care 2008;1:81-6

Price Comparison of Commonly Prescribed Pharmaceuticals in Alberta 2013

Alberta College of Family Physicians

Generic Name	Brand name	Strength	Dosing	90 Day Cost (unless otherwise noted)	Coverage
CARDIOVASCULAR					
Lipid Lowering Agents					
Rosuvastatin	Crestor	10mg	QD	$60	BC / IA covered
Rosuvastatin	Crestor	20mg	QD	$70	BC / IA covered
Atorvastatin	Lipitor	10mg	QD	$70	BC / IA covered
Pravastatin	Pravachol	20mg	QD	$75	BC / IA covered
Simvastatin	Zocor	10mg	QD	$80	BC / IA covered
Atorvastatin	Lipitor	20mg	QD	$85	BC / IA covered
Atorvastatin	Lipitor	40mg,80mg	QD	$95	BC / IA covered
Ezetimibe	**Ezetrol**	10mg	QD	$195	SA req'd for BC and IA

http://www.acfp.ca

"Come on, it just makes sense"

CHAOS trial[1] found 400-800 IU of Vitamin E reduced non-fatal MI (but nothing else)

And so, the unsinkable ship set sail

But, that 1 study was the tip of the iceberg

Focusing on high-quality RCTs:

Overall, antioxidants increased mortality 1.05 (1.02-1.08)[2] for NNH of 180.[3]

Beta-Carotene (Provitamin A): RR 1.07 (1.02 - 1.11)

Vitamin A: RR 1.16 (1.10 - 1.24)

Vitamin E: RR 1.04 (1.01-1.07)

1) Lancet 1996; 347: 781-6 2) JAMA 2007;297:842-57
3) ACP Journal Club 2007;147(1):4.

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)**

The Evidence

"There is a striking lack of evidence to support the vast majority of sports-related products that make claims related to enhanced performance or recovery, including drinks, supplements and footwear"

BMJ Open 2012;2:e001702. doi:10.1136/

"A meta-analysis of data from cyclists in time trials concluded that relying on thirst to gauge the need for fluid replacement was the best strategy."

Br J Sports Med 2011;45:1149–1156. doi:10.1136/bjsm.2010.077966

Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis

Marc Miravitlles*, Frank Kruesmann#, Daniel Haverstock+, Renee Perroncel+, Shurjeel H. Choudhri+ and Pierre Arvis§

4,003 sputum samples
Pathogen identified
green - 59%
yellow - 46%
rust - 39%
white -18%

"patterns of colours were similar for all species isolated; therefore no specific colour can be associated with a given microorganism"

"it should be noted that the presence of a microorganism in the sputum does not confirm its role as a cause of an exacerbation"

Eur Respir J 2012;39:1354–60

James McCormack and G. Michael Allan

Numbers

	Major coronary events (%)	
	Primary	Secondary
Placebo	5	15
Statin	4	11
RRR	20	25
ARR	1	4
NNT	100	25

The chance of "X"

WITH NO TREATMENT

The chance of "X"

WITH TREATMENT

Baseline risk
RRR, ARR, NNT
Difference between groups

A Simple A fib Table

$CHADS_2$ Score	Patient's ANNUAL risk (%) of ischemic stroke			Difference in benefit between ASA and OAC
	No therapy	ASA	OAC	
0	1.9	1.5	0.6	0.9
1	2.8	2.2	0.9	1.3
2	4	3.1	1.3	1.8
3	5.9	4.6	1.9	2.7
4	8.5	6.6	2.8	3.8
5	18	14	6	8

Bleed risk/yr- aspirin 1%, warfarin 2-3%, dabigatran 2%

Primary prevention of CVD with a Mediterranean diet - 4.8 years, 58% men, 67 y/o, 48% diabetics, 40% statins, BMI 30, 83% HTN

	Mortality (%)	MI, stroke, and death from CVD (%)	MI(%)	Stroke (%)
Low-fat	4.7	4.4	1.6	2.4
Mediterranean diet with EVOO	4.6	3.8	1.5	1.9
Mediterranean diet with NUTS	4.7	3.4	1.3	1.3
Relative risk reduction	NSS	~20-30%	NSS	~20-40%
Absolute risk reduction		~1%		~1%
Number needed to treat		~100		~100

N Engl J Med 2013

Risk: Relative, Absolute & NNT

If you don't know where you start, it's hard to know where you finish.

- If you don't know where you start, it's hard to know where you finish.
- Zoster Vaccine reduces shingles up to 70%

Zoster Vaccine reduces shingles up to 70%

Study	Placebo	Zoster Vac	Benefit	NNT (3 yrs)
Age 50-59 (3 yrs)	2.03%	0.62%	1.41%	71
Age ≥60 (3 yrs)	3.42%	1.67%	1.75%	58

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

- One in 350 for post-herpetic neuralgia.

Tools for Practice Nov 12, 2012

Who really benefits from treatment?

	Total	HDL	LDL	Age	Smoke	BP	10 yr Risk
Mrs Fats	7.5	1.0	5.2	35	No	120	1.7%
Mr Norm	4.9	1.0	2.6	55	Yes	140	13.6%

Mrs Fats: lowest risk but LDL > 5 = Medication
Mr Norm: Moderate risk but in target = No Medication

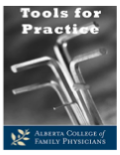
2009 Canadian Cardiovascular Society guidelines: Can J Cardiol 2009;25(10): 567-79.

Who really benefits from treatment?

	Risk* (x10 yrs)	Med	Treating (statin) 5 years		
			Risk	Benefit (~28%)	New risk
Mrs Fats	1.7%	Yes	0.6%	0.17%	0.4%
Mr Norm	13.6%	No	6.2%	1.7%	4.5%

The patient who "should" be treated gets10% of the benefit the patient not treated could get!

James McCormack and G. Michael Allan



Omega-3 Fatty Acids (Fish Oil) for Patients with Cardiovascular Disease (CVD)

Clinical Question: Do omega-3 fatty acid supplements reduce the risk of recurrent cardiovascular events in patients with existing cardiovascular disease (CVD)?

Evidence:
Three recent high-quality randomized controlled trials (RCTs)[1-3] and a subsequent meta-analysis (20,485 patients)[4] did not show a CVD or mortality benefit with omega-3 supplementation:

- 4837 Dutch patients with previous myocardial infarction (MI)[1]
  - Major cardiovascular events and cardiac interventions at 3.3 years: omega-3s 14.0% vs placebo 13.8% (p= 0.93)
- 2501 French patients with recent MI, unstable angina, or ischemic stroke[2]
  - Non-fatal MI, stroke, or cardiovascular death at 4.7 years: omega-3s 6.5% vs placebo 6.1% (p=0.64)
- 3851 German patients post-MI[3]
  - Sudden cardiac death at 1 year: omega-3s and placebo = 1.5% (p=0.84)

Another RCT published after the meta-analysis also found no cardiovascular benefit from 6 years of omega-3 supplementation in 12,536 diabetic or 'near diabetic' patients, 59% of whom had previous CVD.[5]

Tools For Practice

76 statin patients reporting myalgia (age 62, 42% male - 57% recurrent pain)

randomized to CoQ10 60 mg twice daily or placebo

Table 2
Results of visual analog scale

Measurement Period	CoQ10		Placebo		p Value
	Patients (n)	Mean Score (cm)	Patients (n)	Mean Score (cm)	
Baseline	40	6.0 ± 2.2	36	5.9 ± 2.0	0.94
1 month	34	3.9 ± 2.2	32	4.0 ± 2.2	0.97
2 month	31	3.8 ± 2.2	30	3.8 ± 2.7	0.96
3 month	27	3.2 ± 2.3	26	3.1 ± 2.2	0.94

Data are presented as mean ± SD.
CoQ10 = coenzyme Q10.

Am J Cardiol 2012;110:526–9

ORIGINAL INVESTIGATION

Dietary Fiber and Risk of Coronary Heart Disease

A Pooled Analysis of Cohort Studies

Mark A. Pereira, PhD; Eilis O'Reilly, MSc; Katarina Augustsson, PhD; Gary E. Fraser, MBChB, PhD; Uri Goldbourt, PhD; Berit L. Heitmann, PhD; Goran Hallmans, MD, PhD; Paul Knekt, PhD; Simin Liu, MD, ScD; Pirjo Pietinen, DSc; Donna Spiegelman, ScD; June Stevens, MS, PhD; Jarmo Virtamo, MD; Walter C. Willett, MD; Alberto Ascherio, MD

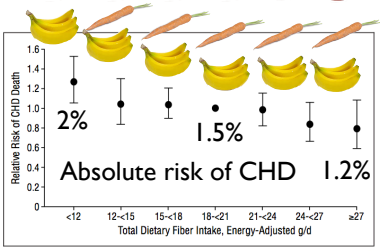
Arch Intern Med 2004;164:370-6

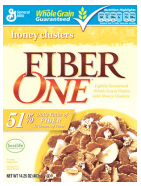
10 prospective cohorts - 6-10 years
336,244 - avg age ~ 50-55
5,249 events

for each 10g/day increment of dietary fiber
CHD was reduced by 14% CI (4-22)

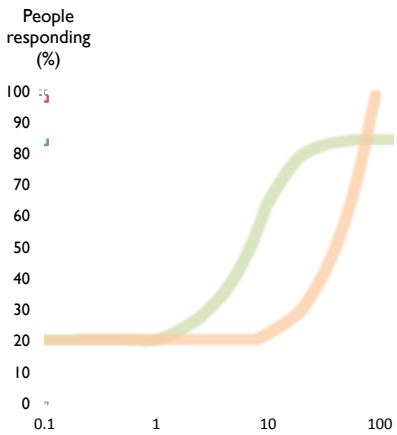
55 y/o
increase fiber from none to a lot for 5-10 years
1 in 125 get CHD benefit

Lifetime risk of CHD 40%





Relative risk of death from coronary heart disease (CHD) by category of total dietary fiber intake. The relative risks are adjusted for the same variables as in Table 3. Error bars indicate 95% confidence intervals.



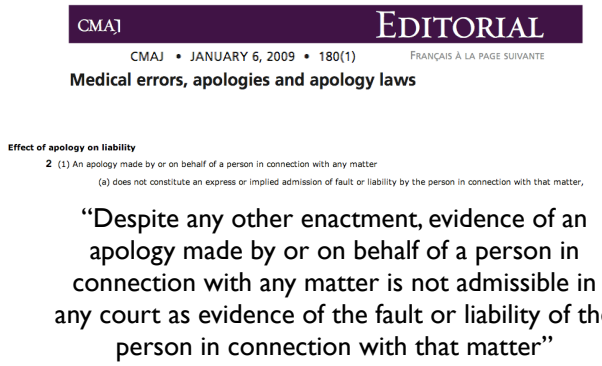
PDR recommendations		% BENEFIT	% HARM
	Placebo	20	20
	5	40	20
Starting dose	10	65	25
	20	80	30
Maximum dose	40	83	50
	80	84	90

It's a dose thing

"more than 80% of ADRs causing admission or occurring in hospital ... are dose related, an 'accentuation' of the known pharmacological effect of the drug, and thus predictable and potentially avoidable"

Br J Clin Pharmacol 2004; 57:121–6

James McCormack and G. Michael Allan



CMAJ EDITORIAL

CMAJ • JANUARY 6, 2009 • 180(1) FRANÇAIS À LA PAGE SUIVANTE

Medical errors, apologies and apology laws

Effect of apology on liability

2 (1) An apology made by or on behalf of a person in connection with any matter

(a) does not constitute an express or implied admission of fault or liability by the person in connection with that matter,

? *Act*,
therwise
:hat

in any

"Despite any other enactment, evidence of an apology made by or on behalf of a person in connection with any matter is not admissible in any court as evidence of the fault or liability of the person in connection with that matter"

How to decrease chance of lawsuits

1. BC has an apology law - So apologise!!!
2. Put in place something that will prevent the error in the future
3. Don't be a JERK
4. If there is negligence - **$$$$$$$$**

G. Michael Allan

Chronic Neuropathic Pain

G. Michael Allan
Associate Professor & Director of EBM, Dept of Family Med, U of A
Director of Evidence and CPD, Alberta College of Family Physicians

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty:** G Michael Allan
- **Relationships with commercial interests:**
  - **None**

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

- **This program has received financial support from** n/a **in the form of** n/a.
- **This program has received in-kind support from** n/a **in the form of** n/a.
- **Potential for conflict(s) of interest:**
  - None
  - None

CFPC CoI Templates: Slide 3

Mitigating Potential Bias

- n/a

Neuropathic Pain

- Diabetic neuropathy
- Post-herpetic neuralgia
- Trigeminal neuralgia
- Other causes: Radiation injury, some drugs, trauma, nerve injury (spinal cord/brain or peripheral), alcohol injury (via B1 def), Guillain Barre, HIV, etc.

Overview of Evidence Quality

- Poor quality with lots of Outcomes,
- Differing Cut-offs, Generally
  - Moderate improvement of ≥30%
  - Substantial improvement of ≥50%

G. Michael Allan

Anti-Depressants

- Cochrane rev: 61 RCTs in neuropathic pain
  - Neuropathic pain types: diabetic neuropathy (17), postherpetic neuralgia (11[+1 with trigeminal]), Mixed 12), Central (5), Atypical facial pain (5), others (e.g. HIV, burning mouth, post-surg, etc)
  - Types of anti-depressants: TCAs (31 placebo, 17 active), SSRI (4), Venlafaxine (6), Other (buproprion, St Johns Wort)
- Mainly versus Placebo, some head to head.

Central Pain is post stroke or trauma/spinal cord injury

Summary of Results: For moderate improvement in pain

Drug/Intervention	Relative Benefit	NNT	Heterogeneity (I stat)
TCA overall	2.1 (1.8 - 2.5)	3.6	?
Amitriptyline	2.23 (1.4 - 3.7)	3.1	85%
Imipramine	19 (4.0 - 90.8)	2.2	12%
Desipramine	5.75 (2.3 – 15.1)	2.6	0%
Venlafaxine	2.16 (1.5 - 3.1)	3.1	50%

* I calculated this from the meta-graph.

Summary of Results: For moderate improvement in pain

Drug/Intervention	Relative Benefit	NNT	Heterogeneity (I stat)
Diabetic Neuropathy	12.41 (5.3 - 29.2)	1.3	0%
Post-Herpetic Neuralgia	2.33 (1.7 – 3.2)	2.7	83%
Facial Pain	1.67 (1.2 – 2.3)	3.4	0%
Central Pain	3.5 (1.3 – 9.3)	2.4*	73%
HIV Pain	Likely not sign.		

* I calculated this from the meta-graph.

Issues

- Heterogeneity
  - Authors did not try explain this
  - ? older studies having better results
  - Lots of small studies is also contributing
- Limited data
  - Mean data not shown (Change in pain scales)
  - No "risk of bias" table.
    - Unclear AC 75%, Clear AC is 25%
    - Mean JADAD score 3.4 (out of 5)

Cochrane Database Syst Rev. 2007 Oct 17;(4):CD005454.

Other Issues

- No consistent difference between TCAs.
- No difference vs tramadol, ASA, or anti-convulsants.
  - Maybe better than Benzo's
  - Maybe worse than morphine.
  - TCA maybe slightly better than SSRI.
- SSRI – Mixed info. May be helpful but limited data.
- AE (to quit): TCA (NNH 28) & Venlafaxine (NNH 16)
  - Minor AE: TCA (6) and Venlafaxine (9)

Duloxetine (cymbalta)

- Cochrane review: 3 RCTs of Diabetic Neuropathy
  - Duloxetine 60mg OD for 12 weeks.
- Benefits
  - Change (0-10 pain scale): 1.62 placebo & 2.66 duloxetine.
  - Maybe some QOL sub-scores (like physical) some improvement

Get a 50% improvement on 60mg Duloxetine	Control	Duloxetine	Relative Benefit	NNT
	29%	48%	1.65 (1.3 – 2.0)	6

Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007115.

G. Michael Allan

Duloxetine (cymbalta)

- AE: NNH (to quit) 17, RR 1.7 (1.2 - 2.3)
  - Somnolence, nausea, dry mouth, & dizziness ≈2 times
  - AE were dose dependent
- Issues
  - Generally good quality but 1 Funder & ? Complete reporting
  - 120mg ≈ 60 mg (& 20mg only a little worse)
  - Minimal heterogeneity.
- CDR looked at 3 RCTs: Recommended after two less costly meds are tried.

Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007115. CEDAC meeting July 2008 CADTH

Gabapentin

- Cochrane: 29 studies, 3571 participants
  - Most Post-herpetic, Diabetic neuropathy, & Mixed neuropathy
- Duration: 4-14 weeks
- Quality:
  - Blinding 86%, AC: 52%
  - Data reporting, small study size and short study duration issues in ≥50%.
- Dose often between 1200 (often 1800) and 3600mg

Cochrane Database Syst Rev. 2011 Mar 16;(3):CD007938.

Outcomes Overall

Outcome	Gabapentin	Placebo	Relative Risk	Hetero	NNT/H
≥50% pain reduction	32.7%	18.7%	1.7 (1.5, 2.0)	30%	8
Much or very much better	39.2%	23.1%	1.6 (1.4, 1.9)	59%	7
Substantial Improvement	31.5%	16.8%	1.8 (1.6, 2.1)	34%	7
≥Moderate Improvement	42.9%	25.6%	1.7 (1.5, 1.9)	17%	6
Withdrawal due to AE	11.3%	8.3%	1.4 (1.1, 1.7)	0%	32
1 or more AE	66.2%	54.0%	1.3 (1.2, 1.4)	46%	9
Serious AE	4%	3.2%	1.3 (0.9, 2.0)	0%	-
Somnolence	16.3%	5.4%	3.2 (2.5, 4.2)	0%	10
Dizziness	20.6%	6.6%	3.3 (2.6, 4.1)	0%	8
Peripheral Edema	8.1%	2.7%	3.4 (2.2, 5.3)	33%	19
Ataxia/gait Disturbance	8.8%	1.2%	4.5 (1.9,10.8)	4%	14

NNT calculated off pooled results. (Their numbers don't quite match though so I redid)

Remaining Issues

- Mean Pain scales
  - Moves pain (vs placebo) ≤1 point on 10 pt scale
- Factors on effectiveness
  - Dose: Insufficient data
  - Increasing duration: slight decrease in effectiveness.
  - Differing conditions: no effect
- Publication Bias: Hidden trial data
  - 40% trials unpublished, 68% outcomes not reported
- See Other Evidence, Two pages Next

N Engl J Med 2009;361:1963-71. Therapeutics Letter 75. 2009: http://www.ti.ubc.ca/PDF/75.pdf

Pregabalin

- Cochrane: 14 trials (3680 pts)
  - 95% PHN or Diabetic neuropathy
  - Dose 150-600mg, Duration mean 9.8wks
- Quality: Mean is 1.6 out of 3.
- Benefits improve slightly at higher dose

	NNT ≥30%	NNT ≥50%
PHN	3-4	4-7
Diabetic Neuropathy	5-7	5-8

Cochrane Database Syst Rev. 2009, (3): CD007076.

Pregabalin: Harms

- Serious AE not significantly higher.
- AE not significantly at 150mg
- ≥1 AE: 300mg-600mg NNH 7
- Somnolence (NNH 4-12), Dizziness (3-8),
- Withdrawal due to AE (300mg-600mg):
  - Rates: 11-19% vs 5-6% (Placebo), NNH 16-8 (most 8-10).

Pregabalin: Sum-Up

- "No direct clinical trial evidence that pregabalin has a therapeutic advantage over gabapentin."[1]
- In the only trial with TCA, amitriptyline superior to placebo but not pregabalin.[1]
- **Bottom-line: Pregabalin will cause a 50% or more pain reduction for one in 4-8 patients.**
  - **About one in 7 AE and 10 quit due to AE**
  - **Benefits & harms increase at higher doses.**

1. CDR Sept 23, 2009, pregabalin review)

Second or Third-Line:

Opioids for neuropathic pain

- Cochrane: 23 RCTs (727 pts)
  - Given 28 d median, Generally good quality
- Outcomes:
  - Change (vs placebo) on 100 pt scale: 12.77 (9.1, 16.4)
  - ? Slightly better vs other chronic meds but data very limited.
  - ? slight effect on other outcomes (function, QOL, etc)
- Harms (NNH): Nausea (5), Constipation (5), Drowsiness (7), Dizziness (8), Vomiting (9)
  - Withdrawal for AE: 10.8% vs 4.5%, NNH 16
- Bottom-Line: Effects similar to others but as mean response used, can not give an NNT for benefit. Lots of harms.

Cochrane Database Syst Rev 2006 (3): CD006146.

Drug Combinations

- Cochrane: 21 high quality RCTS
  - 4 Opioids +gabapentin/pregabalin; 2 opioid + TCA; 1 TCA and gabapentin; 3 fluphenazine + TCA; etc
- "Multiple, good-quality studies demonstrate superior efficacy of two-drug combinations. However, the number of available studies for any one specific combination, as well as other study factors (e.g. limited trial size and duration), preclude the recommendation of any one specific drug combination for neuropathic pain."
- As efficacy increases so does AE
- Bottom-Line: Likely worth a try (45% of neuropathic patients will need 2+ drugs)

Cochrane Database of Syst Rev 2012; (7): CD008943.

Carbamazepine

- Cochrane: 14 RCTs
  - Mess of small studies (all but two <60), short duration (all but two <8 weeks), many were cross-over, lots active comparators.
  - Quality: Poor
- Benefit: Any pain improvement 69.4% vs 11.3%, NNT 2
- Harms: One or more AE, 65.3% vs 27.2%, NNH 3
- **Bottom-Line**: Data positive (the best NNT) but evidence very poor. Should be low on the list.

Cochrane Database Syst Rev. 2011, (1): CD005451.

Valproate

- Cochrane: 3 RCTs (129 pts)
  - 8-12 weeks & Quality poor
- Outcomes: 2 of 3 mean improved pain
  - ≥50% pain (1 study - PHN): NNT 3 (Stat Sign by me)
- Harm: ? nausea and drowsiness. 1 pt had LFT disruption causing withdrawal
- **Bottom-Line**: Weak, bias evidence of probable effect. Should be low down on the list of choices

Cochrane Database Syst Rev 2011, (10): CD009183.

G. Michael Allan

Capsaicin Patch 8%

- Cochrane[1] + Meta[2] + RCT[3]
  - 8% Capsaicin Patch, applied 30-90 minutes (generally 60) on affected area, once then nothing over 3 months. 4% Lidocaine applied first for 60 mins
  - Quality: mixed. Industry funded and written by employees
- Outcome,
  - PHN: 50% pain relief, Difference 29% vs 21%, NNT 13,
  - HIV Neuropathy: ≥30% pain 34% vs 18%, NNT 7
- Harm: NNH 10 for one or more AE
  - For irritation on application: NNH 8
- **Bottom-Line**: This seems to be moderately effective but also has AE (seems a little unusual?).

1) Cochrane Database Syst Rev 2009, (4): CD007393. 2) Clin J Pain 2012;28:101–107) 3) Neurology 2008;70;2305-2313.

Lacosamide (anti-epileptic)

- Cochrane: 5 RCTs in Diabetic Neuropathy (1863 patients)
  - Dose 200, 400 or 600mg total (divided BID)
  - 4-12 wks after titration
- Effects: For 400mg
  - Substantial (≥50% improve): NNT 10
  - Global improve: NNT 12 (least bias)
- AE worse with higher dose. E.g. Withdrawal due to AE
  - No increase at 200mg, 400mg (NH 12), 600mg (NNH 4)
  - Main types: Dizziness, tremor, nausea, vomiting,
- Anti-convulsant only: Notice of compliance Sept 30, 2010 for partial-onset seizures not controlled.
- Bottom-Line: Too new with too many other options

Cochrane Database Syst Rev. 2012 Feb 15;2:CD009318.

Capsaicin: Cream

- Cochrane 2012: Focus on low dose (which is cream)
  - 6 trials, 389 patients (small, 6-12 weeks in duration)
  - Dose is 0.075% QID
- Outcomes: Cochrane did not pool. 1 of 5 stat sign
  - No mean data reported
- Harms
  - Withdrawal: 14.9% vs 3.0%, NNH 9
  - Cough & sneeze (NNH 7); Burning, stinging, & erythema (NNH 3)
- **Bottom-line**: It is unclear if any reasonable improvement. Particularly against the adverse events.

1) Cochrane Database Syst Rev 2012, (9): CD010111

Lamotrigine

- Cochrane: 12 RCTs, 1511 patients
  - 200-400mg a day, 8 studies 8+ weeks.
  - Diabetic neuropathy most common
  - Of 8 quality markers, no trial had >4 good quality.
- Outcomes: Inconsistent reporting
  - ≥50% pain (Diabetic): No difference (25.6% vs 24.3%)
  - Others rarely statistical significant
  - Rash: 9.5% vs 5.6% (NNH 25), 1.4 (1.0, 2.0)
- Bottom-Line: Evidence of benefit lacking.

Cochrane Database Syst Rev. 2007 Apr 18;(2):CD006044.

Topical Lidocaine Post Herpetic Neuralgia

- Cochrane: 3 RCTs, 314 pts
  - 5% lidocaine gel or 5% patch (up to TID)
- Outcomes: change in Pain Scale (6 pts?)
  - WMD 0.42 (0.14, 0.69) – (improve 7%)
  - Number to attain 50% or similar not available
- Harms: Similar number of AE in both groups.
  - Lidocaine level ranged from 59ng/ml up to 431 which is too high (but may be wrong)
- **Bottom-Line**: Too little evidence (and small relative benefit) to put high on the list. Likely also limit use to watch for excessive lidocaine levels.

Cochrane Database Syst Rev 2007, (2): CD004846.

Cannabis

- 2 Systematic reviews: oral (spray/tab) & any method
  - 18 RCTs & 7 RCTs
  - High risk of bias from lack of confirmed blinding, low ITT & AC and short (25 days), up to 65% past users
- Outcomes:
  - Oral SMD (intensity of pain by VAS): 0.61 (0.37, 0.84). no NNT data
  - Smoked Studies seemed best (?): all 3 RCT benefit
    - 1 study: to ≥30% pain relief: 52% vs 24%, NNT 4
    - 1 study Nabilone vs opioid: opioid better.
- Harms (NNH): Euphoria (9), Blurred Vision/visual hallucination (3), Disorientation/confusion (15), Speech disorder (5), Ataxia/muscle twitching (5), numbness (5), Impaired memory (8), disturbance in attention/disconnected thought (8): Dysphoria (29?), disassociation & acute psychosis (21)
- **Bottom-Line**: Evidence at very high risk bias. Harms common

Pain Medicine 2009; 10(8):1353-68. *CADTH: 13 July 2010, Cannabinoids for Management of Neuropathic Pain*

Grab-Bag

- No Evidence of Meaningful Effect
  - Brain or Spinal Cord Stimulation
  - Therapeutic touch, Healing touch, Reiki
  - TENS
  - Psychology (CBT)
  - Exercise
  - B-Vitamins
- Systemic Local Anesthetics
  - May work but IV (& risks)
- Anti-Psychotics
  - No consistent evidence
- Chinese Herbs
  - Loosely defined as research

What Works

- TCA's (& maybe Venlafaxine): NNT 2-4
- Gabapentin, Pregabalin, Duloxetine: NNT 4-8
- Opioids
- Combinations
- Other Anti-epileptics
- Others

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FIBROMYALGIA

ARE YOU GOING TO LOVE IT OR LIST IT?

Barry Koehler, MD, FRCPC
Kam Shojania, MD, FRCPC

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty:** Kam Shojania
- **Relationships with commercial interests:**
  - **Grants/Research Support:** Pfizer, Janssen, BMS, Roche, Abbott, Amgen, CIHR, Arthritis Society, Canadian Rheumatology Association
  - **Speakers Bureau/Honoraria:** All of the above , on rare occasion over the past few years.
  - **Consulting Fees:** Augurex
  - **Other:** Rheumatology Head at UBC, VGH, SPH. Consulting for Provincial Blood Coordinating Office, Program Director UBC Rheumatology

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

- **This program has received financial support from** None **in the form of** None
- **This program has received in-kind support from** [None] **in the form of** [None].
- **Potential for conflict(s) of interest:**
  - Only 1 slide with 2 drugs mentioned in my talk and I mention them only to disparage them.

CFPC CoI Templates: Slide 3

Mitigating Potential Bias

- I am biased against the medicalization of society.
- I feel that the discovery of new 'syndromes' was previously helpful in determining causation and treatment (e.g. AIDS) but now used to make health care professionals, alternate care providers and various industries wealthier.
- I will try to mitigate my biases by keeping an open mind to what Dr. Koehler has to say.

Would you trust this man?

How about this man?

Barry Koehler and Kam Shojania

What is fibromyalgia ?

- A new, and disabling disease of unknown origin (waiting to be discovered) ?
- The rheumatologist's 'functional somatic syndrome' (as irritable bowel syndrome is for the gastroenterologist) ?
- A 'mental' illness (a somatoform and/or affective and/or anxiety and/or personality disorder) ?
- A fashionable diagnostic label for common misery (diffuse pain and fatigue) ?
- An opportunity for drug or alternative medicine marketing ?

Correlates

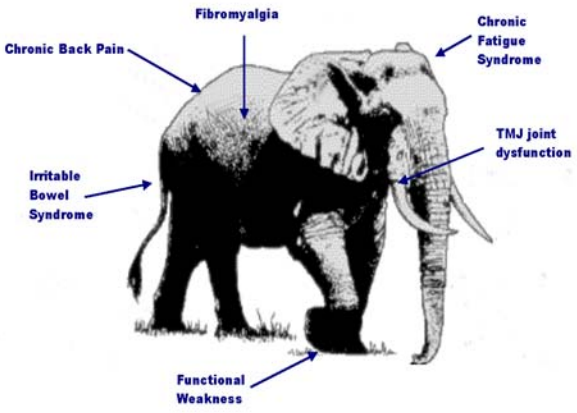
- Is fibromyalgia a useful diagnosis ?
  - For patients/sufferers ?
  - For doctors ?
  - For society ?
- Suggesting/accepting/making a diagnosis of fibromyalgia (FM) has several medical, psychosocial and even moral implications

Problems with 1990 ACR criteria

- Required duration of symptoms
- A number of important non pain symptoms are not taken into account (fatigue, unrefreshing sleep, IBS, psychological distress, etc…)
- Primary or secondary fibromyalgia :
  (Kahn MF. *Rev Prat* 2003;53:1865-72)
- Questionable relevance of tender points :
  « *Tender points, as the essential criterion, was a mistake* » **(Wolfe F. *J Rheumatol* 2003;30:1671-2)**

Why FM should be considered a functional somatic syndrome

- It has no established, satisfying or specific biological explanation
- Most recent 'central sensitization' theories smell like another way to get research funds.
  Wolfe F *et al. Arthritis Rheum* 1997;40:1560-70 & 71-79.
- FM is frequently comorbid with other functional somatic syndromes



Key points in the social construction of fibromyalgia

ACR diagnostic criteria give an illusion of coherence within the chaos of functional symptoms, and brings 'reality' to the 'syndrome' in :

- focusing on pain and ignoring many other symptoms
- alleging objectivity (tender points, pain scales) while distracting from the central symptoms of distress
- Complete avoidance of psychological distress.

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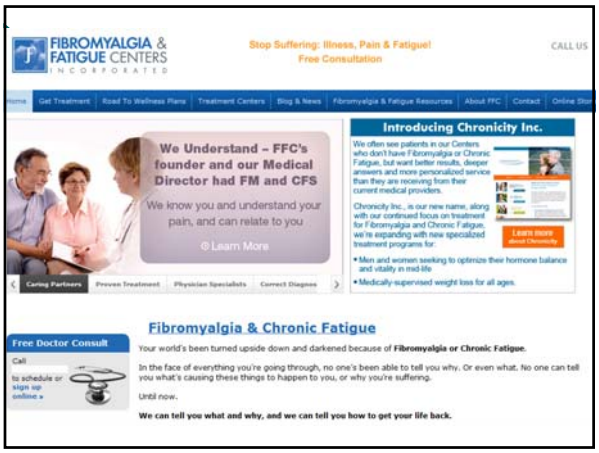

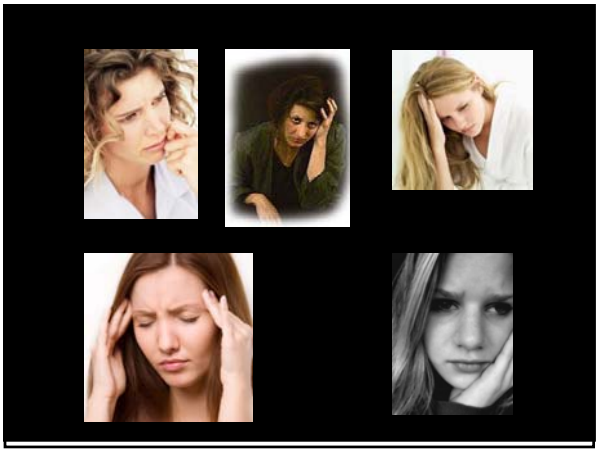

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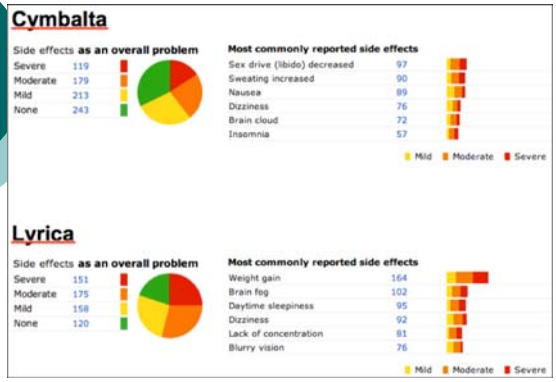

Struggle for legitimacy, claim for disability

FIBROMYALGIA IS REAL

National Fibromyalgia Association and Citrucel® Launch Awareness Day 2006 Campaign

May 12, 2006

"But You Don't Look Sick! The Invisible Pain of Fibromyalgia"

Key points in the social construction of fibromyalgia

- Becoming a fibromyalgic transforms one's identity :

Hadler NM & Greenhalgh S. Labeling woefulness : the social construction of fibromyalgia. *Spine* 2004;30:1-4.

« No one has FM until it is diagnosed »

Ehrlich GE. Pain is real; fibromyalgia isn't. *J Rheumatol* 2003;30:1666-7.

« How the person suffering persistent widespread pain learns to be a patient with FM »

Hadler NM. « Fibromyalgia » and the medicalization of misery. *J Rheumatol* 2003;30:1666-7.

Should we make a diagnosis of fibromyalgia ? YES !

- Prognosis may prove good if the quality of doctor-patient relationship is preserved and if proper management is offered

Goldenberg DL. Fibromyalgia : To diagnose or not. Is that still the question ? *J Rheumatol* 2004;31:633-5.

Should we make a diagnosis of fibromyalgia ? NO !

- The label may be a self-fulfilling prophecy of chronicity and disability

« …support and advocacy group aggravate the problem, disability is certified, a hopeless prognosis is offered… »

Ehrlich GE. Pain is real; fibromyalgia isn't. *J Rheumatol* 2003:30:1666-7.

« the fibromyalgic is transformed into a long-term patient whose life is dominated by, and limited by, disease »

Hadler NM & Greenhalgh S. Labeling woefulness : the social construction of fibromyalgia. *Spine* 2004;30:1-4.

Faculty/Presenter Disclosure Barry Koehler

- **Bias is not only encountered from commercial sources, but also from academic and individual sources. Our responsibility as health professionals is identify these biases, whatever the source.**

- **Relationships with commercial AND OTHER interests:**
  - **Grants / Research Support:**
    - None at present
    - Previous participation in drug research (Phase 2B and 4), funded by Bristol-Myers-Squibb, Schering, Pfizer, Centocor, Janssen, Immunex, The Arthritis Society, Novartis, Ascentia, Abbott, Boerhinger-Ingelheim, Amgen; none presently in progress
  - **Speakers Bureau / Honoraria:**
    - Amgen, Schering, The Arthitis Society, Biovail, Sanofi ... and probably some others
  - **Consulting Fees:**
    - I only wish
  - **Other:**
    - President of Medical Staff, Richmond Hospital 2007-2008
    - Undergraduate medical student teaching, UBC
      - The above both were reimbursed and both involved pressure to comply with certain guidelines which I had no part In developing
    - Participant in GPSC MSK project; supported by BCMA and Ministry of Health
    - Participant in Richmond Division of Family Practice project, supported by BCMA and Ministry of Health
    - Drug reviews for Pharmacsare

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Disclosure of Commercial Support

- **Potential for conflict(s) of interest:**
  - Barry Koehler has received a speaker's fee from the Drug Therapy Course.
  - One of my supervisors during my rheumatology training was Dr. Hugh Smythe, who developed the initial, although no longer utilized, concept of fibromyalgia.
  - I am a shareholder of the Journal of Rheumatology.
  - Having practised with Dr. Shojania for many years, I know that his "open mind" may have allowed for a "brain drain" – but he did help with the office overhead

Mitigating Potential Bias

- If I am not able to present my views, I withdraw from the project.
- If a research study does not seem to have an adequate design, I do not participate.
- I endeavor to identify information as being research-based with good data, research-based with uncertain data, or expert opinion-based (others or my own)

Fibromyalgia: A brief history

JOB HAD FIBROMYALGIA!

- Job 17: 11, 12
  - My days are past, my thoughts are broken off, even the thoughts of my heart,
  - They change the night into day …
- Job 30: 16, 17
  - And now my soul is poured out upon me; the days of affliction have taken hold upon me,
  - My bones are pierced in me in the night season: and my sinews take no rest.

Dr Kam Shojania

Wallace Graham 1953

"It is probable that, in most cases, fibrositis syndrome is precipated by a psychosomatic disorder …. Such a mechanism has long been accepted as the basis for cardiac and gastric complaints …"

Bulletin on Rheumatic Diseases April 1953

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Diagnositic criteria for fibromyalgia - Smythe and Moldofsky, 1969

- 12 of 18 tender points
- Negative control points
- Sleep disturbance
  - Yes, the sleep disturbance was not unique, but they recanted

Fibromyalgia Tender Points

- Occiput
- Anterior transverse process C5/6
- Midpoint of belly of trapezius
- Insertion of supraspinatus
- 2nd costochondral junction
- Extensor insertion of elbow
- Greater trochanter
- Upper outer buttock
- Medial fat pads of knees

Diagnostic Criteria of Fibromyalgia

American College of Rheumatology (1990):

- The presence of widespread pain in four body quadrants for at least 3 months
- Pain and tenderness reports upon palpation at 11 or more of 18 specific areas, referred to as 'tender points'
  - **The big error: The ACR consensus group failed to emphasize control points**

Additional commonly reported symptoms include:

- functional limitations, muscle stiffness, fatigue, irritable bowel syndrome, headaches, sleep disturbance, depression, and anxiety.

Prevalence Rates of Fibromyalgia I

Prevalence of widespread chronic pain in the general population:

- English sample: 11.2%
- Canada & U.S. samples: approximately 10%

Prevalence of FM:

- Canada & U.S. populations: 1 - 2%
- One eastern Canadian city estimates:
  - 5% of women
  - 1.6% of men

Gender & Fibromyalgia

Gender rates of FM:

- 5-10 times more frequent in women
- 80-90% afflicted with FM are women
- Accordingly there is a bias to implicate emotional mechanisms in the etiology of FM
  - Historical gender bias
  - Psychological diagnoses, like hysteria and anorexia, were more commonly diagnosed in women
- But there have been other illnesses which have been attributed to psychosomatic causes:
  - multiple sclerosis
  - systemic lupus erythematosus
  - rheumatoid arthritis

Most of all, fibromyalgia remains a valuable concept for patients

- It provides an understanding of their chronic pain problem
  - "I'm not crazy".
  - The pain is real but is not causing organic damage.
  - It provides a framework around which to build a management programme.
- Providing the diagnosis does not cause functional deterioration.
  - Review at 18 and 36 months of newly diagnosed fibromyalgia cases showed significant improvement in:
    - Satisfaction with health
    - Reporting of fewer symptoms and major symptoms
    - No other differences in clinical status or health services

White KP, Nielson WR, Harth M, Ostbyte T, Speechley M. Does the label 'Fibromyalgia' alter health statusfunction, and health service utilization? A prospective, within-group comparison in a community cohort ofadults with chronic widespread pain. Arthritis Care Res 47; Jun 2002: 260-65

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Medical Hypotheses: Part I

Muscle Structures
- Some abnormalities found, but not specific to FM

Sleep
- Stage 4 sleep disruption reported but not unique

Growth Hormone
- ↓ found in adults with similar symptoms to FM
- Replacement therapy →↑ quality of life - inconsistent finding

Sensory neuropathy
- In some diabetic patients

Lesions in lower cervical and lumbar vertebrae
- Postulated microscopic nerve root impingement
- Independent hypotheses by Smythe and Gunn

Neuroendocrine Function
- Deficiencies in some neuroendocrine functioning
- Similar findings in depressed patients

Neurochemical/transmitter
- ↑ levels of substance P, ↓ levels of serotonin, involved in pain transmission
- ↓ serotonin also found in depressed patients

Medical Hypotheses: Part II

- Stress-response System
  - impaired stress response
  - response to personal stressors have not examined
  - depression & anxiety overlap
- Brain Imaging
  - brain activation patterns support ↓ pain threshold
  - cerebral cortical regions may be involved in pain sensitivity differences
- Sensory Processing
  - ↓ pain threshold & ↑ pain sensitivity across sensory modalities
  - slower speed of recovery from noxious stimulation
- Gender & Pain
  - ↑ pain sensitivity & ↓ pain threshold and tolerance in healthy women
  - differences in gender role expectations & coping strategies
- Diathesis-stress Model
  - Underlying genetic and environmental predispositions become expressed in stressful situations
  - Personalities associated with marginally adaptive coping styles typically decompensate with the stress of an injury, chronic pain, or disability.
- Hypervigilance Model
  - Chronic pain patients may have ↑ sensitivity to pain because of ↑ awareness and preoccupation with noxious stimuli
- **Neuroplasticity *The flavour of the month***

What's the message?

Where ignorance is rampant, theories abound

But wait, but wait, but wait …

- The times and definitions, they are a'changing ….

ACR 2010 Provisional Criteria for Fibromyalgia

- Consist of 3 calculations
  - Widespread pain index (WPI)
  - Symptom severity (SS) scale score

1) WPI: note the number areas in which the patient has had pain over the last week.

- In how many areas has the patient had pain? Score will be between 0 and 19.

- Shoulder girdle, left
- Hip (buttock, trochanter), left
- Jaw, left
- Upper back
- Shoulder girdle, right
- Hip (buttock, trochanter), right
- Jaw, right
- Lower back
- Upper arm, left
- Upper leg, left
- Chest Neck
- Upper arm, right
- Upper leg, right
- Abdomen
- Lower arm, left
- Lower leg, left
- Lower arm, right
- Lower leg, right

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- 2) SS scale score:
  - Fatigue
  - Waking unrefreshed
  - Cognitive symptoms

  For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:
  - 0 no problem
  - 1 slight or mild problems, generally mild or intermittent
  - 2 moderate, considerable problems, often present and/or at a moderate level
  - 3 severe: pervasive, continuous, life-disturbing problems

- 3) Considering somatic symptoms in general, indicate whether the patient has:*
  - 0 no symptoms
  - 1 few symptoms
  - 2 a moderate number of symptoms
  - 3 a great deal of symptoms
- The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.

- * Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen,nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears,vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

- A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:
  - 1) Widespread pain index (WPI) 7 and symptom severity (SS) scale score 5 or WPI 3–6 and SS scale score 9.
  - 2) Symptoms have been present at a similar level for at least 3 months.
  - 3) The patient does not have a disorder that would otherwise explain the pain.

Should we make a diagnosis of fibromyalgia ? NO !

- Not any more, but we're stuck with it!
  - **Conversation with Dr. Maryann Fitzcharles, McGill, member of the ACR committee which developed the new criteria:**
    - **BK: « Maryann, why didn't you get them to change the name from 'fibromyalgia'? »**
    - **Maryann: « I tried, but they refused. »**
  - **So, for the wrong reasons, Dr. Shojania is right. There was a potential for the study of a discrete set of patients (12 tender points, negative control points) but the potential was never developed.**

When you diagnose fibromyalgia I

- Co-existence of fibromyalgia with other rheumatic diseases, rheumatic or others, mandates a careful musculoskeletal examination.
- The presence of fibromyalgia does not invalidate another MSK or other disorder.
- Identification of fibromyalgic component prevents overtreatment of the associated disease; eg, rheumatoid arthritis

When you diagnose fibromyalgia II

- If no other considerations than fibromyalgia, inform the patient that he/she fufils criteria for the *syndrome* of fibromyalgia.
- Tell the patient what this means
  - Chronic pain condition
  - Not curable but treatable
  - No damage to tissues, despite pain

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When you diagnose fibromyalgia III

- Tell the patient what you are *not* going to do – "I'm not going to make the pain go away.
- Tell the patient what you *are* going to do -
  - Treat to Target
  - Counseling re non-medical methods of pain management
  - Reiteration of "benign" nature of pain
  - Emphasis on "getting on with life", not waiting for a (non-existent) cure
  - Realistic approach to work

Fibromyalgia - Treat to Target I

- Functional assessment
  - PT, OT, general conditioning
  - Be structured in reviewing in this
  - Use an appropriate health professional
- Mood assessment
  - Be structured
  - Use an appropriate health professional
  - "Living with Chronic Pain" programme

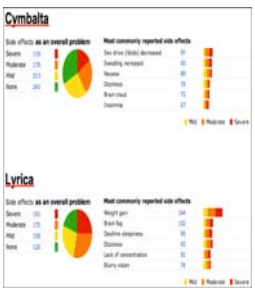
Fibromyalgia - Treat to Target II

- Sleep assessment
  - Be structured
  - Emphasize that interventions are meant to improve sleep, not likely to improve pain (contrary to Dr. Google)
- Risk assessment
  - Particularly medication use
  - Opiates impose risk, no studies to show long term benefit

FIBROMYALGIA - Treatment

- De-emphasize medications
  - NSAID's
  - Sleep-modifying agents
  - Opioid analgesics
  - Local injections
- Can be tried, always with caveats re limited benefit
- Give defined trial; placebo effect can be as long as 6 months

Carette S, Bell M, Reynolds J, Haraoui B, McCain G, Bykerk V, Edworthy S, Baron M, Koehler B, Fam A, Bellamy N, Guimont C. A controlled trial of amitriptyline cyclobenzaprine and placebo in fibromyalgia. Arthritis Rheum 1994;37 (1):32-39.



- Oops, Dr. Shojania did show a bias to which he did not admit – TI bias
  - He showed more concern for side effects than benefits

National Comorbidity Survey

- in the presence of chronic pain

- Major Depression
  10.3%
- Anxiety Disorders
  17.2%
- Alcohol Abuse/ Dependence
  9.7%

"These conditions are more common in the chronic pain population. In our clinic, over 50% have at least one."

Kessler, Arch Gen Psych 1994, 51:8-19

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Why do 'fibromyalgia' patients resist the idea of a comorbid mood disorder?

- Stigma
- Lack of public knowledge
- Depressive symptoms are often masked by somatic complaints
- Lack of abstract thinking
- Possibility that mood disorder may be 'non-compensable'

FIBROMYALGIA AND TRAUMA

- About 5-10% of population have fibromyalgia; about 1% of the population have rheumatoid arthritis.
- Both have unknown etiology; we do not believe that RA is induced by trauma.
- It is more likely that fibromyalgia occurs coincidentally post-trauma.

Simulation of fibromyalgia

8 patients with fibromyalgia, 19 volunteers (half encouraged to simulate fibromyalgia)

- 1/3 of simulators felt to have fibromyalgia
- 1/5 of fibromyalgics thought to be simulators

Khostanteen I, Tunks E, Goldsmith C, Ennis J. J Rheum 2000; 27: 11, 2671-2676

FIBROMYALGIA AND DISABILITY

- No completely satisfactory tests that objectively help with the DX of FM and assess the degree of disability
- Patients with FM rate :
  1. Quality of life poorer than RA and OA.
  2. Ability to perform ADL's same as RA.
  3. Lowest global self-assessment and functional scores together with the highest pain scores.

ASSIGNING DISABILITY I

- Disease or syndrome
  - Cannot discuss diminished function in the absence of some type of entity
- Impairment
  - There must be an identifiable, organic lesion
- Disability
  - The impairment must result in diminished function to an organ or system

ASSIGNING DISABILITY II

- Handicap
  - The disability leads to some type of loss of personal function

Can an individual with fibromyalgia have disability/handicap? If not, how is a disability assessment dealt with?

ASSIGNING DISABILITY III

- No impairment = no *physical* disability
- Your best statement is, "The patient reports that he/she is able/unable to perform the following activities".
- You are not obligated to answer queries for which you have no data; e.g., frequency of lifting various weights. Suggest a formal functional assessment.

ASSIGNING DISABILITY IV

- If no impairment to relate to disability, how to explain your patient's diminished level of function?
- Cherchez
  - "la mood"
  - "la deconditioning"
  - "la milieu sociale"

Some final thoughts

"The sorrow which has no vent in tears may make other organs weep"

Henry Maudsley, MD
(1835-1918)

- Mother Nature is doing her best to heal your patients; try not to kill them with your treatment.
- A little gray hair is a small price to pay for this much wisdom.

Barry Koehler and Kam Shojania

Osteoporosis - Give me a break?

NO! Avoid a break!

Is it justified to screen?

Number Needed To Screen to Detect an Undiagnosed Case of OP by Screening Everyone ≥65 Years in Canada:

- Men = 12 (95% CI 10,14)
- Women: = 5 (95% CI 5,5)

Sawka et al. Arthritis Rheum 2004;50:5269

Is it justified to treat?

Number needed to treat

	Risedronate 5.0 mg
New Fractures (All Patients)	15
New Fractures (≥ 2 Baseline Fractures)	11

Number-Needed-to-Treat = Number of women that need to be treated for 3 years to save a fracture (vs. control)

One big exception …

- Patients on high dose or long term corticosteroids should simply be put on treatment
- Forget about doing the DEXA; just treat

Chart audits can be interesting

- Chart audit of 20 patients on chronic prednisone for various reasons.
- 6/20 were not on a bisphophonate
- 8/20 were not on appropriate calcium
- Common reasons: Bisphosphonate ran out, not restarted. GI side effects.

A 48-week RCT involving 477 patients receiving steroids who also received alendronate or placebo demonstrated a 2.3% and 3.7% in incidence of vertebral fracture, respectively (RRR = 38%; ARR = 1.4%; P= NS). 5

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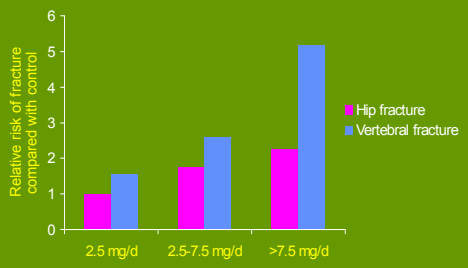
Fracture Risk and Dose of Corticosteroids



Relative risk of fracture by dosages of corticosteroids of prednisolone. van Staa TP, et al, 1998.

Calcium and Vit D

- A systematic review of 5 RCTs (N=274) confirmed clinically and statistically significant prevention of bone loss at the lumbar spine for patients receiving glucocorticoids who also received calcium (500–1000 mg daily) and vitamin D (400–800 IU) daily.

Co-administration of Bisphosphonate

- A two-year RCT of 208 patients receiving steroids who also received alendronate or placebo demonstrated an incidence of vertebral fracture of 0.7% and 6.8% (NNT=16; RRR=90%; ARR = 5.9%; P= .026), respectively
- A 1-year RCT of 184 men on or off steroids using risedronate found an 82.4% decreased incidence of vertebral fractures compared with those who received placebo (NNT = 5; P= .008).

Management

- Most importantly, do not use steroids if at all possible
- Second best: get the patient OFF steroids.
  - e.g. DMARDs for RA, SLE, PsA
  - Add MTX for PMR or Temporal Arteritis
- Use of steroids in RA – only for bridging. Try IM depomedrol 80mg instead of oral prednisone
- There is rarely a role for long term prednisone in rheumatic disease (and we suspect for other diseases as well)
- Make other lifestyle changes: Smoking cessation, Avoiding EtOH overuse. Adequate Ca, Vit D

Pharmacological management

- If long term steroids (>3months) are likely, consider comanagement with a bisphosphonate while the patient is on steroids.
- Baseline need for BMD is debatable. We know that most patients will have a rapid decline in BMD in the first few months.

DEXA – Its pitfalls and limitations

- In one centre, 22% of DEXA's were interpreted incorrectly; apparent decrease in BMD of 11-12%.

Schneyer CR. Abs ASBMR 2001

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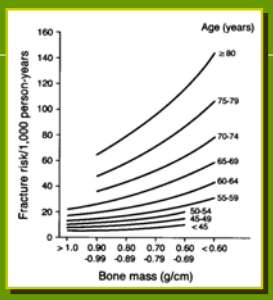
DEXA

- BMD increases from L1→L5
- Age-related degenerative change in lumbar spine may increase BMD from 9.5-14%
  - <50 yrs <10% probability
  - 55 yrs 40%
  - 70 yrs 85%
- Message: If patient is high risk, do not be dissuaded by high BMD in lumbar spine

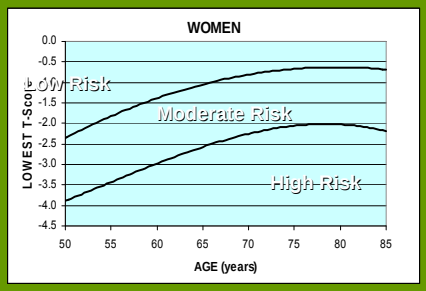
BMD PREDICTS FRACTURES

Fracture Risk
vs. BMD
At Different Ages



Hui et al. J Clin Invest 1988; 81:1804-9

USING LOWEST T-SCORE TO FIND 10-YEAR FRACTURE RISK - WOMEN



WHAT'S WRONG WITH T-SCORES?

Advantages

- Unitless
- Basis for the majority of osteoporosis guidelines
- Simplicity

Disadvantages

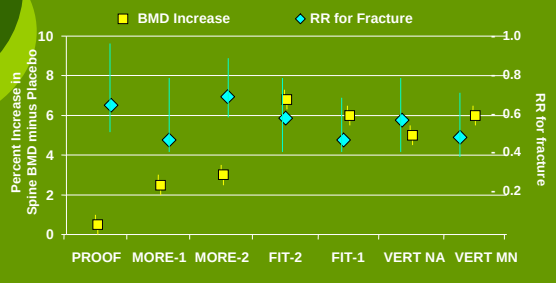
- Depends on site measured
- Depends on technology
- Depends on reference database—population mean and standard deviation
- Only includes BMD information and not additional risk factors

Adapted from Faulkner K. Osteoporos Int 2005;16(4):347-52.

DEXA

- Decrease, no change, or increase in BMD does not change the risk reduction for fracture after treatment is initiated, for either femoral neck or lumbar spine.

Post-Treatment Increases in BMD Over 3 to 5 Years and Relative Risk For Vertebral Fracture



Watts NB, 1999 ASBMR

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When to repeat DEXA

- For those at risk who are not receiving treatment (other than calcium and vitamin D)
- Frequency of repetition dependent on risk estimate.

Should a DEXA be repeated?

- Once on therapy, baseline BMD is no longer as predictive; the decrease in fracture risk is > predicted by increased BMD

Sakar S. JBMR 2002

Bone-Density Testing Interval and Transition to Osteoporosis in Older Women

- Our data indicate that osteoporosis would develop in less than 10% of older, postmenopausal women during rescreening intervals of approximately 15 years for women with normal bone density or mild osteopenia, 5 years for women with moderate osteopenia, and 1 year for women with advanced osteopenia.

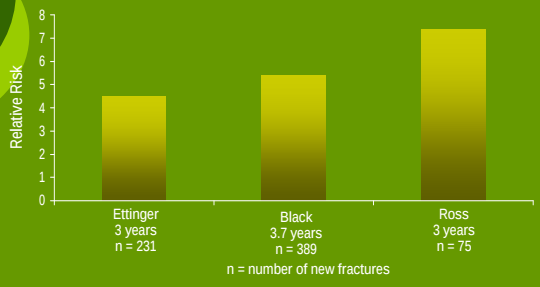
- Margaret L. Gourlay, M.D., M.P.H., Jason P. Fine, Sc.D., John S. Preisser, Ph.D., Ryan C. May, Ph.D., Chenxi Li, Ph.D., Li-Yung Lui, M.S., David F. Ransohoff, M.D., Jane A. Cauley, Dr.P.H., and Kristine E. Ensrud, M.D., M.P.H. for the Study of Osteoporotic Fractures Research Group N Engl J Med 2012; 366:225-233 January

How to assess BMD when a patient is receiving a medication

- Don't measure it!
- Lateral views of the spine
- It is better to assess compliance than repeat the BMD.*
  - An HRT study showed that 80% of eligible patients started therapy, 58% were still taking therapy after 8 months, and 46% at 4 years.

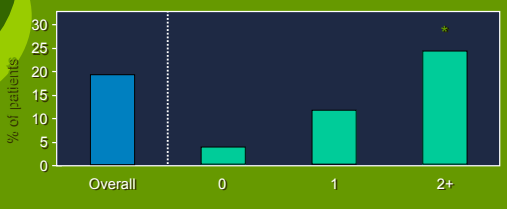
*Cummings et al J Bone Miner Res 2000;15:5144

Prevalent Vertebral Fractures Predict New Fractures



Ettinger B. JAMA 1999;282:637; Black D. J Bone Miner Res 1999;14:821; Ross P. Osteoporos Int 1993;3:120

Incident Vertebral Fracture Predicts Subsequent Fracture Within 1 Year

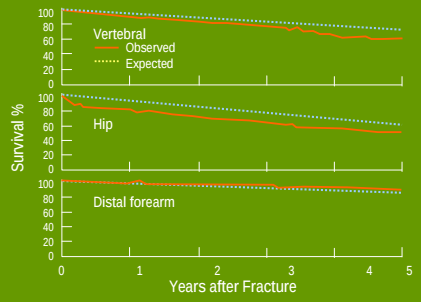


* $p < 0.05$ vs. patients with no prevalent vertebral fractures

Lindsay R *et al. JAMA* 2001;285:320-23.

Barry Koehler and Kam Shojania

Survival Rates after Fracture



Cooper C. Am J Epidemiol 1993;137:1001

Are we treating secondary osteoporosis? Chart review (2º & 3º hospitals)

- 121 patients with hip fracture
  - 81% women, 55% in community
- 26% mentioned osteoporosis in the chart
- 0% prescribed bone density testing
- 0% had bone density in chart
- 16% received drug therapy (calcitonin, bisphosphonate, OHT)
- 8.3% were given Ca and Vit D
- None were referred for OP therapy after DC

Dagenais P, Pinsonneault L, Osteoporosis management in elderly patients admitted with hip fracture. Abstract. ACR 2001

Are we treating secondary osteoporosis? (2)

- 170 patients with hip fracture - most from fall
- 4% on calcium
- 2% on vit D
- 2% alendronate
- 9% on any of the above

Kamel HK, Hussain MS, Tariq S, Perry HM. Failure to diagnose and treat osteoporosis in elderly patients hospitalized with hip fracture Am J Med Sept 2000, Volume 109; 326-8

Are we treating secondary osteoporosis? (3)

- 3 Ontario hospitals, fragility fractures.
- 228 patients out of 2694 fracture clinic visits (56% agreed to study)
- 20% of the group who had a fragility fracture had undergone investigation or adequate treatment of osteoporosis at 1 year follow-up.

Hajcsar EE, Hawker G, Bogoch ER. Investigation and treatment of osteoporosis in patients with fragility fractures. CMAJ Oct 2000; (163):819-22.

Look at the Risk Groups Risk Factors for PMO

- Major risk factors
  - Age >65 years
  - Vertebral compression fracture
  - Fragility fracture after age 40 years
  - Family history of osteoporotic fracture (especially maternal hip fracture)
  - Systemic corticosteroid therapy of >3 months duration
  - Early menopause (before age 45 years)
  - Maternal hip fracture and/or previous hip fracture
  - Smoking history
- AND Propensity to fall
  - Difficulty rising from a chair
  - Poor tandem gait
  - Poor psychomotor skills
  - Recent fall-related injury

2002 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada CMAJ 2002; 167(10 suppl):S1-S34

Compute in additional Risk Factors

- Each factor effectively increases risk categorization to the next level:
  - from low risk to moderate risk, or
  - from moderate risk to high risk
- When both factors are present the patient should be considered at high risk regardless of the BMD result.

Take home messages

- Don't treat the worried not-at-risk, except with calcium (including diet, vitamin D, and exercise)
- Be abstemious in repeating DEXA's but be diligent about reviewing treatment
- Always treat after fragility fracture
- Always treat if cortisone Rx >3 months

Thyroid: tests & controversies

The Patient Clinic

Tom Elliott MBBS

VGH/UBC endocrinologist
Medical director
thepatientclinic.ca

Thyroid – the BIG 3

The Patient Clinic

- function: history, physical, TSH
- anatomy: look & feel
- etiology: usually apparent

TSH rules.....

The Patient Clinic

- TSH best screening test unless
  - Head injury
  - Suspicion of hypopituitarism or CNS disease
    - Menstrual disturbance
  - Other endocrinopathy
- consider free T4

Hypothyroidism

The Patient Clinic

- High specificity:
  puffiness around face
  goitre
  cold intolerance
  Low specificity
  fatigue, weight gain

Thyroxine Dosage

The Patient Clinic

- 1.6 mcg/kg usually, ½ dose otherwise
- Repeat TSH after >4 weeks
  ? Target bottom ½ RR

Hyperthyroidism

The Patient Clinic

- High specificity:
  weight loss
  heat intolerance
  shaking, sweating, palpitations
  muscle weakness
- Low specificity
  fatigue, anxiety

Nuclear medicine studies

- Diagnosis
  - Graves vs thyroiditis
  - Toxic nodule/multi-nodular goitre
  - **NOT for thyroid nodule work-up**
- Treatment – radioactive iodine

Anti-thyroid dosing

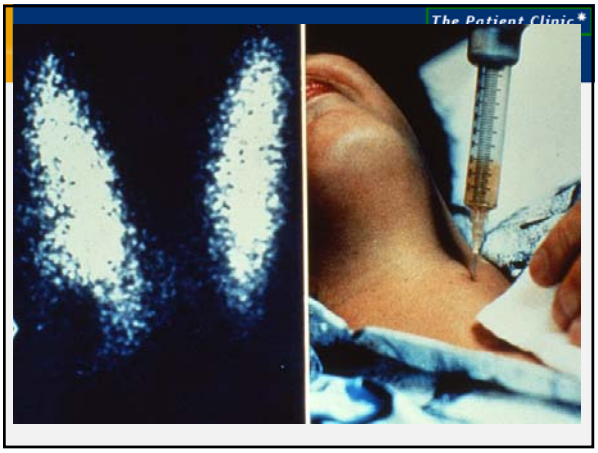
- Methimazole/PTU
  - Monthly free T4 (not TSH)
  - Target top half reference range
  - Treat 6-18 months

Look & feel

- Look: watch neck while patient swallows
- Feel - use your thumbs

Thyroid nodules

- FNAB is solitary
- Consider FNAB dominant nodule if multinodular
- Rx thyroid hormone if TSH elevated
- Rx radioactive iodine if thyrtoxic
- Low threshold for surgery



Take home - DOs

The Patient Clinic

- History & physical still in fashion
- Use TSH for screening & Rx hypothyroidism
- Use Free T4 for monitoring hyperthyroidism
- FNAB for thyroid nodules
- Surgery for worrisome or big nodules
- Don't order thyroid antibodies

Take home – DON'Ts

The Patient Clinic

- Order thyroid antibodies routinely
- Order thyroid US routinely
- Order radionuclear studies routinely
- Use T3 routinely
- Fuss over sub-clinical hypothyroidism

Tom Elliott

Diabetes is a condition, not a disease....

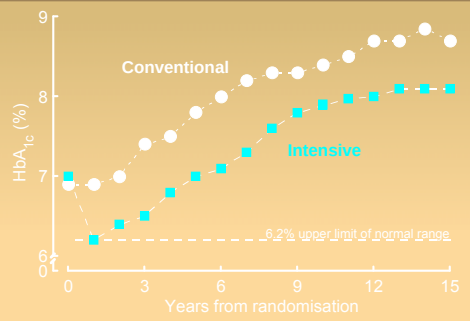
Tom Elliott MBBS, FRCPC

medical director, bcdiabetes.ca
skeptic, medicalmyths.ca
straight-talker, rateyourmd.com vs rateyourpatient.ca
cycling enthusiast
Canucks fan, passittobulis.com

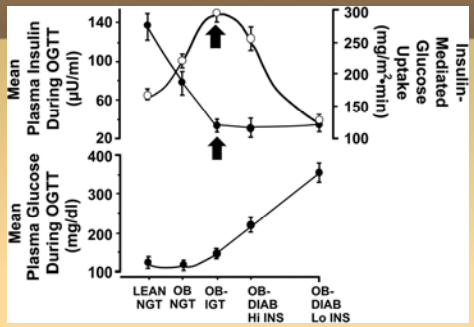
Take home messages

- Diabetes is caused by progressive insulin deficiency
- Lower is not better*
- Metformin then insulin +/- GLP-1 rules
- Once is better than twice daily

Type 2 Diabetes is progressive
(ukpds 1998)



Type 2 & its progression is caused by insulin deficiency
DeFronzo 2009 http://diabetes.diabetesjournals.org/content/58/4/773.full



Type 2 & its progression is caused by insulin deficiency
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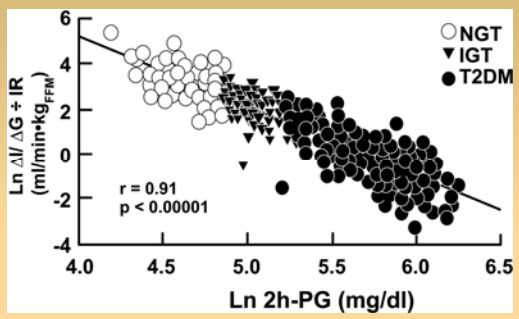
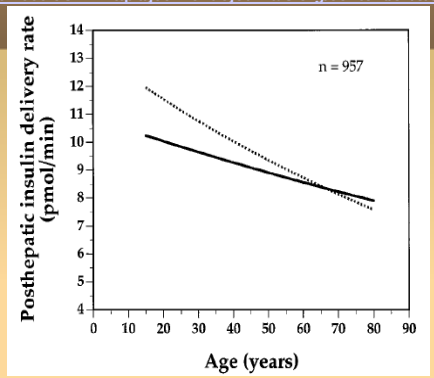


Insulin secretion falls with natural ageing
Iozzo 1999 JCEM http://jcem.endojournals.org/content/84/3/863.full

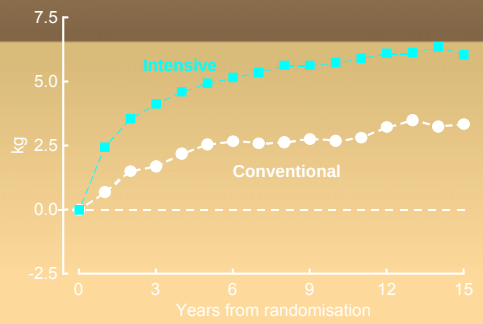


ACCORD & ADVANCE are a bust

nejm.org/doi/full/10.1056/NEJMe0804182

Outcome (intensive vs. standard)		
Median glycated hemoglobin at study end (%)	6.4 vs. 7.5†	6.4 vs. 7.0†
Death		
From any cause (%)	5.0 vs. 4.0†	8.9 vs. 9.6
From cardiovascular causes (%)	2.6 vs. 1.8†	4.5 vs. 5.2
Nonfatal myocardial infarction (%)	3.6 vs. 4.6†	2.7 vs. 2.8
Nonfatal stroke (%)	1.3 vs. 1.2	3.8 vs. 3.8
Major hypoglycemia requiring assistance (ACCORD), or severe hypoglycemia (ADVANCE) (%/yr)	3.1 vs. 1.0†	0.7 vs. 0.4
Weight gain (kg)	3.5 vs. 0.4	0.0 vs. −1.0†

UKPDS weight change



bcdiabetes.ca treatment philosophy

evidence-based medicine

simplicity & economics

"get your diabetes over with before breakfast"

- Once daily testing
- Once daily medication

Lifestyle therapy is always #1

If A1c is above target ask:

"have you been good"

diet "nothing is forbidden"

"everything you eat (except fat) turns to sugar

"your body can only handle a moderate amount of starch/carb/junk food"

Exercise – get out your prescription pad & prescribe

Testing in all except

needle phobia & A1c to target at diagnosis

needle phobia & A1c < 8.5 no insulin or secretagogues

Testing schedule

Default: before breakfast daily

- reduce to M/W/F once A1c to target for 6 months
- reduce to once weekly once A1c to target for 12 months

Consider: 2 hr pc testing

- meal-planning/carb-counting
- for rapid insulin titration

Consider: before meal testing

Pharmacotherapy

http://www.bcdiabetes.ca/handouts?folder=For+Physicians&folder=Diabetes

medication is added step-wise until blood sugar targets reached. Medication is only stopped if ineffective or unacceptable side-effects or if insulin therapy leads to acceptable control (exception metformin - never stopped, see below).

Glycemic targets: general

in hospital	FBS 5.0-10.0
NH or age >85:	A1c < 9.0, FBS 5.0-10.0
age 75-84:	A1c < 8.0, FBS 5.0-8.0
age 55-74:	A1c < 7.5, FBS 5.0-7.0
age 40-54:	A1c < 7.0, FBS 5.0-7.0
age < 40:	A1c < 6.5, FBS 4.0-6.0

Glycemic targets: special

vasculopathy:	A1c < 8.0, FBS 5.0-7.0
diabetes > 20 yr:	A1c < 8.0, FBS 5.0-7.0
significant neuropathy/retinopathy:	A1c < 6.5, FBS 4.0-6.0

First line = metformin

all patients eGFR > 30, A1c > 6.0 or BMI > 25

once daily SR 500 mg preferred ($0.61 vs $0.14)

Start at one & increase Q4 days to max tolerated based on eGFR

> 50	2000 mg/day
40-50	1500 mg/day
30-40	1000 mg/day
20-30	500 mg/day

Second line ?????

GLP-1 agonist (if BMI > 30 & cost not a consideration, $5-9/day)

or

DPP-4 inhibitor (if cost not a consideration, average $2.80 per day)

or

Sulfonylurea - default gliclazide SR 30 mg ($0.15), push to ii daily

or

basal insulin – default glargine ($0.06 per unit vs

GLP-1 agonists

liraglutide start at 0.6 mg acb (increasing to 1.2 & 1.8 mg after one & two weeks respectively, side-effects permitting): $9.00 at full dose

or

exenatide start 5 ug BID (before breakfast & dinner) for one month increasing to 10 ug BID thereafter, side-effects permitting: $5.50 at full dose

or

clinical trial with bcdiabetes.ca (up to 5 years Rx, placebo-controlled 50:50)

Basal insulin

Insulin glargine (or detemir) 6+ units qam (or 0.1 U/kg qam, whichever is greater), increasing by 1-2 units per day until target FBS met. Do not split dose unless > 80 units per day or patient has day-time lows with morning highs.

or

NPH 6+ units HS (or 0.1 U/kg HS, whichever is greater), increasing by 1-2 units per night until target FBS met. Do not split dose unless > 60 units per day or FBS to target but A1c high.

Mealtime rapid insulin

Insulin glulisine is same price as regular insulin (Toronto, Novolin R, Humulin R) but quicker to hit & of shorter duration & doesn't require snack

Insulin glulisine 1+ units immediately before largest meal of day (or meal with highest post-prandial reading), increasing by 1 units per day vs 2hr pc 6-10. Introduce carb-counting early if patient amenable & motivated. Starting carb-ratio 10:1 (20:1 in Type 1s).

Management scenario #1 obese, third party insurance

personal diet coach & personal trainer

metformin SR 500→1000→1500→2000 (+ prn)

Liraglutide 0.6→→→1.8 (?→3.0) mg/day (+ prn)

gliclazide MR 30→60 mg/day, (+ prn)

insulin glargine, (+ prn)

insulin glulisine at dinner

Management scenario #2 non-obese, third party insurance

personal trainer

metformin SR 500→1000→1500→2000 (+ prn)

DPP-4 inhibitor i daily (+ prn)

gliclazide MR 30→60 mg/day, (+ prn)

insulin glargine, (+ prn)

insulin glulisine at dinner

Management scenario #3 no third party insurance

lifestyle therapy, gym membership

metformin 500 mg ½ BID→i BID → ii BID (+ prn)

gliclazide MR 30 I daily → ii daily (+ prn)

sitagliptin 100 mg i daily (Special Authority)(+ prn)

insulin glargine, (+ prn)

insulin glulisine

Take home messages

- Diabetes is caused by progressive insulin deficiency
- Lower is not better
- Metformin then insulin +/- GLP-1 rules
- Once is better than twice daily
- To win is better than to lose

The Tricky Treatment of Acute Headaches

Tina Korownyk
University of Alberta

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty:** Tina Korownyk
- **Relationships with commercial interests:**
  - **Not applicable**

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

- **No commercial support**
- **Potential for conflict(s) of interest:**
  - Not applicable

CFPC CoI Templates: Slide 3

Mitigating Potential Bias

- Not applicable

Objectives for Acute Headache Management

- Classification – what if we get it wrong?
- Common medications in the office setting
  - Comparative effectiveness
  - Risk vs benefit
- Recurrence

Acute headache Classification

- Emergency Department Patients reporting headache:
- 54% had primary headache disorders
  - Migraine (22%)
  - Tension type headache (11%)
  - 18% were "unspecified"

What do GPs use for themselves?

	Any use reported* (N = 275)	Most frequently used (N = 265)
Paracetamol, N (%)	87 (31.6)	16 (6.0)
Aspirin, N (%)	45 (16.4)	23 (8.7)
Opiate analgesics, N (%)	24 (8.7)	1 (0.4)
NSAIDs, N (%)	234 (85.1)	86 (32.4)
Triptans, N (%)	202 (73.4)	128 (48.3)
Ergot alkaloids, N (%)	7 (2.54)	2 (0.7)
Others, N (%)	11 (4.0)	9 (3.4)

Headache. 2011 Jul-Aug;51(7):1122-31.

Current Guidelines (Italian 2012)

- Symptomatic treatment alone recommended when attacks are non-disabling or, if disabling, occur < 4 days per month.
- Stratified approach depending on severity
- The most appropriate drug, lowest useful dose as early as possible
- Preparations with only one active principle preferred
- Rescue drugs should be provided in case of first choice medication failure

Canadian CMAJ 1997

A sphinx-like series of systematic reviews…

(2hr headache relief vs Placebo)

- Paracetamol 1000mg NNT = 5[1]
- Aspirin NNT = 5[2]
- Ibuprofen 400mg NNT = 4[3]
- PO Sumatriptan 100mg NNT =4[5]
- SC Sumatriptan 6mg NNT = 3[4]

1) 1) Cochrane Database Syst Rev. 2010 Nov 10;(11):CD008040 2) Cochrane 2010(4): CD008041 87 3) Ann Pharmacother. 2007 Nov;41(11): 1782-91 4) Cochrane Issue 2. Art. No.: CD009665 5) Cochrane 2012 Feb 15;2:CD008615

Benefit Above Placebo

Placebo 2hr relief = 36%[1]

Placebo 2hr pain free – 10%[1]

DRUG	DOSE	NNT			
		2 hr RELIEF	2 hr Pain Free	24 HR RELIEF	NNH
Acetaminophen[1]	1000mg	5	12		NNHp=21
Aspirin[2]	1000mg	5	9	7	
Ibuprofen[3]	200mg	8	13	NSS	NSS
Ibuprofen[3]	400mg	4	9	NSS	NSS
Sumatriptan po	50mg	4	7	6	13 (Chest pain = 69)
Sumatriptan po[5]	100mg	4	5	6	6 (Chest pain = 44)
Sumatriptan sc[4]	6mg	3	3	7	5

1)Cochrane 2010;(11):CD008040 2)Cochrane 2010(4): CD008041 87 3) Ann Pharmacother. 2007 Nov;41(11):1782-9 4) Cochrane Database of Systematic Reviews 2012, Issue 2, Art.

Comparisons…

Paracetamol 1000mg + Metoclopramide	=	Sumatriptan 100mg[1]
ASA 1000mg	=	Sumatriptan 50mg[3]
Parenteral Ketorolac	>	Intranasal sumatriptan[2]

1) Cochrane Database Syst Rev. 2010 Nov 10;(11):CD008040 2) Headache. 2013 Feb;53(2): 277-87 3) Cochrane 2010(4): CD008041 87

Triptan Terrors

- Mrs. M. Grain is in asking about triptans for her migraines. She has a friend who says they work really well, however read on the internet that they cause heart attacks. You tell her:
  1) A heart attack is not the worst thing that could happen to you today
  2) They may have symptoms that FEEL like a heart attack but are really nothing
  3) We probably should use caution if you have known CAD, otherwise they are quite safe

Terrible Tricks of Triptans

- Case reports of angina-like chest pain, MI, and ventricular arrhythmias
  - 35 yr old woman – cardiac arrest w/in mins of first time SC sumatriptan.[1]
  - 56 yr old woman, post menopausal, ex smoker, on estrogen, MI at 20mins, normal cardiac cath [2]
  - 2009 review, 32 case reports of vascular events[3]
  - "Occurred in pts with known and subsequently defined coronary artery disease"[2]
- Concerns about CV safety limit use of triptans[4]

1)Neurology. 1995 Jun;45(6):1211-3 2)*Headache* 1996;36:329–331 3) Headache. 2009 May;49(5):762-4. Neurology 1997;48:1542-1550 4) *1) Headache*. 2004;44:414-425

Terrible Tricks of Triptans

- Prospective cohort 12 339 migraineurs x 12 mo[1]
  - No clear evidence harm
- Double blind crossover RCT – 19 migraineurs[2]
  - No change in myocardial perfusion (PET) with sumatriptan

1) Cephalalgia. 1999 May;19(4):223-31 2) Neurology 1997;48:1542-1550

Sumatriptan SC vs placebo

Symptom	Trials	Patients	Treatment (%)	Placebo (%)
Chest pain	6	466	4	1
Feelings of heaviness	7	962	6	3
Paraesthesia/ numbness	10	1241	7	3
Neck/back pain	5	603	5	1
"Serious Adverse Events"	16	4741	0.25	0.57

Cochrane 2012, Issue 2. Art. No.:CD009665

The Triptan Cardiovascular Safety Expert Panel

- 2004 Consensus statement:
- *"In patients at low risk of coronary artery disease, triptans can be prescribed confidently without the need for prior cardiac status evaluation"*
- "Triptan Syndrome"
  - Chest and neck tightness, chest pain, in 4-8% of pts treated[2]

1) Headache. 2004;44:414-425. 2) J Headache Pain 2012;13:S13-S70

Haunted by Headaches

- Mrs. M Grain is in to see you regarding her headache (again!). She reports that last time she was seen in ER, however by the time she got home her headache had returned. This makes her really quite angry.
- What do you do?

1) Double dose the triptans
2) Standing order for demerol
3) Send her to a different emergency
4) Offer a dose of oral dexamethasone

A Cryptic Recurrence of Headaches

- Moderate to Severe headaches reoccur in ~31% of patients seen in ED within 24hrs
- Independent predictors of poor outcome:
  - severe baseline pain
  - baseline nausea
  - positive depression screen
  - longer duration of headache

Ann Emerg Med. 2008 Dec;52(6):696-704

The Mysterious benefit of NSAIDS & Triptans

- Double blind RCT, 410 pts
- Naproxen 500mg vs Sumatriptan 100mg on ED discharge
- 73% reported headache w/in 48hrs
- 1° outcome: change in pain 2 hrs after ingestion of either med
  - No difference in pain scale (4.3 vs 4.1 pts; 11 pt scale)
- 71% naproxen and 75% sumatriptan would use the same medication again
- Adverse events similar, mild (GI)

Ann Emerg Med. 2010;56:7-17.

Consequences of Inappropriate Classification

- Migraine patients had greater heterogeneity in response vs the non migraine patients (P=0.05).[1]
- Similar findings in other ED settings.[2]
- Classification schemes that do not predict response to treatment or prognosis are of little value to clinicians.

1) Ann Emerg Med. 2010;56:7-17.
2) Friedman BW, Hochberg ML, Esses D, et al. Applying the International Classification of

Does the addition of Dexamethasone Decrease Recurrence?

- Double blind, placebo controlled RCT, 63 patients, median age 39yrs, 3 Emerg Depts,
- 8mg dexamethasone po vs placebo (following tx)
- F/U at 48-72hr by phone, recurrent headache:
- Dex 27% vs Placebo 39%
  - RR 0.69 (CI 0.3-1.45) p=0.47

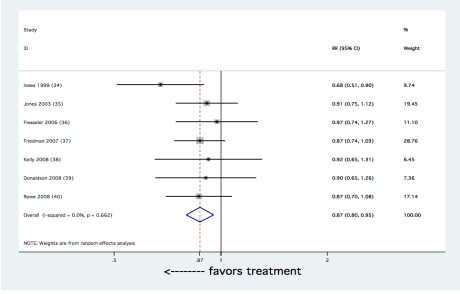
Emerg Med J. 2008 Jan;25(1):26-9.

Does the addition of Dexamethasone Decrease Recurrence?

- Sys Rev, 7 trials, 742 Emergency Pts
- Treated with dexamethasone (8-24mg) in addition to standard migraine therapy
  - (6 trials IV, 1 oral therapy)
- Significant reduction in rate of moderate-severe headache at 24-72hrs follow up
- RR 0.87 (CI 0.80-0.95), NNT = 10
- Comments: high quality trials (Jadad 5), did not control for initial tx (which may impact recurrence)

Acad Emerg Med. 2008 Dec;15(12):1223-33.

Does addition of Dexamethasone decrease recurrence?



Academic Emergency Medicine
Volume 15, Issue 12, pages 1223-1233, 27 OCT 2008 DOI: 10.1111/j.1553-2712.2008.00283.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1553-2712.2008.00283.x/full#f2

Headaches – R.I.P.

1) Proper classification of primary headaches does not necessarily predict response to tx
2) Many options for tx with similar efficacy Individual response and side effect profile should be considered
3) Dexamethasone may be an option to prevent recurrence in select patients

Mike Kolber

Proton Pump Inhibitors in Primary Care 2013

Mike Kolber BSc, MD, CCFP, MSc
DTC April 2013

Conflict of Interest

- Academic Family Physician
- Clinical work in Peace River, Alberta
- No funding from industry
- Supported by University of Alberta department of Family Medicine and Alberta College of Family Physicians

Mr. **P**eter **P**aul **I**ngram

42 yo male programmer complains of daily post prandial (coffee, beer) retrosternal chest discomfort. As an evidence based health care provider, you:

A) Give him a rx for Esomeprazole 40 mg / day x 3 month x 3 repeats, as "I will give him the most expensive and therefore the best PPI and I wont have to see that sucker again for a year"
B) Send him to the pharmacy for OTC Ranitidine
C) Tell him to buy shares (and bottles) of TUMS
D) Tell him to ↓ weight, ↓coffee, beer and elevate head of the bed
E) Give 8 weeks of your cheapest PPI

How many Canadians take PPIs?

- 26 million Rx 2012
- All PPIs in top 50 Rxs in Canada: Pantoprazole #5
- Esomeprazole (Nexium): $250 million in 2012

http://www.canadianhealthcarenetwork.ca/pharmacists/news/special-reports/top-100-drugs-19660/4

Appropriate PPI uses

- Short Term
  - Acute treatment UGI bleeding, PUD
  - ICU patients on ventilator / coagulopathy
- Long Term
  - GERD: earn your LT PPI!
    - Dyspepsia
  - Barrett's esophagus
  - Gastroprotection
  - Post PUD and GI bleeds*

Inappropriate PPI Uses

- Up to 60% of patients may not have appropriate indication for long term PPI[1]
- Admitted to medicine ward[2]
  - 40% put on, 50% discharged w PPI (10% had indication)
- Long term care[3]
  - 27% advanced dementia
  - 18% took in last week of life!
- Asthma, cough, atypical ENT symptoms: does not work![4,5]
- Routine Post cholecystectomy

[1]*BMJ 2008;336:2*, [2]*Ann Pharmacother* 2006;40:1261, [3]*J Am Geriatr Soc 2010: 58; 880*
[4]*NEJM 2009;360:1487*, [5]*Chest 2005; 128:1128*

Mike Kolber

How well do PPIs work? UGI bleeding

- PPI before endoscopy for GI bleed:
  - ↓endoscopic stigmata of bleeding
  - no diff surgery, mortality
- PPI after endoscopic dx of PUD:
  - ↓re-bleed: PPI 10.6%, control (mostly H2Ant) 17.3%: NNT 15
  - ↓surgery: NNT 33
  - No diff in mortality

Health Technol Assess 2007;11(51), *Cochrane Reviews 2010 CD005415*

How well do PPIs work? Preventing NSAID associated PUD

- 40% chronic NSAID users → endoscopic ulcer[1]
  - Only 1.5 - 4% / year → clinical PUD
- Misoprostol 800 ug vs placebo[2]: RA + NSAIDs: 40%↓clinical PUD
  - ARD = 0.4% → NNT = 250 x 6 months to prevent 1 clinical PUD
- PPI vs Placebo: PUD in patients with > 3 /12 NSAIDs[1] (1' prevention)
  - Endoscopic ulcers: PPI < placebo (8 vs 20%, ARD = 12%: NNT 9 over 3-6/12)
- PPI vs H2Ant[3]: recurrent PUD: PPI < H2Ant (28 vs 41%, NNT = 8 over 6/12)
- PPI vs Misoprostol: patients with previous PUD or GU
  - Miso 400 ug[4]: equal initial ulcer healing
    - Recurrent PUD @ 6 months: miso > PPI (51% vs 39%; ARD 12%, NNT 8
  - Miso 800 ug[5]: GU healing miso NSS > PPI (93% vs 82%)
    - AEs misoprostol > PPI (31% vs 16% PPI (diarrhea))

[1]*Health Tech Assess* 2007;11(51) [2]*Ann Int Med 1995*:123:241 [3]*NEJM 1998;338: 719*
[4]*NEJM 1998;338: 727* [5]*Arch Intern Med. 2002;162:169*

Hp eradication in NSAID users

- 1000 patients: UGI bleed 2' to PUD + HP positive
  - 56 years, 75% males, 23% smokers
  - 41% NSAIDs or ASA
- Post eradication:
  - 9% using NSAIDs or ASA, only 8% PPI or H2ANT
  - 5 re-bleeds in 2 years (0.5%)
    - 3 restarted NSAID, 2 Hp re-infection
- Prevention of recurrent NSAID associated PUD[2]:
  - Hp eradication > PPI, misoprostol (NNT 7)

Am J Gastroenterol 2012; 107:1197, [2]*Health Technol Assess* 2007;11(51)

Who Needs Gastroprotection?

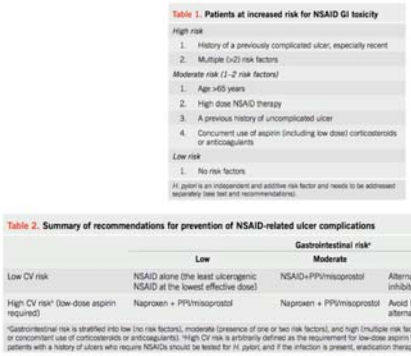


Table 1. Patients at increased risk for NSAID GI toxicity

High risk
1. History of a previously complicated ulcer, especially recent
2. Multiple (>2) risk factors
Moderate risk (1–2 risk factors)
1. Age >65 years
2. High dose NSAID therapy
3. A previous history of uncomplicated ulcer
4. Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants
Low risk
1. No risk factors

H. pylori is an independent and additive risk factor and needs to be addressed separately (see text and recommendations).

Table 2. Summary of recommendations for prevention of NSAID-related ulcer complications

	Gastrointestinal risk*		
	Low	Moderate	High
Low CV risk	NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	NSAID+PPI/misoprostol	Alternative therapy if possible or COX-2 inhibitor+PPI/misoprostol
High CV risk† (low-dose aspirin required)	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternative therapy

*Gastrointestinal risk is stratified into low (no risk factors), moderate (presence of one or two risk factors), and high (multiple risk factors, or previous ulcer complications, or concomitant use of corticosteroids or anticoagulants). †High CV risk is arbitrarily defined as the requirement for low-dose aspirin for prevention of serious CV events. All patients with a history of ulcers who require NSAIDs should be tested for *H. pylori*, and if the infection is present, eradication therapy should be given.

Am J Gastroenterol 2009; 104:728

Who needs gastroprotection?

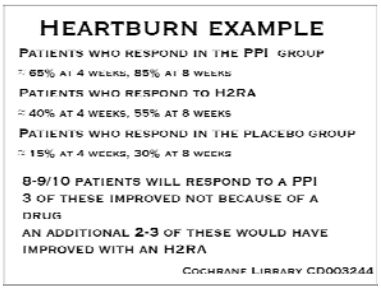
Risk factors for nonsteroidal anti-inflammatory drug (NSAID)-associated serious gastrointestinal adverse events

Characteristic	Odds ratio (95% CI)
History of ulcer complications	13.5 (10.3-17.7)
Multiple NSAIDs	9.0 (5.7-14.2)
High-dose NSAIDs	7.0 (5.2-9.6)
Concomitant anticoagulant use	6.4 (2.8-14.6)
Age ≥ 70 years	5.6 (4.6-6.9)
Age ≥ 60 years	3.1 (2.5-3.7)
Concomitant corticosteroid use	2.2 (1.4-3.5)
History of cardiovascular disease	1.8 (1.1-3.2)

Data from references 12, 13, 27 and 28

Can J Gastro 2002: 16: 231

How well do PPIs work? GERD



Cochrane Systematic Reviews 2007, Issue 2. Art. No.: CD003244

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GERD
Are PPIs equally effective?

- Depends who takes you golfing!
- Yes!
- Individual patient responses

Khan, Cochrane Systematic Reviews 2007, CD003244

If all the same → use the cheapest!
90 days cost – Alberta 2013

- Rabeprazole 20mg: $55
- Lansoprazole 30mg: $75
- Omeprazole 20mg: $80
- Pantoprazole 40mg: $80
- Tecta $85
- **Nexium 40mg: $195**
- Ranitidine 150mg bid: $45

PRICE COMPARISON OF COMMONLY PRESCRIBED PHARMACEUTICALS IN ALBERTA 2013

What about BID PPI?

- No difference c/w once daily PPI[1]
- 25% Nova Scotians, 23% US Veterans started on BID PPI[2,3]
- Reserve BID PPI for your patient with classic GERD still symptomatic on once daily PPI

[1] *Khan, Cochrane Systematic Reviews 2007, CD003244*
[2] *Zacny, Gastroenterology 2004 April; 126(4) Supp 2: W1277, A603*
[3] *Gawron,* J Gen Intern Med 2013 DOI: 10.1007/s11606-013-2345-0

How long initial treatment?
Earn your Long Term PPI!

- Try ? 8 weeks and re-evalute[1]
- If better with PPI and non-pharm → dc PPI
- If symptoms recurrence → restart
  - daily or less frequent
  - On demand

[1] *Armstrong Can J Gastro 2004 (19): 15*

On Demand PPIs

- Equals continuous PPIs for patients w/o visible esophagitis[1]
- **Most GERDs are NERDs!**
  - NO esophagitis on endoscopy[2]
  - On demand should work in most patients
- GERD patients: followed LT[3]
  - 80% PPIs: 50% daily, 30% on demand

[1] *Pace,* Aliment Pharm 2007; 26: 195, [2] *Armstrong Can J Gastro 2004 (19): 15*
[3] *Nocon, Aliment Pharm 2007; 25: 715*

Can patients stop PPIs?

- Yes, 27% of PPI users x 4 years → successfully dc[1]
- Predictors of step-off therapy: older age and dyspeptics[2]
  - Less successful: heartburn

[1] *Bjornsson Aliment Pharm 2006 ;24: 945,* [2] *Am J Gastro* 2009; 104:S27

Mike Kolber

Stopping PPIs
Cold Turkey or taper?

- RCT taper vs. not taper off PPIs
  - More successful in getting off PPIs (NS)[1]
- 120 healthy volunteers (no GERD sx)
  - RCT to placebo or PPI then dc
  - 20% developed GERD sx after dc PPI
- I tapper!

[1]*Bjornsson Aliment Pharm 2006 ;24: 945*
[2]*Reimer, Gastroenterology 2009;137:80*

Plavix - PPI Interaction

- Observational studies: PPIs interact with clopidogrel → ↓ anti-platelet effect → ? ↑ CV events[1,2,3]
- COGENT: RCT clopidegrol + omeprazole 20 mg vs clopidegrol[4]
  - No diff in CV events
  - ↓GI events w omeprazole
  - Determine if need to Plavix 'forever'
  - Determine if need PPI
  - If need LT PPI: OK, could use pantoprazole

[1]*JAMA 2009;301(9):937* [2]*CMAJ 2009; 180: 713*
[3]*Am J Gastro 2010; 105:2430,* [4]*NEJM 2010;363:1909*

PPI and PAE
(Potential Adverse Events)

PPI Potential Adverse Effects

- Gastrointestinal
  - Nuisance diarhea, lymphocytic colitis
  - C. diff. and c. diff recurrence
- Pneumonia
- Osteoporosis and hip #
- Others: VB12 deficiency, Hypomagnesemia, interstitial nephritis

PPI and GI AEs

- Nuisance diarhea: 5-10% / microscopic colitis[1]
- Clostridium difficile
  - ORs: 1.93[2] to 2.05[3]
- In patients with C Diff: risk of recurrence ↑ with PPI[4]
  - PPI 25.2% no PPI 18.5%
  - ARD ? 7% NNH = 15
- Risk of recurrence > initial, PPI > H2A

[1] *Aliment Pharmacol Ther 2010; 32: 1124,* [2]*Am J Gastro* 2012; 107:1011
[3]Am J Gastro 2007;102:2047, [4]*Arch Intern Med. 2010;170(9):772*

Putting it all together
PPI and C diff[3]

- Community[1] = 1/1000 → ADD PPI = 2/1000
- Hospital admissions[2]
  - Without antibiotics 5 / 1000 ADD PPI → 5 extra cases
  - With antibiotics 42/1000 ADD PPI → 36 extra cases
  - On PPI at admission 53/1000 ADD Abx → 45 extra cases

Summary: community risk low: always ask if need PPI at hospital admissions (especially if contemplating Abx)

[1]*BMC Infectious Diseases 2011, 11:194,* [2]*N Engl J Med 2011;365:1693*
[3]*Am J Gastro* 2012; 107:1011,

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PPI and pneumonia

- CAP Rates: primary care 360,000 patients x 7 years[1]
  - Non PPI users 0.6% / year vs current PPI users 2.5%
  - Adjusted: **1 additional case per 100 patients / year**
- SR PPIs[2] or Acid ↓ meds[3] : CAP OR 1.36 (1.12–1.65)
  - Higher dose PPI → ↑risk[1,3]
  - New starts (< 30 days) > LT use?[5]
- Recurrent CAP[4]: if start PPI after 1st pneumonia
  - 15% vs 8% no PPI → ARD = 7%, NNH = 15 over 5 years
- *Summary: Overall risk low, if have pneumonia → limit concomitant PPI*

[1]*JAMA 2004;292:1955* [2]Aliment Pharmacol Ther 2010; 31: 1165
[3]*CMAJ* 2011. DOI:10.1503, [4]*Am J of Med 2010 123, 47*
[5]*Ann Intern Med.* 2008;149:391-398.

Bad Pharma?

Occurrence of Community-Acquired Respiratory Tract Infection in Patients Receiving Esomeprazole

Retrospective Analysis of Adverse Events in 31 Clinical Trials

Lennart Esthorn and *Svante Joelson*
Clinical Drug Safety, AstraZeneca R&D, Mölndal, Sweden

Conclusions: This pooled analysis found no causal association between acid-suppressive therapy with esomeprazole and increased risk of community-acquired RTI, including pneumonia, in patients receiving this agent for gastric acid-related disorders.

Drug Safety 2008; 31 (7): 627

PPI and fractures

Systematic Review	# of Studies	RR / OR with PPI	RR / OR with H2ANT	Comments
BMJ 2012[1]	11	1.30 (1.25, 1.36)	NR	
Ann Fam Med 2011[2]	11	1.29 (1.18, 1.41)	1.10 (0.99-1.23)	Overall fracture
Am J Med 2011[3]	11	1.30 (1.19-1.43)	1.12 (0.97-1.30)	Hip fracture
Am J Gastro 2011[4]	16	1.25 (1.14, 1.37)	NR	Hip fracture ST use > LT use
Eur J Gastro 2011[5]	7	1.24 (1.15, 1.34)	NR	Hip only
Bone 2011[6]	12	1.23 (1.11, 1.36)	1.12(0.99–1.27)	Hip

[1]*Khalili, BMJ 2012;344:e372 doi: 10.1136,* [2]*Eom, Ann Fam Med 2011;9:257*
[3]*Yu, Am J Medicine 2011; 124:519,* [4]*Ngamruengphong, Am J Gastroenterol 2011; 106:1209*
[5]*Ye, Eur J Gastro Hepat 2011; 23:794, Kwok, Bone 2011; 48 : 768*

Putting it all together Attributable Fracture risk

- Nurses Health Study: prospective cohort, 80,000 healthy US nurses, mean 66 years, data on PPI / Hip # for 8 years[1]
  - Hip fracture risk not on PPI = 1.5 / 1000
  - Hip fracture risk on PPI = 2 / 1000
  - ARD = 0.5 / 1000
  - NNH = 2000 x 8 years for 1 additional hip fracture
    - Smoking ↑ risk > PPI and duration of use
    - Risk ? baseline if stop > 2 years

BMJ 2012;344:e372 doi: 10.1136

Are PPI associated Adverse Events due to residual confounding?

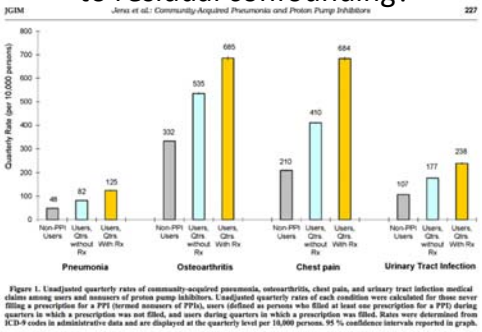

Figure 1. Unadjusted quarterly rates of community-acquired pneumonia, osteoarthritis, chest pain, and urinary tract infection medical claims among users and nonusers of proton pump inhibitors. Unadjusted quarterly rates of each condition were calculated for those never filling a prescription for a PPI (termed nonusers of PPIs), users (defined as persons who filled at least one prescription for a PPI) during quarters in which a prescription was not filled, and users during quarters in which a prescription was filled. Rates were determined from ICD-9 codes in administrative data and are displayed at the quarterly level per 10,000 persons. 95 % confidence intervals reported in graph.

J Gen Intern Med 2012; 28(2):223–30

Summary PPI AEs

- Attributable risk of AEs low, but a ton of people on them
- Limit AEs by judicious use of PPIs
- If have patient with C diff, CAP, osteoporosis or hip # → consider stopping PPI if possible
- Chronic PPI: lowest dose shortest amount of time

Mike Kolber

PPI Summary 2013

- Earn your LT PPI, cheapest, lowest dose (on demand)
- Clean up the: "I don't know why I take PPIs"
  - Taper, then DC
- Plavix – PPI interaction: likely not a big deal
  - Review plavix length of therapy and need for PPI
- PPI and diarhea common
- Attributable risk of AEs low….but….
  - If have C. diff or pneumonia → consider DC PPI

Thank you!

mkolber@ualberta.ca

G. Michael Allan

The Common Cold

G. Michael Allan,
Director EBM, Associate Prof, U of A, & Director of Evidence and CPD Program, ACFP

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty:** G Michael Allan
- **Relationships with commercial interests:**
  - **None**

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

- **This program has received financial support from** n/a **in the form of** n/a.
- **This program has received in-kind support from** n/a **in the form of** n/a.
- **Potential for conflict(s) of interest:**
  - None
  - None

CFPC CoI Templates: Slide 3

Mitigating Potential Bias

- n/a

Cause of Infection

- Caused by a large array of viruses;
  - rhinovirus accounts for 24-52% of clinical cases
  - Or 52-76% of infections with an identified pathogen
- No pathogen identified in 31-57% of upper respiratory tract infections (URTIs), likely due to
  - Poor collection technique,
  - Sampling late in the illness (with low counts)
  - Or previously unidentified agents.[2]
- 5% of clinically diagnosed common colds have bacterial infection (with/out viral co-infection)

Spread & Symptoms

- Spread: (direct and indirect)
  - hand contact with secretions from an infected person
  - aerosol of the secretions/virus.
- Incubation period varies, but slightly <2 days for rhinovirus.[3]
- Symptoms typically peak at 1-3 days and last 7-10 days, can persist for 3 weeks.[2,4-6]
- Symptoms vary among individuals and with different infective agents.
- Fever: common in children, but rare or mild in adults.[2]

G. Michael Allan

Clinical Cold Info

- Incidence of the common cold declines with age: over 1 year,[6-10]
  - Children <2 have approximately 6,
  - adults have 2-3
  - elderly have one.
- Stress[11] and poor sleep[12] may increase the risk in adults, while daycare[13] in preschool children.

Research Overview

- Poor Studies
- Tons of outcomes with unclear reporting
- Combined outcomes difficult to interpret.

Prevention: Vitamin C

- Evidence: Meta-analysis (29 RCTs, 11,306 participants)
  - 0.2-3gm (1gm mostly)
- Effect
  - Community participants, no effect, Risk Ratio 0.97 (0.94-1.00)
    - Duration down: 9.1% (12.6%, 5.6%)
    - Severity down: SMD 0.12 (-0.17, -0.07): No meaningful difference
  - Not better with higher dose.
  - High stress participants, colds reduced, Risk ratio 0.48 (0.35, 0.64)
- Harms: None reported
- Bottom-line: No meaningful benefit.

Prevention: Ginseng (Cold Fx™)

- Evidence: Systematic review (5 RCTs) and 1 RCT new
- Effect:
  - Pooled 5 RCTs, no significant reduction in colds RR 0.70, (0.48, 1.02).
  - Results are inconsistent (heterogeneity i^2=68%)
  - 1 RCT: no significant difference from placebo (p=0.23)
- Harms: No consistent difference in adverse events
- Bottom-line: Unclear benefit

Prevention: Zinc

- Evidence: Meta-analysis (2 RCTs, 400 pts, age 5-8)
  - Zinc sulfate tablets 10 mg and 15 mg
- Effect:
  - Pooled 2 RCTs, significant reduction in colds, rate ratio 0.64,(0.47,0.88)
  - About 0.5 -1.4 less colds over 5-7 “winter” months
- Harms: 3 children in one RCT had mild GI discomfort. No other significant differences noted
- Bottom-line: Likely beneficial

Prevention: Probiotics

- Evidence: Systematic review and meta-analysis (10 RCTs, 3451 participants)
- Effect:
  - Pooled 6 RCTs, significant reduction in number with ≥1 colds, OR 0.58, (0.36, 0.92).
    - Studies inconsistent (heterogeneity i^2=69%)
  - Best studies (both in kids, lactobacillus versions)
    - Community 0.6 less URTI per 100 days
    - Hospital: NNT 30 to avoid URTI during admission
- Harms: No difference in adverse events
- Bottom-line: May be beneficial

G. Michael Allan

One Hit Wonders

- Exercise: (45 min 5 d/wk), 1 poor RCT (post overweight menopausal women)
  - Reduce colds 0.41 less per yr.
- Garlic: 1 poor RCT, 146 participants,
  - Garlic 24 colds vs 65 placebo (P<.001) x12 wks.
- Gargling: 1 RCT (Japanese 384 adults) Tap water or diluted iodine (7%) gargled
  - Water Reduced RR 0.64 (0.42, 0.99). Not Iodine.
- Bottom-line: Too Little Evidence (all poor quality except gargling)

Evidence of No benefit

- Echinacea
  - Evidence: Systematic review (2 RCTs, 519 participants)
  - Bottom-line: No benefit
- Homeopathy:
  - Evidence: 3 RCTs (170, 142, 199 children aged ≤10)
  - Bottom-line: No (in placebo trials) benefit
- Vitamin D
  - Evidence: 2 RCT (164 male military recruits, 322 health workers or students)
  - Bottom-line: No benefit

Prevention: Physical intervention

- Evidence: Systematic review of RCT to case-control
- Effect: General reduced risk with hand-washing, hand disinfectant, glove wearing and masks
- Harms: N95 masks offer no advantage over normal surgical masks, and are uncomfortable and irritate the skin
- Bottom-line: Likely beneficial

Treatment: Traditional

Pain and Fever

- NSAIDs (mostly ibuprofen)
  - Meta-analysis (9 RCTs, 1069 adults)
  - Improved some pain areas (ear, muscles and headache) but not sore throat. Nothing for other cold Sx.
- Acetaminophen
  - 2 RCTs (90 children, 392 adults), + 2 meta-analyses on fever
  - Fever reduction & mild analgesia better than placebo
  - Vs Ibuprofen: At 4 to 6 hours, approximately 15% more ibuprofen patients had fever reduction (NNT 7).
- Bottom-Line: Work o.k. for fever & (most) pain
  - Ibuprofen >Acetaminophen in peds (need good hydration)

Antihistamine: Alone or with Friends

- Antihistamines Alone: (3 sys rev, up to 22 RCTs)
  - Many outcomes, None reached clinical significance
- Antihistamine Combinations (1 sys rev, 27 RCTs)
  - With decongestants, global symptoms, NNT 4.
  - with analgesia, global symptoms, NNT 4-7.
  - With decongestant& analgesia, global, NNT 6.
- Bottom-line: Antihistamines alone, nothing meaningful. Combos small impact (NNT 4-7), but should not be used in children under 6.

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A little, not a lot.

- Decongestants: Oral and topical nasal decongestants
  - Oral: small effect on congestion symptoms (4-6%).
  - Topical: small effect on congestion Sx (≈10 better on VAS)
  - Harms: Small increase in insomnia?
- Cough Suppressants (Antitussives, mucolytics, expectorants, etc):
  - 1 meta-analysis (18 RCTs, 3421 adults; 8 RCTs, 616 children)
  - Children: no benefit
  - Adults: some inconsistent benefit with some combination products and dextromethorphan
- Bottom-line: Adults: Small effect, uncertain clinical significance. Not in children

Did you know about,….

- Ipratropium 168µg - 42 µg (1-2 sprays, 3-4 times per day)
  - Evidence: 1 meta-analysis (7 RCTs, 2144 adults and children 5 years and older)
- Improved rhinorrhea but not nasal congestion.
  - Global symptom improved for 10-15% more ipratropium users
- Harms: Increased epistaxis, nasal dryness and mouth dryness (Odds Ratio 2-3)
- Bottom-line: Probable benefit

Wait a minute,…

- Vicks VapoRub™ (One night 5-10 mls on chest & neck)
  - 1 RCT (138 kids age 2-11 yrs) versus placebo
  - No improvement in cough or rhinorrhea but small improvement in sleep for child and parent
    - Global symptoms about 4 (out of 42).
  - More AE: burning skin (28%), eyes (16%) & nose(14%)
  - Bottom-line: Unclear if benefit but harms present
- Antibiotics: 6 RCTs, 1047 adults and children
  - No benefit but more AE (RR 1.8, 1.01 to 3.21)
  - Bottom-line: No benefit. Harms present

Treatment: Alternative

Heaven only knows: part 1

- Nasal Irrigation: Sys Rev (3 RCTs, 618 pts)
  - Nasal symptom score, no diff. Rest inconsistent
  - Harms: 13% nasal irritation, 30% dry nose, 40% of infants intolerant
- Humidified air: Sys rev (6 RCTs, 394 pts)
  - Fewer pts persistent symptoms (OR 0.31, 0.16, 0.60).
  - Results very inconsistent (heterogeneity i^2=89%).
  - More harms including increased congestion
- Bottom-Line: No consistent effect except harms.

Heaven Only Knows: Part 2

- Ginseng: 1 RCT (46 children aged 3-12)
  - No benefits studied (or reported?). Only report AE
- Bottom-Line: No research?
- Chinese Herbs: Sys rev (17 RCTs, 3212 pts)
  - None the same, 1 of 17 showed global Sx improve
- Bottom-Line: Nothing reliable

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Heaven only knows: Part 3+

- Echinacea: Sys rev (14 RCTs, 2090 pts)
  - Not pooled: Inconsistent
  - 1 of 6 to 5 of 10 studies show an effect on sum cold score at different time points.
  - No evidence of harms
- Bottom-line: Unclear evidence of benefit

- Vitamin C: Meta-analysis (7 trials, 3249 colds)
  - 7 pooled studies, No effect on duration
- Bottom-Line: WE KNOW: No benefit

Zinc: oral or intranasal

- Oral: Zinc gluconate 23mg lozenge q2 hrs most common
  - Meta-analysis (17 RCTs, 2121 participants)
  - Pooled 8 RCTs, reduce duration of cold 1.65 days (2.5, 0.8) (adults benefit but no kids)
  - Harms: Increased adverse events (bad taste and nausea)
- Bottom-line: Probable benefit in adults, harm present. No benefit in children

- Intranasal zinc: 3 RCTs
  - No significant effect colds but AE present including possible permanent loss of Smell
- Bottom-Line: Don't use nasal zinc.

Hold on Honey, Here's something that works

- Honey, one dose at bed, 2.5 to 10gm
  - 3 RCTs (105, 139, 300 children). Most children age 1-5 years
  - Children evidence of benefit over placebo and dextromethorphan.
  - No data in adults
  - No consistent adverse events
- Bottom-line: Small benefit for cough in children (over age 1)

Additional Points.

- Almost all of this research is at high risk of bias
  - Finding or exaggerating benefits
- Probably patient interaction a good way to go.
- Delayed Antibiotic if
  - Patients really want Abx (confirmed) and
  - You suspect there may be a bacterial co-infection, delayed Abx will reduce

Prevention Summary

	Preventive therapy
What Works	Physical Maneuvers (e.g. hand-washing), Zinc (maybe)
Unclear if Works	Probiotics (?), Ginseng (Cold Fx), Exercise, Gargling, Garlic,
Doesn't Work	Vitamin C, Echinacea, Homeopathy, Vitamin D

Treatment: Traditional

	What	How
What Works	NSAIDs	For Pain only
	Acetaminophen (probably)	Pain and fever only
	Ibuprofen Superior to Acetaminophen	Fever (pediatric)
	Antihistamines with decongestants or analgesics	Small-Moderate effect overall (Not children <6)
	Topical Decongestants	Small effect (at best) nasal symptoms (no children)
	Intranasal ipratropium	Nasal symptoms

Unclear	Cough Suppressants (adults)
	Vicks VapoRub
Doesn't work	Antihistamines alone
	Oral Decongestants
	Cough suppressants (pediatric)
	Antibiotics

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Treatment: Alternative

	What	How
Works	Oral Zinc (adults)	Overall Symptoms (1d)
	Honey (Pediatrics >1 year)	Small Cough reduction
Unclear	Nasal Irrigation	
	Humidified air	
	Nasal Zinc (Also harms)	
	Echinacea	
	Ginseng	
Doesn't Work	Oral Zinc (children)	
	Vitamin C	
	Chinese Herbs	

Double Trouble, Boil and Bubble: *C. difficile* and MRSA

Natasha Press
Infectious Diseases, St. Paul's Hospital
April 12, 2013

Recent guidelines

- www.idsociety.org
- 2010: Clinical Practice Guidelines for Clostridium difficile infection in Adults
- 2011: Management of Patients with Infections Caused by Methicillin-Resistant Staphylococcus Aureus

Conflict of interest

- Advisory board/Honoraria
  - BMS, Gilead, Iroko International, Merck, Pfizer
- UBC ID program has multiple pharmaceutical companies contributing to the residents' educational fund

The Human Microbiome Project

Clostridium difficile

- Objectives:
- What's new:
  - Probiotics
  - Fecal microbiota transplant
  - Fidaxomicin

Natasha Press

C. diff: Who to test

- Risk factors:
  - Antibiotic history
  - >Age
  - Duration of hospitalization
  - PPI

C. diff: Who to test

- Symptoms:
  - Diarrhea (> 3 bm/d)
  - Abdominal cramping/discomfort
  - Fever
- ⇧WBC

How to test

- Stool for C. diff
- WBC
- creatinine

C. diff: How to treat

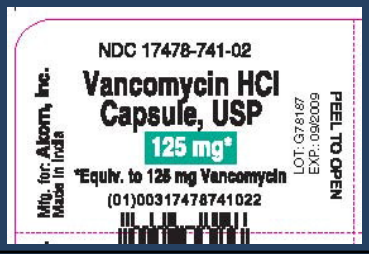
- Oral vancomycin (never use IV)
- Oral metronidazole

Severity of disease

- Is this severe disease?
- WBC > 15
- Creatinine > 1.5xN
- Other factors:
  - Age > 60, temp > 38.3, albumin < 25

Severe initial episode

- **Vancomycin po 125 mg qid x 10-14 days**



Natasha Press

How will you manage this patient?

- Discontinue abx
- Start empiric treatment
- (don't wait for lab results if patient is sick)
- Avoid antiperistaltic agents

- Infection control:
  - Contact precautions
  - Hand hygiene (soap & water)

When can po metronidazole be used?

- **Mild-moderate disease:**
  - **WBC <15**
  - **N creatinine**
- **metronidazole 500 mg po tid**

Recurrence

- First recurrence → go through same steps as initial episode
- Second recurrence → tapered then pulsed vancomycin dosing

Second recurrence

- Prolonged courses
- Tapering doses
- Pulsed doses

Week	Vanco Dose
1	125 mg qid
2	125 mg qid
3	125 mg bid
4	125 mg qd
5 and 6	125 mg q2-3days

McFarland LV et al. Am J Gastroenterol 2002; 97(7):1769-1775
Tedesco FJ et al. Am J Gastroenterol 1985;80:867-8

Please do not do these things:

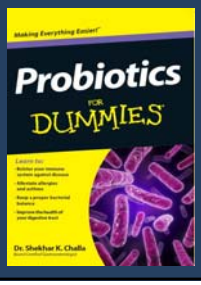
- Do not test:
  - Test of cure
  - Formed stools

- Do not give metronidazole for > 2 weeks
  - Does not penetrate formed stool
  - Peripheral neuropathy

Probiotics

- Insufficient evidence for treatment
- Insufficient evidence for prevention

- Problems:
- Single strains vs. mixtures of organisms
- Concentrations
- Small studies, poor methodology



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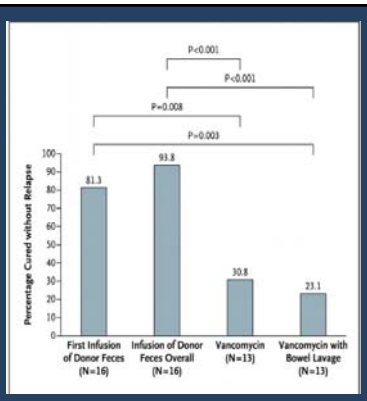
Fecal Microbiota Transplantation

ORIGINAL ARTICLE

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

- RCT
- 3 groups:
  - Oral vanco x 14 days
  - Oral vanco x 4 days then lavage then fecal replacement
  - Oral vanco x 14 days then lavage



Fidaxomicin

- 200 mg po bid x 10 days = $2600
- Cure:
  - Fidaxomicin = vancomycin = 90%
- Recurrence:
  - vancomycin 25%, fidaxomicin 15%
  - NNT = 10
  - Or $26,000 to prevent one recurrence

C. difficile

- Oral metronidazole for mild-moderate
- Oral vancomycin for severe
- Oral fidaxomicin for the 1%
- Fecal microbiota transplant for recurrent, chronic

Methicillin Resistant *Staphylococcus aureus* (MRSA)

- Objectives:
- MRSA skin and soft tissue infections (SSTIs):
  - Treatment
  - Decolonization

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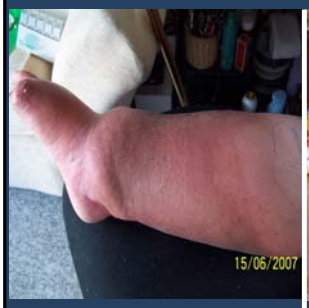


Non-purulent Cellulitis (no wound or abscess)

DDx: -**Gp A Streptococcus**
- *S. aureus* & others

Cellulitis with wound or abscess

DDx: – **S.aureus**
– Gp A Streptococcus
– others

Do Oral MRSA Antibiotics Cover Group A Streptococcus?

TMP-SMX: active in vitro; but ineffective vs GAS pharyngitis

Clindamycin: 73% susceptible[1]

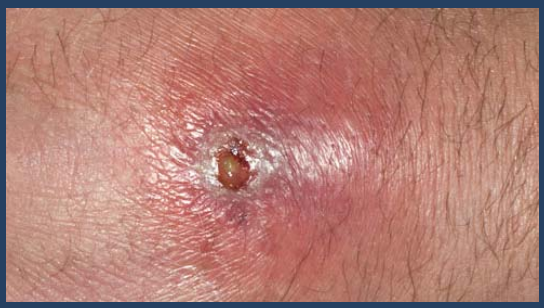
Tetracycline (doxycycline): 47% susceptible[1]

[1]Tan K, Romney M, Champagne S. AMMI, 2008

Skin & Soft Tissue Infections: Oral Rx

Cellulitis (no WND, abscess, or pus)	Abscess or WND infection +/- cellulitis	Wound/cellulitis and modifying factors (e.g. bites, diabetes..)
Gp A Strep (GAS)	*S. aureus*, Gp A Strep	*S. aureus*, GAS, &/or others
keflex	I&D; (septra or doxy) + keflex	based on clinical context

Recurrent MRSA SSTIs



Decolonization for recurrent MRSA

- Doesn't always work
- Doesn't always last
- No one knows the best approach

Recurrent MRSA SSTIs

- Keep wounds covered
- Regular bathing and cleaning of hands
- Avoid reusing/sharing personal items (e.g. towels)

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Decolonization for recurrent MRSA

- No screening
- Mupirocin ointment to nares twice daily x 5-10 days
- +
- Chlorhexidine wash for 5-10 days

- Or bleach bath

- Instructions:
- Fill tub with water
- Add ¼ cup bleach
- Soak for 15 minutes twice weekly

Interpersonal transmission

- Household contacts may have identical MRSA (40%)
- Personal and environmental hygiene
- Decolonize household contacts

Scand J Infect Dis. 2007

Preventing surgical-site infections

- 25% of surgical site infections are caused by *Staph aureus*
- >50% arise from endogenous flora
- Pre-op: 5 days of mupirocin-chlorhexidine in select patients

Bode et al. NEJM 2010

MRSA SSTI conclusions

- Treat empirically for MRSA if wound/abscess
- Septra, clindamycin, doxycycline
  + keflex
- Decolonization for recurrent infections:

–mupirocin +

–bleach baths or chlorhexidine body washes

- Decolonization pre-op for select patients: mupirocin-chlorhexidine

Conclusions

- Antibiotic stewardship

- *C. difficile* – reduce unnecessary abx use
- ¼ received only unnecessary abx
- ¾ received ≥1 unnecessary dose

Infect Control Hosp Epi 2013

- MRSA – due to abx selective pressure
- Abx use correlates with risk for MRSA colonization and infection

Don't mess with the microbiome

Gillian de Gannes

Chronic Hand Dermatitis

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24th Annual Drug Therapy Decision Making Course
The Fairmont Waterfront Hotel
13 April 2013

Faculty/Presenter Disclosure

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- **Grants/Research Support:** WorkSafeBC, Canadian Dermatology Foundation, Galderma Canada Inc., Abbott Laboratories Ltd., LEO Pharma Inc., Janssen-Ortho Inc., Cipher Pharmaceuticals Inc., Pfizer Pharmaceuticals, Kao Corp., Amgen Canada Inc.
- **Speakers Bureau/Honoraria:** Astellas, La Roche-Posay Canada (L'Oreal Canada Inc.), LEO Pharma Inc., Dermik/Sanofi-Aventis, Stiefel Canada Inc., Graceway Canada Company, Galderma Canada Inc., Actelion Pharmaceuticals Canada Inc., EMD Serono Canada Inc., Schering-Plough Canada Inc. (Merck), Abbott Laboratories Ltd., Amgen Canada Inc. (Pfizer), Janssen-Ortho
- **Consulting Fees:** Spexell Pharma, Graceway Canada Company, LEO Pharma Inc., Astellas, Dermik/Sanofi-Aventis, Stiefel Canada Inc., Amgen Canada Inc., Schering-Plough Canada Inc. (Merck), Abbott Laboratories Ltd., Actelion Pharmaceuticals Canada Inc., Galderma Canada Inc., Valeant Canada, Tribute Pharmaceuticals, Janssen Inc., BIO-K+ International Inc., Johnson & Johnson Inc.

Disclosure of Commercial Support

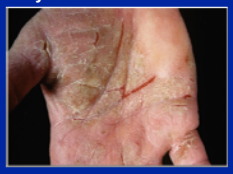
- No commercial support.
- Potential for conflict(s) of interest:
  - Dr. Gillian de Gannes has received Speakers Bureau/Honoraria/Consulting Fees from Actelion Pharmaceuticals Canada Inc.
  - Actelion Pharmaceuticals Canada Inc. distributes/benefits from the sale of a product that will be discussed in this program: Toctino (alitretinoin).

Mitigating Potential Bias

- CME/CPD material is peer reviewed
- all the recommendations involving clinical medicine are based on evidence that is accepted within the profession
- all scientific research referred to, reported, or used in the CME/CPD activity in support or justification of patient care recommendations conforms to the generally accepted standards

What is Chronic Hand Dermatitis?

- Inflammatory skin disease characterized by:[1,2]
  - Scaling
  - Hyperkeratinization
  - Erythema
  - Vesicles
  - Deep, painful fissures
- Chronic disease[1]
  - Persists for > 3 months or
  - Recurring ≥ 2 times within 12 months
  - Even with adequate treatment and adherence



1. Lynde CW, et al. Canadian Hand Dermatitis Management Guidelines. J Cutan Med Surg 2010;14(6):267-284;
2. Diepgen TL, et al. Contact Dermatitis 2007;57:203-210.

Variants of Hand Dermatitis

- contact (irritant & allergic) dermatitis
- atopic dermatitis
- nummular dermatitis
- hyperkeratotic dermatitis
- pompholyx
- frictional dermatitis
- chronic vesicular hand dermatitis

Warshaw E, Lee G & Storrs FJ. Dermatitis 2003;14(3):119-137

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Patch Testing

allergens applied to back on day 1
allergens removed on day 3 (48 hr reading)
reassessed on day 5-7 (delayed reading)

investigate for allergic contact dermatitis

Emollients

√ no fragrance
√ no botanical extracts

Skin Barrier Repair Devices

√ no fragrance
√ no botanical extracts
√ ceramides

cotton gloves for working hands

Dr. Neil Kitson

Topical Corticosteroids

Pros[1]

- Fast acting
- Intermittent or continuous applications:
  - Limited treatment duration for most potent TCS
- Majority of mild symptoms respond to TCS
- Evidence level A[2]

Cons[1]

- Can be misused
- Potential for skin barrier disruption
- Long-term use may lead to significant atrophy and erythema
- Tachyphylaxis (really means the patient stops using the medication)

1. Marks R. Practical Problems in Dermatology, 2nd edn. 1996;
2. Lynde CW, et al. Canadian Hand Dermatitis Management Guidelines. J Cutan Med Surg 2010;14(6):267-284)

Phototherapy in Hand Dermatitis

- Not universally available[1]
- Usually used in combination with other treatments[1]
- Controlled studies show benefit in hyperkeratotic dermatitis:[2]
  - Magnitude of effect variable
  - Frequent relapse after cessation of therapy
- Inconvenient for many patients[1]
- Evidence level B[1]

1. Lynde CW, et al. Canadian Hand Dermatitis Management Guidelines. J Cutan Med Surg 2010;14(6):267-284;
2. Halpern SM. Br J Dermatol 2000;142:22–31

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Systemic Treatments in CHD

- **Approved** (Evidence Level A)
  - Alitretinoin
- **Not approved** (Evidence Level B)
  - Oral corticosteroids
  - Oral retinoids (acitretin)
  - Oral immunosuppressants (cyclosporine)

van Coevorden AM. Br J Dermatol 2004;151(2):446–51

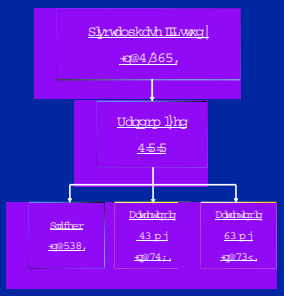
Alitretinoin (9-cis retinoic acid)

- Endogenous, naturally-occurring physiological substance
- Exact mechanism of action in treatment of CHD unknown
- Binds to retinoic acid receptors (RARs) and retinoid X receptors (RXRs):
  - anti-inflammatory and immunomodulatory properties
- Rapid metabolism and excretion
- Plasma concentrations return to endogenous levels within 1-3 days of discontinuation
- Elimination half-life 2-10 hours

1. Cheng C. Expert Opin Investig Drugs 2008;17(3):437–443;

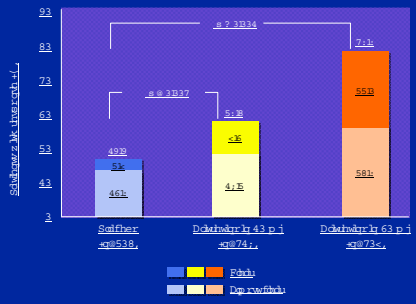
BACH Study Design

- 1,032 patients with severe refractory CHE from 111 centres in Europe and Canada
- Double-blind, randomized, placebo controlled, parallel-group trial
- Once daily for 12 or 24 weeks, depending on response to treatment



Ruzicka T. Br J Dermatol 2008;158(4):808–817

Patient Response With Alitretinoin



Ruzicka T. Br J Dermatol 2008;158(4):808–817

Efficacy By Type of CHD (12 or 24 week LOCF)

Classification	Placebo	Alitretinoin 10 mg	Alitretinoin 30 mg
Hyperkeratotic			
N	170	362	349
Responders, n (%)	21 (12%)	102 (28%)	170 (49%)
Pompholyx			
N	55	109	112
Responders, n (%)	9 (16%)	25 (23%)	37 (33%)
Fingertip			
N	101	180	196
Responders, n (%)	18 (18%)	53 (29%)	87 (44%)

- Alitretinoin works in all types of CHD
- Most effective in hyperkeratotic CHD

Ruzicka T. Br J Dermatol 2008;158(4):808–817

BACH Efficacy Conclusions

- Largest study ever conducted in CHD
- Alitretinoin highly effective in treating severe CHD
  - 75% median reduction in signs and symptoms after 24 weeks
  - 48% of patients have clear/almost clear skin at end of treatment (12-24 weeks)
- All individual symptoms of CHD improved
- Works in all forms of CHD:
  - Most effective in hyperkeratotic CHD

1. Ruzicka T. Br J Dermatol 2008;158(4):808–817;
2. Elsner P. EADV 2008: Abstract FC10.105

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Safety Conclusions

- Well tolerated in patients with severe CHD unresponsive to TCS[1,2]
- AEs are dose-dependent, manageable and consistent with retinoid class effects:
  - Headache most common AE[1,2]
  - Mucocutaneous effects occur in ~10% of patients[1]
- Remains well tolerated after a second 12-24 week course of treatment:[2]
  - No new safety signals
  - No significant late-arising toxicities

1. Ruzicka T. Br J Dermatol 2008 Apr;158(4):808-817.
2. Bissonnette R et al. Br J Dermatol 2010; 162(2): 420-6.
3. Ruzicka T et al. EADV 2008, Abstract PC10.107

Contraindications

- Pregnancy
- Breastfeeding women
- Hepatic insufficiency
- Severe renal insufficiency
- Uncontrolled hypercholesterolemia and/or hypertriglyceridemia
- Hypervitaminosis A
- Hypersensitivity to alitretinoin, other retinoids or any of the excipients (allergies to peanut or soya)
- Receiving concomitant tetracyclines

Dosing and Administration

- Recommended starting dose 30 mg once/day with a meal
- Dose reduction to 10 mg may be considered in patients with unacceptable side effects
- 12-24 weeks treatment course depending on response
- Patients who relapse may benefit from further treatment courses

Take Home Messages

- Chronic hand dermatitis is a common disorder
- Consider other diagnoses when treatment fails (patch test for allergic contact dermatitis)
- When topical corticosteroids and phototherapy fail to control the disease consider systemic therapy
- There is a new therapy for this chronic disease (alitretinoin – a systemic retinoid)

Reference

Lynde CW, *et al.*

Canadian Hand Dermatitis Management Guidelines.

Journal of Cutaneous Medicine & Surgery

2010;14(6):267-284

Adil Virani

Antipsychotic dose escalation or combinations in Schizophrenia: **An Effective Strategy or Prescriber's Delusion?**

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Disclosure

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

I receive honoraria for work related to providing advice about rational drug use from:

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

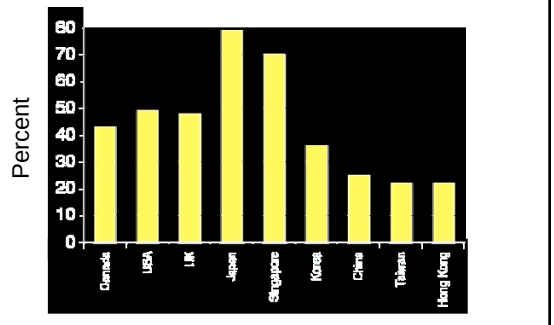
Learning Objectives

1. Describe what percentage of patients with schizophrenia have an inadequate response from regular antipsychotic doses.
2. List the benefits and harms of using high dose antipsychotics and combination antipsychotics.
3. Understand the results from a CADTH Systematic Review of the relevant available evidence.
4. Describe limitations in current literature regarding the use of high dose antipsychotics and combination antipsychotics.

Background:

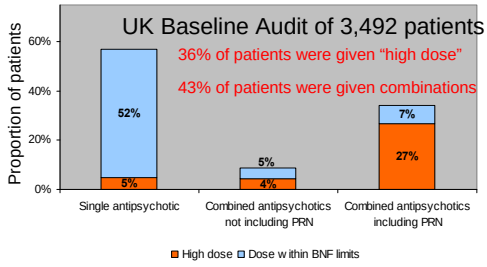
- ~1 in 3 patients with schizophrenia have a poor response to treatment
- Psychiatrists utilize "high dose" and/or try multiple antipsychotics simultaneously (combination therapy) to improve response in refractory patients
- Canadian Psychiatric Association (CPA) and NICE guidelines do not recommend these strategies

Antipsychotic Polypharmacy



(*Procyshyn Pharmacopsych 37:12, 2004; Faries BMC Psych 5:26, 2005; Paton J Psychopharmacol 17:223, 2003; Sim Br J Clin Pharmacol 58:178, 2004*)

FIGURE 1: The proportion of the total national sample prescribed a standard or high dose of single or combined antipsychotics at BASELINE audit.



A baseline audit of 3,492 patients on 218 wards in 32 participating Trusts found that over a third (36%) of patients were prescribed a high dose of antipsychotic medication, and 43% were prescribed more than one antipsychotic. 31% of patients were

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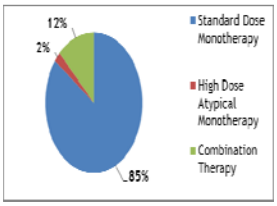
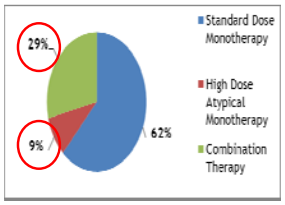
How often are these strategies employed?

Patients receiving antipsychotics, ON 2009



Antipsychotic expenditure – ON 2009



Based on patient-level data from Ontario Drug Benefits Program, 2009 from IMS Brogan. All Patients.

BC spent $69.2 million on antipsychotic drugs in 2009

Reference: CADTH, Current Utilization Report, 2012.

Practitioners' justifications of high dose therapy and polypharmacy

Most common rationalisations:

- Insufficient response to or relapse whilst on monotherapy (Bains and Nielssen, 2003; Harrington et al., 2002; Haw and Stubbs, 2003a),
- Concerns about safety (Bains and Nielssen, 2003; Haw and Stubbs, 2003a)
- Concerns about adherence (Bains and Nielssen, 2003; Paton et al., 2002)
- Desire to leave medications unchanged if patients were reasonably well
- Desire to not contribute to further deterioration if they were not well (Haw and Stubbs, 2003a)

Griffiths et al Aust N Z J Psychiatry May 2012

Why are psychiatrists using high dose SGAs?

Severity *"If someone is really psychotic, sometimes I have go much above the recommended dose."* Alberta

Partial response *"If the patient is still responding to the medication, but hasn't quite got to where I want him or her to be, then I would still continue increasing it past the maximum recommended dose."* Alberta

Metabolism *"If they smoke, that burns through olanzapine."* BC

'Reasonably tolerated' *"For Zyprexa, the recommended dose, I don't know if it's 20 or 30, but I have put patients on 40 because there isn't as much of an issue with akathisia and extrapyramidal symptoms."* Quebec

Reference: CADTH, Current Practice Data, 2011.

Why are psychiatrists combining SGAs?

Sedation *"I might add a second antipsychotic that's more sedating to help with sleep at night."* Ontario

Adherence *"…treatment advantage by having patients on an atypical plus an injectable because the injectable is sort of a guarantee minimum."* BC

Hope *"The medication is not sufficiently effective, and a higher dose won't be tolerated, but I'm hoping that a second medication will be tolerated."* Ontario

Reference: CADTH, Current Practice Data, 2011.

Which antipsychotics were used most frequently in 'high' doses or as combinations?

Freq of high doses used	Freq of combinations used
Olanzapine (72%)	Olanzapine + Quetiapine (22%)
Quetiapine (13%)	Risperidone + Quetiapine (10%)
Risperidone (6%)	Olanzapine + Risperidone (9%)

Ranking is based on total active months of drug prescribed

% refers to drug's share of antipsychotic high dose or combination expenditure in Ontario in 2009

Reference: CADTH, Current Utilization Report, 2012.

How effective are high dose and combination strategies compared to monotherapy?

What are the potential harms?

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CADTH review methodology

Systematic review:

- Searched MEDLINE (1950-), Embase (1980-), PsycINFO (1967-), Cochrane Central Register, grey literature via internet, bibliographies of selected studies hand searched

Selection criteria:

- Study design: Randomized controlled trials
- Population: Adolescents or adults with schizophrenia or schizoaffective disorder inadequately controlled with 1 or more antipsychotic monotherapies
- Interventions: Second generation antipsychotics (SGA)
- Comparators: Antipsychotic monotherapy at any dose, combinations of antipsychotics at any dose
- Outcomes: Identified *a priori*, included symptoms of schizophrenia, response rate, withdrawals and serious adverse events

Reference: CADTH, Atypical Antipsychotics for Schizophrenia, Project Protocol, 2011.

RCTs examining SGA at high dose

Aripiprazole > 30 mg/day	No RCTs
Clozapine* >600 mg/day	No RCTs
Olanzapine >20 mg/day	5 RCTs (N=468)
Paliperidone >12 mg/day	No RCTs
Quetiapine >800 mg/day	1 RCT (N=131)
Risperidone** >6 mg/day	4 RCTs (N= 570)
Ziprasidone >160mg/day	No RCTs

*Product monograph states maximum 900mg/day
** Product monograph states maximum 16 mg/day

Reference: CADTH, Recommendations for Atypical Antipsychotics, 2011.

RCTs examining SGA combination therapy

Combinations	Aripiprazole	Clozapine	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Clozapine	2 (N=269)	-	-	-	-	-	-
Olanzapine	None	None	-	-	-	-	-
Paliperidone	None	None	None	-	-	-	-
Quetiapine	1 (N=323)	None	None	None	-	-	-
Risperidone	1 (N=323)	6 (N=296)	None	None	None	-	-
Ziprasidone	None	None	None	None	None	None	-
Typical antipsychotics	None	3 (N=44)	None	None	None	None	None

High dose monotherapy: no advantages

Outcomes	Favours	*Total of 9 RCTs, N = 1002*
Response rate	*Not significant*	
Schizophrenia symptom scales	*Not significant,* apart from GAF and BPRS scores which favour clozapine standard dose	
Quality of life	*Not significant*	

High dose monotherapy: uncertain harms

Outcomes	Favours *Total of 9 RCTs, N = 1002*
Mortality	*Not significant* risperidone >6mg/day versus clozapine standard dose. *Not reported* in other RCTs
Suicide	*Lack of evidence*
Hospitalization	*Lack of evidence*
Serious adverse events	*Not significant* (>800mg/day) quetiapine versus (300-800mg/day) quetiapine. *Not reported* in other RCTs.
Withdrawals	*Not significant* apart from withdrawal due to adverse events which favoured high-dose olanzapine over clozapine
Extrapyramidal symptoms	Clozapine standard dose vs riperidone (>6mg/day) # patients with EPS. Risperidone (>6mg/day) over standard dose clozapine for Parkinsonism events. *Not significant* in other RCTs.
Metabolic side effects	*Not significant*
Tardive dyskinesia	*Not significant* or *not reported*
Agranulocytosis	*Not significant*

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Combination therapy: no advantages

Outcomes	Favours	Total of 12 RCTs, N = 942
Response rate	*Not significant*	
Schizophrenia symptom scales	*Not significant,* apart from slight improvement in CGI-I at 16 weeks favouring clozapine combination	
Quality of life	*Not significant*	

Combination therapy: unknown harms

Outcomes	Favours	Total of 12 RCTs, N = 942
Mortality	*Lack of evidence*	
Suicide	*Lack of evidence*	
Hospitalization	*Not significant*	
Serious adverse events	Clozapine monotherapy over clozapine combination therapy (6 RCTs). Favours aripiprazole combination over risperidone or quetiapine monotherapy (1 RCT).	
Withdrawals	*Not significant*	
Extrapyramidal symptoms	*Not significant*	
Metabolic side effects	*Not significant*, apart from prolactin levels which favours combination therapy (1 RCT).	
Tardive dyskinesia	*Lack of evidence*	
Agranulocytosis	*Lack of evidence*	

Receptor profile of atypical antipsychotics

Drug	Dopamine D_2	Muscarine M_1	α_1	Histamine H_1	5-HT $_{2A}$
	EPS, prolactin elevation	Cognitive deficits, dry mouth, constipation, increased heart rate, urinary retention, blurred vision	Hypo-tension	Sedation, weight gain, dizziness	Anti-EPS?
Aripiprazole	++++	-	-	-	+++
Clozapine	+	++	+++	+++	+
Olanzapine	+++	+	++	+++	++
Quetiapine	++	-	+++	+++	+++
Risperidone	+++	-	+++	+	+++
Ziprasidone	+++	-	++	+	+

++++ very high affinity, +++ high affinity, ++ moderate affinity, + low affinity, - negligible affinity

References: *CNS Spectr*. 2005; 8(Suppl 10):5-11; *Primary Psychiatry*. 2007;14(10):23-25.

Supplementary safety review – high dose

Findings:

- Safety evidence is limited, often contradictory, confounded by bias.
- Patients receiving clozapine or high-dose therapy typically have severe or refectory schizophrenia and are at higher risk of adverse events or mortality independent of therapy.

Individual studies of interest:

- High dose clozapine associated increased **seizure** rate (Haddad & Sharma, 2007)
- **Weight gain** associated with clozapine and high dose olanzapine (Simon, 2009)
- **New-onset diabetes** associated with standard dose clozapine (Trenton, 2003)
- High dose asenapine associated with increased completed **suicides** (Citrome, 2009)
- **Myocarditis** (incidence 0.7and 1.2%) associated with both standard and high-dose clozapine (Trenton, 2003; Haas, 2007)
- **Agranulocytosis** is now 0.38% from 1-2% prior to US national clozapine registry (Trenton, 2003)

Reference: CADTH, Systematic Review Atypical Antipsychotics for Schizophrenia, 2011.

Supplementary safety review - combination

Findings:

- Safety evidence is limited, often contradictory, confounded by bias.

Individual studies of interest:

- Reduced 10 year **survival** in patients prescribed more than one antipsychotic (Freudenriech & Goff, 2002)
- Risk of **hospitalization** highest for patients using combination therapy (Stroup, 2009)
- Combination therapy associated **weight gain** of more 7% and 10% (Stroup, 2009)
- **Pancreatitis** may be associated with combination therapy (either with another AAP or with haloperidol) (Koller, 2003)

Reference: CADTH, Systematic Review Atypical Antipsychotics for Schizophrenia, 2011.

Limitations:

- **Sparse evidence base**
- **None of the included studies were rated as being of high quality**
- **All are of short-duration (8 to 26 wks for high dose and 6 to 16 wks for combination)**
- **Most RCTs were underpowered for clinically relevant outcomes (ex. N=296 is the sum of patients from the 6 combination RCTS).**

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Research Gaps

Populations:

- Patients < 18 years of age
- Subgroups likely to achieve greater benefit with combination or high-dose use
- Patients who are partial responders to standard-dose SGA monotherapy

Outcomes:

- Mortality
- Hospitalizations
- Suicidality
- Relapse rate
- Health-related quality of life
- Level of function
- Long-term adverse effects of high-dose or combination antipsychotic use

Conclusion

High-dose strategies or combining atypical antipsychotics with other antipsychotic agents are **not more effective** and **may be more harmful** than treatment with a recommended dose of one antipsychotic agent.

Acknowledgements:

COMPUS Expert Review Committee:

- Dr. Lisa Dolovich (Chair)
- Dr. Mike Evans (Vice Chair)
- Dr. Michael Allen
- Dr. Scott Klarenbach
- Dr. James Silvius
- Dr. Gary Remington
- Dr. Heather Milliken
- Dr. William Honer
- Dr. Richard Williams
- Dr. Adil Virani
- Mr. Panos Petrides
- Ms. Cathy MacNutt

CADTH Staff

Questions?

Table 2: COMPUS Expert Review Committee Recommendation for Combination and High-Dose Treatment Strategies with Atypical Antipsychotics

CERC recommends that clozapine-based antipsychotic combination therapy should not be used for patients with schizophrenia who inadequately respond to standard-dose clozapine monotherapy.* * The available data for combination therapy with clozapine were primarily for oral risperidone, with some evidence available for aripiprazole and sulpiride. There was no evidence available for other atypical antipsychotic agents.
CERC recommends that non-clozapine-based atypical antipsychotic combination therapy should not be used for patients with schizophrenia who inadequately respond to a standard-dose atypical antipsychotic agent.* * Evidence was available only for the combination of risperidone or quetiapine with aripiprazole. There was no evidence for other combinations involving atypical antipsychotic agents.
CERC recommends that standard-dose clozapine should be used instead of high doses of other atypical antipsychotic agents for patients with schizophrenia who inadequately respond to a standard-dose atypical antipsychotic agent.* * Evidence was available only for use of high-dose risperidone and high-dose olanzapine. There were no studies comparing other atypical antipsychotic agents used at high doses with standard-dose clozapine. Of note, the threshold for defining high-dose olanzapine in the CADTH systematic review was higher than Health Canada-approved doses.
CERC recommends that high doses of a (non-clozapine) atypical antipsychotic agent not be used instead of standard doses in patients with schizophrenia who inadequately respond to a standard-dose antipsychotic agent.* * Evidence was only available for use of high-dose risperidone and high-dose quetiapine. There were no studies comparing other atypical antipsychotic agents used at high doses with standard-dose (non-clozapine) antipsychotic therapy. Of note, the threshold for defining high-dose quetiapine in the CADTH systematic review was higher than Health Canada-approved doses.

What is the alternative?

Canadian Psychiatric Association. Clinical Practice Guidelines. Treatment of Schizophrenia. Can J Psychiatry, 2005:50 (13 Suppl 1).

Mark McLean

Withdrawal Management

Mark McLean MD MSc FRCPC CISAM ABAM

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

- **Faculty:** Mark McLean MD MSc FRCPC CISAM ABAM

- **Relationships with commercial interests:**
  - **Grants/Research Support:** Not applicable
  - **Speakers Bureau/Honoraria:** Not applicable
  - **Consulting Fees:** Not applicable
  - **Other:** Acting Physician Manager of the Addiction Consult Team at Providence Health Care

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

- **No commercial support**

CFPC CoI Templates: Slide 3

Mitigating Potential Bias

- All recommendations involving clinical medicine are based on evidence that is accepted within the profession; and
- All scientific research referred to, reported, or used in this presentation in support or justification of patient care recommendations conforms to generally accepted standards

Sources of information for this presentation:

- ASAM – Principles of Addiction Medicine
- BCMA/BC MoH - Problem Drinking Part 3 - Office Based Management of Alcohol Withdrawal and Prescribing Medications for Alcohol Dependence Effective date: April 1, 2011
- Miller NS, Gold MS. Management of Withdrawal Syndromes and Relapse Prevention in Drug and Alcohol Dependence. Am Fam Physician. 1998 Jul 1;58(1):139-146.

Substance Withdrawal

"the development of a substance-specific maladaptive behavioral change, usually with uncomfortable physiological and cognitive consequences, that is the result of a cessation of, or reduction in, heavy and prolonged substance use"

- American Psychiatric Association

Signs and symptoms of withdrawal

- Usually are opposite to a substance's pharmacologic effects
- Are similar for substances in a given pharmacologic class, but vary by time of onset, duration, and intensity, depending on the properties of the agent, the duration of use, and the degree of neuroadaptation

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Signs and Symptoms of Alcohol and Drug Withdrawal

Drug	Peak period	Duration	Signs	Symptoms
Alcohol	1-3 days	5-7 days	Elevated blood pressure, pulse and temperature, hyperarousal, agitation, restlessness, cutaneous flushing, tremors, diaphoresis, dilated pupils, ataxia, clouding of consciousness, disorientation	Anxiety, panic, paranoid delusions, illusions, visual and auditory hallucinations (often derogatory and intimidating)
Benzodiazepines and other sedative hypnotics	Short acting: 2-4 days; Long acting: 4-7 days	Short acting: 4-7 days; Long acting: 7-14 days	Increased psychomotor activity, agitation, muscular weakness, tremulousness, hyperpyrexia, diaphoresis, delirium, convulsions, elevated blood pressure, pulse and temperature, tremor of eyelids, tongue and hands	Anxiety, depression, euphoria, incoherent thoughts, hostility, grandiosity, disorientation, tactile, auditory and visual hallucinations, suicidal thoughts
Opiates	1-3 days	5-7 days	Drug seeking, mydriasis, piloerection, diaphoresis, rhinorrhea, lacrimation, diarrhea, insomnia, elevated blood pressure and pulse (mild)	Intense desire for drugs, muscle cramps, arthralgia, anxiety, nausea, vomiting, malaise
Stimulants	1-3 days	5-7 days	Social withdrawal, psychomotor retardation, hypersomnia, hyperphagia	Depression, anhedonia, suicidal thoughts and behavior, paranoid delusions
PCP/psychedelics	Days to weeks	Days to weeks	Hyperactivity, increased pain threshold, nystagmus, hyperreflexia, hypertension and tachycardia, eyelid retraction (stare), agitation and hyperarousal, dry and erythematous skin, violent and self-destructive behaviors	Anxiety, depression, delusions, auditory and visual hallucinations, memory loss, irritable and angry mood and affect, suicidal thoughts

Goals of Withdrawal Management

1. Assure clinical stability of the patient
2. Encourage ongoing treatment (e.g. rehabilitation) of the patient's substance dependence
   - Recovery programs may include referrals for problems such as medical, legal, psychiatric, and family issues

Pharmacologic Management of Substance Withdrawal

There are two general strategies:

1.Suppressing withdrawal through use of a cross-tolerant medication, and

2.Reducing signs and symptoms of withdrawal through alteration of another neuropharmacologic process

Either or both can manage withdrawal syndromes effectively

Suppression of Withdrawal

- Usually a longer acting cross-tolerant medication is used to provide a more controlled withdrawal
- Examples include use of methadone for opioid detoxification and diazepam for alcohol detoxification

Can withdrawal be treated on an outpatient basis?

- Detoxification may take place in a variety of settings
- Multiple instruments have been designed to facilitate selection of an appropriate level of care
- Relative contraindications to outpatient treatment:
  - a history of severe withdrawals,
  - medical comorbidities, and
  - lack of support from a responsible person

Management of Alcohol Withdrawal

Mark McLean

DSM-IV-TR Diagnostic Criteria for Alcohol Withdrawal

From: American Psychiatric Association - Diagnostic and statistical manual of mental disorders, 4th ed., text rev.

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.

B. Two (or more) of the following, developing within several hours to a few days after Criterion A:

1. autonomic hyperactivity (e.g., sweating or pulse rate >100)
2. increased hand tremor
3. Insomnia
4. nausea or vomiting
5. transient visual, tactile, or auditory hallucinations or illusions
6. psychomotor agitation
7. anxiety
8. grand mal seizures

C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

Alcohol Withdrawal - severity

- 20% have no significant symptoms
- 20% have only vegetative (physical) signs, such as tremor and sweating, but no psychologic symptoms
- 40% have both vegetative and mild to moderate psychologic symptoms, primarily anxiety
- 20% have both vegetative and severe psychologic symptoms with either disorientation, delirium, or hallucinations
- Very few patients in alcohol withdrawal experience the adrenergic and clinical manifestations of delirium tremens

Predictors of Severe Alcohol Withdrawal

- High scores on withdrawal scales early in the course of withdrawal are predictive of the development of seizures and delirium
- Low scores on withdrawal scales over the first 24 hours have consistently been found to be at little or no risk for severe withdrawal
- Other risk factors for severe withdrawal include
  - a history of prior DTs or withdrawal seizures
  - Marked autonomic hyperactivity, commonly measured as elevated heart rate on admission,
  - elevated blood alcohol level at the time of admission,
  - serum electrolyte abnormalities,
  - medical comorbidity, particularly infection
- Characteristics that have not been useful in triaging patients include amount of daily intake, duration of heavy drinking, age, and gender

MANAGEMENT OF ALCOHOL WITHDRAWAL SYNDROMES: General Principles

- The primary goals of treatment are:
  - First - assure clinical stability of the patient, and
  - Second - encourage ongoing treatment (e.g., rehabilitation) of the patient's alcohol misuse
- Perform an assessment for the presence of medical and psychiatric problems:
  - Are there acute conditions that require hospital treatment?
  - Are there chronic conditions that may alter the management of withdrawal because they could be exacerbated significantly by the development of withdrawal or its treatment?
- Pertinent laboratory tests generally include CBC, electrolytes, Mg++, Ca++, phosphate, liver enzymes, INR, albumin, UDS, pregnancy test, and blood alcohol level.
- Others may include skin test for tuberculosis, chest x-ray, electrocardiogram, and tests for viral hepatitis, other infections, or sexually transmitted diseases.
- Maintain adequate fluid balance / correction of electrolyte deficiencies, and attend to nutritional needs.
  - Patients in early withdrawal often are overhydrated so that aggressive hydration usually is not necessary unless there have been significant fluid losses from vomiting or diarrhea.
- Supportive care and reassurance from health care personnel are important elements of comfortable detoxification and help to facilitate continuing treatment.
  - Simple interventions such as reassurance, reality orientation, monitoring of signs and symptoms of withdrawal, and general nursing care are effective.

Pharmacologic Management of Uncomplicated Alcohol Withdrawal Syndrome: Benzodiazepines (BZ)

- Benzodiazepines are the cornerstone of pharmacologic management of alcohol withdrawal.
  - BZ are pharmacologically cross-tolerant with alcohol and enhance GABA-induced sedation.
  - Meta-analysis of prospective placebo-controlled trials have shown a highly significant reduction in seizures (risk reduction 7.7 sz / 100 treated), as well as in delirium (risk reduction 4.9 / 100 treated).
- All BZ are similarly efficacious in reducing signs and symptoms of withdrawal
- Longer-acting agents such as diazepam may be more effective in preventing seizures, because they may contribute to an overall smoother withdrawal course, with a reduction in breakthrough or rebound symptoms.
- In patients with liver disease and older patients, shorter-acting agents such as lorazepam or oxazepam may be preferable.
- Another consideration in the choice of BZ is the rapidity of onset.
  - Certain agents with rapid onset of action(such as diazepam, alprazolam, and lorazepam) demonstrate greater abuse potential than do agents with a slower onset of action (such as clonazepam and oxazepam).

Outpatient alcohol withdrawal management

- For alcohol withdrawal, about 80% can be treated as outpatients
- Relative indications for inpatient treatment include:
  - a history of alcohol withdrawal seizures or delirium,
  - pregnancy,
  - medical or psychiatric illness,
  - a history of severe withdrawals, or
  - lack of a reliable support system
- Essential components to a successful outpatient detoxification include a positive and helpful social support network and ready access to the treatment provider, who monitors the detoxification
- Advantages of outpatient detoxification:
  - Less expensive
  - The patient's life is not disrupted as much
  - The patient does not undergo an abrupt transition from a protected inpatient setting to the everyday home and work settings

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Contraindications to Outpatient Alcohol Withdrawal Management:

- History of withdrawal seizure or withdrawal delirium
- Multiple failed attempts at outpatient withdrawal
- Unstable associated medical conditions: Coronary Artery Disease (CAD), Insulin-Dependent Diabetes Mellitus (IDDM)
- Unstable psychiatric disorders: psychosis, suicidal ideation, cognitive deficits, delusions or hallucinations
- Additional sedative dependence syndromes (benzodiazepines, gamma-hydroxy butyric acid, barbituates and opiates)
- Signs of liver compromise (e.g., jaundice, ascites)
- Failure to respond to medications after 24-48 hours
- Pregnancy
- Advanced withdrawal state (delirium, hallucinations, temperature > 38.5 °)
- Lack of a safe, stable, substance-free setting and care giver to dispense medications

From: BCMA/BC MoH - Problem Drinking Part 3 - Office Based Management of Alcohol Withdrawal and Prescribing Medications for Alcohol Dependence
Effective date: April 1, 2011

Treating alcohol withdrawal with Diazepam (Valium)

Schedule	Day 1	Day 2	Day 3	Day 4
Rigid	10 mg QID	10 mg TID	10 mg BID	10 mg HS
Flexible	10 mg Q4-6H PRN based on symptoms*	10 mg Q6-8H PRN	10 mg Q12H PRN	10 mg HS PRN
Front loading**	20 mg Q2-4H until sedated; then 10 mg Q4-6H PRN Max 60 mg/day	10 mg Q4-6H PRN Max 40 mg/day	10 mg Q4-6H PRN Max 40 mg/day	None

* Pulse rate >100 per minute, diastolic BP > 90 mm Hg or signs of withdrawal.
** Frequently, very little additional medication is necessary after initial loading.

NB: Benzodiazepines should be discontinued after withdrawal symptoms resolved (5-7 days).

From: BCMA/BC MoH - Problem Drinking Part 3 - Office Based Management of Alcohol Withdrawal and Prescribing Medications for Alcohol Dependence
Effective date: April 1, 2011

When conducting outpatient withdrawal, do the following:

- Start on a Monday or Tuesday unless weekend coverage is available
- **See the patient daily for the first three to four days and be available for phone contact**
- **Consider daily dispensing of medications**
- **Have the patient brought to the office by a reliable family member or caregiver**
- Prescribe thiamine (Vitamin B1) 100 mg daily for five days
- Encourage fluids with electrolytes, mild foods and minimal exercise
- Avoid natural remedies, caffeine or any activity that increases sweating (e.g., hot baths, showers and saunas/sweat lodges)
- Assess vital signs, withdrawal symptoms, hydration, emotional status, orientation, general physical condition and sleep at each visit
- Encourage patient to call local (including health authority/municipal) Alcohol and Drug or Employee Assistance Programs and attend AA meeting on day 3
- Monitor for relapse, explore cause, and correct if possible. If unable to address cause, refer to inpatient detox

Adapted from: BCMA/BC MoH - Problem Drinking Part 3 - Office Based Management of Alcohol Withdrawal and Prescribing Medications for Alcohol Dependence
Effective date: April 1, 2011

Anticonvulsants for Alcohol Withdrawal

Carbamazepine:

- Widely used in Europe for alcohol withdrawal and has been shown to be equal in efficacy to benzodiazepines for patients with mild to moderate withdrawal.
- Fixed, tapering doses are without significant toxicity when used in 5- to 7-day protocols, and are associated with less psychiatric distress, a faster return to work, less rebound symptoms, and reduced post treatment drinking.
  - e.g. - Carbamazepine 300–400 mg twice daily on day 1, tapering to 200 mg as single dose on day 5.
- When compared with placebo, there is significantly less use of benzodiazepines for breakthrough symptoms.
- Does not potentiate the CNS and respiratory depression caused by alcohol, does not inhibit learning (an important side effect of larger doses of benzodiazepines), and has no abuse potential.
- Has well-documented anticonvulsant activity and prevents alcohol withdrawal seizures in animal studies.

Sodium Valproate:

- Although the evidence base is smaller, use of tapering doses of sodium valproate could be used in similar fashion.
- Both these agents have interactions with other drugs and have hepatic and hematologic toxicities, and thus must be used carefully, if at all, in patients with certain comorbid medical and psychiatric disorders.

Phenytoin:

- Although early trials indicated Phenytoin may prevent withdrawal seizures, more recent, methodologically sound trials have failed to show evidence that phenytoin is effective in preventing recurrent withdrawal seizures.

Other:

- Gabapentin and vigabatrin show promise for use in alcohol withdrawal as they may have fewer side effects and a better safety profile than carbamazepine and sodium valproate.

Data from ASAM. Addiction medicine essentials: Clinical Institute Withdrawal Assessment of Alcohol Scale, revised (CIWA-Ar), 2001. Stuppaeck CH, Barnas C, Falk M, et al. Assessment of the alcohol withdrawal syndrome—validity and reliability of the translated and modified Clinical Institute Withdrawal Assesment for Alcohol scale(CIWA-A). Addiction 1994;89(10):1287–12

Thiamine in Alcohol Withdrawal

- Alcohol-dependent patients are at risk for thiamine deficiency, which may lead to Wernicke disease and the Wernicke-Korsakoff syndrome.
- Wernicke disease is a neurologic emergency that should be treated by the immediate parenteral administration of thiamine, with a dose of 50 mg intravenously and 50mg intramuscularly.
- Delay in provision of thiamine increases the risk of permanent memory damage.
- The provision of intravenous glucose solutions may exhaust a patient's reserve of B vitamins, acutely precipitating Wernicke disease.
  - Therefore, intravenous glucose always should be accompanied by the administration of thiamine in the alcohol dependent patient.
- To reduce the risk of these sequelae, all patients presenting with alcohol withdrawal should receive 50 to 100 mg of thiamine at the time of presentation, followed by oral supplementation for several weeks.
- Patients with symptoms of Wernicke disease, those who are to receive glucose-containing intravenous solutions, and those at high risk of malnutrition should receive their initial dose parenterally.

Management of Sedative-Hypnotic Withdrawal

Mark McLean

Sedative-Hypnotic Withdrawal Syndrome

- Due to GABA receptor activity, marked similarities exist among the withdrawal syndromes seen with alcohol, benzodiazepines, barbiturates, and other sedative-hypnotic agents
- Can occur after both high- and low-dose use — even use at therapeutic levels monitored by a physician
- Usually after discontinuation of daily therapeutic dose (low dose) use of a sedative-hypnotic for at least 4 - 6 months or, at doses that exceed two to three times the upper limit of recommended therapeutic use (high dose), for more than 2 - 3 months
- The time course and severity of the withdrawal syndrome reflects the influences of:
  - Potency (higher potency BZ associated with more intense withdrawal)
  - Dose (affects severity),
  - duration of use (affects severity), and
  - duration of drug action /half-life (affects latency of onset)
- Withdrawal must be differentiated from symptom recurrence

Clinical Manifestations of Sedative-Hypnotic Withdrawal

Vital Signs
- Tachycardia
- Hypertension
- Fever

Central Nervous System
- Agitation
- Anxiety
- Delirium
- Hallucinations
- Insomnia
- Irritability
- Nightmares
- Sensory disturbances
- Tremor

Ears
- Tinnitus

Gastrointestinal
- Anorexia
- Diarrhea
- Nausea

High-Dose (Severe) Withdrawal
- Seizures
- Delirium
- Death

(Principles of Addiction Medicine - TABLE43.2)

PATIENT EVALUATION AND MANAGEMENT

Evaluation and Assessment

- Evaluating patients for BZ cessation and detoxification requires a combination of clinical, diagnostic, consultation and liaison, counseling, and pharmacologic management skills
- The clinician must be flexible and able to tolerate ambiguities and variations in the course of withdrawal, while supporting the patient (who generally experiences significant apprehension and anxiety)

Options for BZ Withdrawal treatment:

- Tapering
- Substitution and tapering
  - Uncomplicated
  - Complicated
- Adjunctive medications

Tapering: Systematic BZ Discontinuation

- The most widely used and most logical method
- Indicated for use in outpatient ambulatory settings, patients with therapeutic-dose BZ dependence, patients who are dependent only on BZ, and patients who can reliably present for regular clinical follow-up during and after detoxification
- The patient is slowly and gradually weaned from the BZ on which he or she is dependent, using a fixed-dose taper schedule
- The dose is decreased on a weekly to biweekly basis
- The rate of discontinuation for long-term users (>1 year) should not exceed 5 mg diazepam equivalents per week, or10% per week, whichever is smaller
- The first 1/2 of the taper is usually smoother, quicker, and less symptomatic
  - Some patients may want to accelerate the reduction. This acceleration is better tolerated and can be encouraged early in the taper.
- For the final 1/3 of the taper, the rate of reduction should be slowed to half the previous rate
- If symptoms of withdrawal occur, the dose should be held or increased slightly until symptoms resolve, and the taper is then resumed at a slower rate

Standardized advice for BZ Tapers

- Taper medications should be closely controlled by prescribing an amount sufficient only for the time until the next visit
- The prescriber should give a clear message to the patient that lost, misplaced, or stolen medication will not be replaced
- A withdrawal contract between the clinician and the patient is advisable
- A copy of the written schedule of daily doses, covering multiple weeks to months, may help the patient adhere to the reduction plan
- Patients who are unable to complete a simple taper program should be reevaluated and, if indicated, an alternative detoxification method chosen

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BZ Substitution and Taper

- Use a cross-tolerant long-acting BZ (such as diazepam, chlordiazepoxide or clonazepam) or phenobarbital to substitute, at equipotent doses, for the sedative-hypnotics on which the patient is dependent
- At steady state, there is negligible interdose serum level variation with these drugs, reducing the risk that withdrawal symptoms will emerge during a taper
- Chlordiazepoxide, clonazepam and phenobarbital have a low abuse potential
- Added advantages for phenobarbital:
  - It rarely induces behavioral disinhibition and possesses broad clinical efficacy in the management of withdrawal from all classes of sedative-hypnotic agents
  - Most useful and effective in patients with polysubstance dependence, high-dose dependence, and in patients with unknown dose or erratic "polypharmacy" drug use
- When hepatic function is impaired, oxazepam may be a good substitute (requires only conjugation before hepatic excretion). Lorazepam could be considered, but its abuse liability is much higher than that of oxazepam.

Uncomplicated BZ Substitution and Taper

In outpatient settings for patients who are discontinuing short half-life BZs, or for those who are unable to tolerate gradual tapering.

1.Calculate the equivalent dose of diazepam, chlordiazepoxide, clonazepam, or phenobarbital using a Substitution Dose Conversion Table.

- Individual variation in clinical responses to "equivalent" doses can vary, so close clinical monitoring of patient response to substitution is necessary

2.Provide the substituted drug in a divided dose. TID/QID for diazepam, oxazepam, or phenobarbital. BID/TID for clonazepam.

3.During the first week, PRN doses of the BZ the patient has been using can be used while the substituted agent is achieving steady state levels on a fixed dose schedule

4.Adjust the substitution dose so that PRN doses are eliminated. This usually is accomplished within 1 week.

5.Reduce the dose, on a weekly to biweekly basis, as in the simple taper model, by about 10% of the daily dose per week. The first half of the taper usually is smoother, quicker, and less symptomatic than the latter half.

6.For the final 1/3 of the taper, the rate should be slowed. If symptoms of withdrawal occur, maintain the dose for 3 - 4 days to stabilize the patient, then resume the process.

7.Support the patient with short but frequent visits.

Drug Dose Conversion: Equivalent to 60 mg of Diazepam (Valium) and 180 mg of Phenobarbital

Drug	Dose (mg)
Alprazolam (Xanax)	6
Chlordiazepoxide (Librium)	150
Clonazepam	24
Flurazepam	90
Halazepam	240
Lorazepam (Ativan)	12
Oxazepam (Serax)	60
Temazepam (Restoril)	60

American Society of Addiction Medicine: Principles of Addiction Medicine

Withdrawal Emergence PRN Phenobarbital Substitution

- For patients who are unable to complete outpatient tapering regimens, or who are high-dose users, polysubstance-dependent, and experiencing considerable comorbid psychopathology
- This procedure is best used in a 24-hour medically monitored setting

1. Signs and symptoms of withdrawal are treated PRN with 30 - 60 mg of phenobarbital Q1–4H. The period of PRN dosing is influenced by the duration of action of the substances the patient is discontinuing.
2. The patient is monitored hourly to ensure adequate dosing and to prevent oversedation. Ideally, a balance is achieved between the signs and symptoms of withdrawal and those of phenobarbital intoxication.
3. When the patient has received similar 24-hr phenobarbital dose totals for 2 consecutive days, the daily stabilizing dose is given in divided-dose increments over the next 24 hours, which may require medication administration every 3 to 4 hours for patients with high tolerance.
4. After the patient is stabilized, a gradual taper is initiated, as described previously. Patients often can be transferred from an inpatient setting to an intensive (medically monitored) outpatient program after they are stabilized and well established on the tapering portion of the protocol.

Prolonged Withdrawal

- A small proportion of patients experience a prolonged syndrome of withdrawal after long-term benzodiazepine use
- Patients with prolonged withdrawal often experience slowly abating — albeit characteristic waxing and waning— symptoms of insomnia, perceptual disturbances, tremor, sensory hypersensitivities, and anxiety
- The syndrome is notable for its irregular and unpredictable day-to-day course and qualitative and quantitative differences in symptoms from both the pre-benzodiazepine use state and the acute withdrawal period
- The signs and symptoms may persist for weeks to months after discontinuation

Host Factors Affecting Withdrawal

1. Psychiatric Comorbidity
   - Insomnia, anxiety, thought, and mood dis-orders
   - Numerous studies highlight the high (40% to 100%) prevalence of active concurrent psychiatric disorders seen
   - Generalized anxiety disorder (44%), panic disorder (27%), depression (14%), and other (7%).
   - Dependent personality disorder,
   - Patients with panic disorder were more vulnerable to withdrawal than patients with generalized anxiety disorder. Increased withdrawal symptoms also have been associated with high initial anxiety or depression and decreased educational level.
2. Concurrent Use of Other Substances
   - Additional sedative-hypnotic substance increases withdrawal syndrome severity and decreases predictability.
   - A high percentage of alcohol-dependent patients use benzodiazepines regularly, ranging from 30% to 75%.
   - The rate of comorbid alcohol abuse and anxiety disorders is reported to be 18% - 19%.
   - Moderate alcohol use (exceeding one beer or drink per day) is a more significant predictor of benzodiazepine withdrawal severity than dose or half-life of the drug.
3. ? Family History of Alcohol Dependence

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Adjunctive BZ Withdrawal Management Measures

Anticonvulsants

- Their use grew from the success of treating psychiatric disorders and the improved understanding of kindling mechanisms for withdrawal.
- No apparent addiction potential
- May not reduce withdrawal severity, but has been found to be associated with increased rates of BZ abstinence

Carbamazepine and Sodium Valproate

- Actions associated with the neurotransmitters serotonin, GABA, excitatory amino acids, and glutamate
- Carbamazepine: 600 mg/day used alone or in combination with a BZ taper
- Sodium Valproate: 250 mg TID (BID if > age 60) used in combination with a BZ taper
- Continued for a minimum of 2 - 3 weeks after BZ taper is completed and can be tapered to monitor for return of withdrawal symptoms
- Potential adverse effects:
  - Carbamazepine: GI upset, neutropenia, thrombocytopenia, and hyponatremia
  - Sodium Valproate: elevated LFTs, thrombocytopenia, bone marrow suppression, pancreatitis, drug reactions (including rash and erythema multiforme), GI upset, and behavioral changes
  - Initial and ongoing laboratory evaluation and monitoring required

Adjunctive BZ Withdrawal Management Measures

Propranolol

- diminishes the severity of adrenergic signs and symptoms of withdrawal
- should not be used as the sole therapeutic agent in managing withdrawal
- 60 to 120 mg/day, divided TID or QID

Trazodone

- Decreases anxiety in benzodiazepine-tapered patients
- Improves sleep during BZ tapering and when BZ-free
- Improves patients' ability to remain BZ-free after a taper
- Side effects may include dry mouth, morning hangover, drowsiness, dizziness, and priapism

Cognitive Behavioural Therapy (CBT)

- In patients with panic disorder, adding CBT to alprazolam discontinuation improved the rate of successful alprazolam discontinuation
- Spiegel and colleagues (99) reported that patients in the combined taper and CBT groups had greater abstinence from alprazolam at 6 months
- Oude Voshaar reported that adding CBT group therapy did not improve BZ success rates
- Benzodiazepine tapering must be completed before CBT concludes
- CBT can support the withdrawal taper and help with exacerbations of the initial disorder

Management of Opioid Withdrawal

Opioid Withdrawal

- Characterized by two phases:

1. Acute Withdrawal:

- Symptoms include anorexia, GI distress (such as diarrhea and vomiting), thermoregulation disturbances, insomnia, restlessness, irritability, muscle and joint pain, and marked anxiety, dysphoria and opioid craving
- Signs include pupillary dilation, increased HR and BP, rhinorrhea, lacrimation, piloerection, yawning and sneezing
- Generally not life-threatening, but causes marked discomfort, often prompting continuation of opioid use even in the absence of any opioid-associated euphoria

2. Chronic Dependence and Protracted Abstinence:

- Insomnia, abnormalities in BP, HR and body temperature, decreased sensitivity of the respiratory center to carbon dioxide, increased ESR and EEG changes beginning about 6 weeks after withdrawal and persisting for 26 or more weeks
- Continued opioid craving
- A universal definition and diagnostic criteria are lacking, making diagnosis difficult in individual patients

Diagnosis of Opioid withdrawal

- Several clinical tools are available to measure the severity of opioid withdrawal. One such tool is the Clinical Opiate Withdrawal Scale (COWS).
- The onset and duration of withdrawal vary with the potency, dose, and half-life of the drug used, and the duration of drug use

Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____ :_____

Reason for this assessment:_____

Resting Pulse Rate: _____bpm/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81–100 2 pulse rate 101–120 4 pulse rate greater than 120	**GI Upset:** *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting
Sweating: *over past ½ hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient sees having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing Assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

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Management of opioid withdrawal

- Combined general supportive measures and specific pharmacologic therapies
- Do a thorough evaluation to rule out and address other medical problems that may be complicating opioid withdrawal
- The choice of pharmacotherapy used to treat withdrawal may be influenced by the presence and severity of a patient's underlying medical comorbidities
- A physical examination should be performed to detect findings consistent with withdrawal to establish the diagnosis
- General supportive measures for managing withdrawal include providing a safe environment and adequate nutrition, as well as reassuring patients that their symptoms will be taken seriously
- The decision as to whether to perform opioid detoxification on an outpatient or inpatient basis depends on the presence of comorbid medical and psychiatric problems, the availability of social supports (such as family members to provide monitoring and transportation), and the presence of poly-drug abuse
- The preferred method of detoxification also may affect this decision; for example, methadone detoxification is restricted to MDs having an exemption to prescribe methadone

Pharmacologic Therapies for Opioid Withdrawal Management

- Opioid agonists (methadone);
- Alpha-2 adrenergic agonist (such as clonidine);
- A mixed opioid agonist/antagonist (buprenorphine).

Slow Methadone Detoxification

- Establish whether withdrawal will be from from short-acting opioids such as heroin (plasma half-life of morphine, the main metabolite: 3-4 hours) and long-acting opioids such as methadone (plasma half-life: 13-47 hours)
  - For short-acting opioids, the natural course of withdrawal generally is brief, but more intense than for equivalent doses of long-acting opioids. However, there is considerable individual variation, so that strong early withdrawal symptoms from methadone are possible, as are delayed severe heroin withdrawal symptoms.
- Initially, methadone may be given in 5-mg increments as the physical signs of abstinence begin to appear, up to a total of 20 - 30 mg over the first 24 hours
- After day 1, give the majority of the total amount given on the previous day as a single dose, with 5-10 mg PRNs to a maximum of 10 mg PRN per day until stabilized, checking LOC 3 hours after each dose
- After a stabilizing dose has been reached, methadone is tapered by 10-20% a day for inpatients, leading to a 1- 2 week procedure. Remember that blood levels may be rising even though the daily dose is decreasing.
- This treatment strategy can only be employed by MDs licensed to prescribe methadone for the treatment of opioid dependence
- Alternatively, the dose is tapered by 5% per day for outpatients, in a gradual cessation phase lasting as long as 6 months. Some experts recommend a dose-tapering rate of about 3% per week from methadone maintenance.

Buprenorphine (Suboxone) Detoxification

- Buprenorphine is a high-affinity, partial agonist at the mu opioid receptor
- A recent Cochrane systematic review of 18 studies (14 RCTs) found that buprenorphine was superior to clonidine and as effective as methadone for ameliorating withdrawal symptoms, treatment retention, and treatment completion
- In particular, buprenorphine's ceiling on agonist activity reduces the danger of overdose, may limit its abuse liability, and lower its toxicity even at high doses
- Buprenorphine's high affinity for the mu receptor blocks the effects of exogenously administered opioids, suggesting that it reduces illicit opioid use. Its slow dissociation from mu receptors results in a long duration of action.
- Due to the risk of precipitated withdrawal on induction, patients must be in moderate withdrawal (COWS > 12), or more than 24 hours since their last dose of opioids before induction
- Vancouver Detox Protocol:
  - Day 1: 8 mg
  - Day 2: 8 mg
  - Day 3: 6 mg
  - Day 4: 2 mg

Clonidine Detoxification from Opioids

- Gold et al: both morphine and clonidine block activation of the locus ceruleus, a major noradrenergic nucleus that shows increased activity during opioid withdrawal
- Clonidine activates alpha-2 adrenergic receptors
- Use in opioid withdrawal is off-label
- Reduces or eliminates most of commonly reported withdrawal symptoms, including lacrimation, rhinorrhea, restlessness, muscle pain, and gastrointestinal symptoms
- However, symptoms such as lethargy and insomnia often persist
- Potential side effects: Sedation and dizziness from orthostatic hypotension
- Day 1: Administer 0.1 mg of clonidine Q4-6H PRN
- Day 2: Increase by 0.1 – 0.3 mg/day, to a max of 1.2 mg/day, according to BP and withdrawal symptoms
- Average maximum dose required was 0.8 mg/day
- At the end of the detoxification period (days 5 - 7 in heroin detoxification)taper clonidine by 0.1 to 0.2 mg daily to avoid rebound hypertension, headaches, and reemergence of withdrawal symptoms

Adjuncts to Opioid Withdrawal Treatment

- NSAIDS
- Acetaminophen
- Benzodiazepines (long-acting)
- Antipsychotics

Stimulant withdrawal

Stimulants (Cocaine, Amphetamines and Derivatives) Withdrawal

- Abrupt cessation of stimulant use is associated with depression, anxiety, fatigue, difficult concentrating, anergia, anhedonia, increased drug craving, increased appetite, hypersomnolence, and increased dreaming (because of increased REM sleep)
- Most symptoms are mild and self-limited, resolving within 1 to 2 weeks without treatment
- Supportive rather than specific treatment
- Observation and monitoring for depression and suicidal ideation, which may be severe and persistent
- Since stimulant withdrawal may cause significant irritability and insomnia, diazepam 5 - 10 mg orally Q6H (or PRN) for two to three days may be useful in patients with moderate withdrawal symptoms
- For severe withdrawal symptoms with persistent depression, therapy may be initiated with antidepressants such as desipramine 50 mg per day, titrated upward every other day by 50 mg until 150-250 mg per day. The dosage is maintained for three to six months and gradually tapered.

Marijuana Withdrawal

Marijuana Withdrawal

- Not a recognized syndrome in the DSM-IV-TR
- Reported by up to 1/3 of heavy marijuana users in the community and more than half of those seeking treatment for marijuana dependence
- Symptoms are primarily psychologic, including irritability, anxiety, depression, restlessness, anorexia, insomnia, and vivid or disturbing dreams
- Much less common are physical symptoms such as gastrointestinal distress, diaphoresis, chills, nausea, shakiness, and muscle twitches
- Often mild and has been compared to tobacco withdrawal
- It can serve as a negative reinforcer for relapse among users trying to maintain abstinence

Management of Marijuana Withdrawal

- Rarely requires treatment for medical or psychiatric reasons
- Treatment might be warranted to reduce the risk of relapse in persons trying to abstain, but there are no clinical trials
- In non–treatment-seeking research subjects, agonist substitution with oral synthetic THC (dronabinol) does substantially suppress withdrawal symptoms

Phencyclidine and Other Psychedelic Agents

- Acute symptoms of withdrawal from psychedelic agents may be diminished or reversed by using therapy with haloperidol (Haldol), 5 to 10 mg intramuscularly or orally every three to six hours as tolerated and needed for behavior control.
- Lorazepam, 1 to 2 mg intravenously, or diazepam, 5 to 10 mg orally every three to six hours, can also be given as needed.
- Behavior control may also be indicated (e.g., isolation and restraints).

After treatment of withdrawal:

- The appropriate level of care and content of treatment following detoxification must be clinically determined, based on the patient's individual needs
- Biopsychosocial factors to be considered in determining the continuing treatment plan include medical and psychiatric conditions, motivation, relapse potential, and available support systems

The New Therapeutics: Ten Commandments

Thou shalt treat according to level of risk rather than level of risk factor.

Thou shalt exercise caution when adding drugs to existing polypharmacy.

Thou shalt consider benefits of drugs as proven only by hard endpoint studies.

Thou shalt not bow down to surrogate endpoints, for these are but graven images.

Thou shalt not worship Treatment Targets, for these are but the creations of Committees.

Thou shalt apply a pinch of salt to Relative Risk Reductions, regardless of P values, for the population of their provenance may bear little relationship to thy daily clientele.

Thou shalt honour the Numbers Needed to Treat, for therein rest the clues to patient-relevant information and to treatment costs.

Thou shalt not see detailmen, nor covet an Educational Symposium in a luxury setting.

Thou shalt share decisions on treatment options with the patient in the light of estimates of the individual's likely risks and benefits.

Honour the elderly patient, for although this is where the greatest levels of risk reside, so do the greatest hazards of many treatments.

Thanks for your questions and discussion.

Thanks for completing your course evaluations.

HAVE A SAFE TRIP HOME

We hope to see you next year!