22nd ANNUAL DRUG THERAPY DECISION MAKING COURSE

Encouraging Healthy Skepticism

April 1st and 2nd, 2011

Fairmont Waterfront Hotel
Vancouver, B.C.

Friday Syllabus

SKEPTICEMIA

When skepticism gets into your blood

There is no cure

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
DR'S. ROBERT RANGNO, JAMES MCCORMACK and
MICHAEL ALLAN

“A truth's initial commotion is directly proportional to how deeply the lie was believed. It wasn't the world being round that agitated people, but that the world wasn't flat. When a well-packaged web of lies has been sold gradually to the masses over generations, the truth will seem utterly preposterous, and its speaker a raving lunatic."

- Dresden James

Course Directors

Bob Rangno, Emeritus Prof., Med./Pharmacology, UBC & SPH
James McCormack, Prof., Pharm. Sciences, UBC

Guest Faculty

G. Michael Allan, Assoc. Prof., Fam. Practice, University of Alberta
& Medical Director, Towards Optimized Practice
Mike Kolber, Assoc. Prof., Family Med., University of Alberta
Tina Korownyk, Asst. Prof, Family Med., University of Alberta
Mark McConnell, Internal Medicine, LaCrosse, Wisconsin

Local Faculty

Martin Dawes, Prof. and Head, Dept. of Family Practice, UBC
William Honer, Prof., Psychiatry, UBC, BC Mental Health and Addictions Research Institute
Val Montessori, Clin. Assoc. Prof., Medicine, Infectious Diseases, UBC & SPH
Bob Nakagawa, Asst. Deputy Minister, Pharmaceutical Services, B.C. Ministry of Health
Natasha Press, Clin. Assoc. Prof., Med., Infectious Diseases, UBC & SPH
John Sloan, Clin. Prof., Family Practice, UBC
Adil Virani, Assoc. Prof, Pharm. Sciences, UBC, & Director, Pharmacy Services, FHA

FHA – Fraser Health Authority
SPH – St. Paul's Hospital
UBC – University of British Columbia

22nd Annual
Drug Therapy Decision Making Course
Friday April 1, 2011

Happy April Fool's Day

07:00 Registration (Muffins & Coffee)

Chair - Bob Rangno and James McCormack

"Skepticemia – It Gets Into Your Blood"

08:00	Welcome and Introduction	Bob Rangno
08:10	"Won't get fooled again" – The WHO, what why, where and when of therapeutics	Mike Allan and James McCormack

"Why do Fool's fall in Love"

08:50	Take Nothing for Granted	Martin Dawes
09:10	Questions	
09:20	Drugs for and against female sexual function	Tina Korowynk
09:40	Heartburn – are you in love or is it the chili?	Mike Kolber
10:00	Questions	
10:20	Refreshment Break	

"Only Fool's Rush In" to treatment

10:40	The evidence on diet – is it true you are what you eat?	John Sloan
11:00	Insomnia – "Help me make it thru the night"	Adil Virani
11:20	Questions	
11:30	Alzheimer's treatment – who are we fooling?	Mike Allan
11:50	ADHD – what's wrong with fooling around?	Adil Virani
12:10	Questions	
12:30	Lunch	

Chair - Bob Rangno and James McCormack

"Fooled Around and Fell In love"

13:30	A quick run through Traveller's diarrhea	Val Montessori
13:50	Cutting the crap on CAP	Natasha Press
14:10	Questions	
14:20	Bedbugs - not the kind with two legs	Val Montessori
14:40	Otitis and conjunctivitis – "Ears looking at you kid"	Natasha Press
15:00	Questions	
15:20	Refreshment Break	

“Believe it or Not”

15:40	A cute use of ugly steroids	Mike Kolber
16:00	Antipsychotics as antidepressants - antiintuitive?	Bill Honer
16:20	Questions	
16:30	Osteoporosis – is it the bones or the data that are fragile?	Tina Korownyk
16:50	Questions	
17:00	Adjourn	

Some reasons we get fooled again and again

Most things aren't much or any better
Guidelines / opinions
Statistical tests / meta-analyses
Statistical breakpoints / significance
Clinical significance
Surrogate markers
Selective reporting
Physiological mechanisms
Measuring everything

New and improved vs Unsafe/withdrawn

The last decade (2000s)

Drugs considered to provide substantial improvements (PMPRB)

19

drugs removed from the market (FDA etc)

23

2000	Enbrel	Tumour necrosis factor for rheumatoid arthritis
	Rilutex	Amyotrophic lateral sclerosis
	Visudyne	Age-related macular degeneration
2001	Cerezyme	Gaucher disease - glucocerebrosidase deficiency
	Prevnar	Pneumococcal vaccine for children
2002	Gleevec	Chronic Myeloid Leukemia
2003	Xigris	For severe sepsis
2004		
2005	Sensipar	Hypercalcemia in patients with parathyroid carcinoma

2006	Myozyme	Pompe disease - alfa glucosidase deficiency
	RotaTeq	Vaccine prevents severe rotavirus gastroenteritis in children
	Fuzeon	HIV treatment
	Macugen	Wet age-related macular degeneration
2007	Aldurazyme	Enzyme replacement Mucopolysaccharidosis
	Replagel	Enzyme replacement - alfa-galactosidase A deficiency
	Spirafil	Anti-fungal
2008	Revlimid	Treatment for multiple myeloma
	Lucentis	Age-related macular degeneration
	Relistor	Constipation secondary to narcotic drugs
2009	Sprycel	Chronic Myeloid Leukemia

What guidelines should/could Offer

Ideally: A clear and balanced synopsis of the best available evidence

Alternatively: We need to read 7,287 articles per month relevant to primary care

That means: 21 hours of reading every day[1]

Also: Acknowledgement of what isn't known

simple and practical tools to estimate patients' risk of a clinically relevant event

Focus - risk assessment, shared-decision making, less on arbitrary breakpoints

costs of therapies/comparisons between therapies

1. Med Libr Assoc 2004;902:429-37

A sample of evidence vs opinion

Recommendation	Guideline	Evidence
Ordering CRP for CVD	Yes	No
Regular home glucose test	Yes	No
ASA in DM	Yes	Maybe
Lubricant for PAP test	No	Yes
BMD testing after med	1-3 yrs	≥3yrs
Some Antidepressants better	Yes	No
Glucose Targets	<7	variable

Recent 'wrongness'

mar 2010	ACCORD	Aggressive BP lowering -	NO CVD benefit
Mar 2010	ACCORD	Adding fibrate to statin in diabetics	NO CVD benefit
Aug 2010	CRESCENDO	Rimonabant - multiple	NO CVD benefit - plus drug Harm
Aug 2010	VALISH	Aggressive BP lowering -	NO CVD Benefit
Sep 2010	AASK	Aggressive BP lowering - CKD	No CVD or Renal benefit
mar 2011	ROADMAP	Olmesartan - type 2 diabetes	Decreased microalbuminuria More fatal cardiovascular events
Mar 2011	ACTIVE	Irbesartan for A fib	NO overall CVD benefit, dec CHF, more renal dysfunction

G. Michael Allan and J. McCormack

What they should Offer

	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

Relative risk reductions with different interventions in DM2

	Treat BP	Treat Lipid	Treat Sugar
CVD events	~ 50%	~20-25%	~ 12.5%
Mortality	16%	8%	NSS

Diabetes Care 2010;33(1): S11-61, Ann Intern Med 2008;148:846-54, Lancet 2009;373:1765–72, Lancet 2008; 371:117–25, Ann Intern Med 2003;138:587-92

Depression

Patients who respond in the SSRI group ≈ 60% - 40% in primary care?Am J Psychiatry 2009; 166:599–607

Patients who respond in the placebo group ≈ 45%

6/10 patients will respond to an antidepressant

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

Cochrane Library CD007954

Heartburn

Patients who respond in the PPI group
≈ 65% at 4 weeks, 85% at 8 weeks

Patients who respond to H2RA
≈ 40% at 4 weeks, 55% at 8 weeks

Patients who respond in the placebo group
≈ 15% at 4 weeks, 30% at 8 weeks

8-9/10 patients will respond to a PPI
3 of these improved not because of a drug
an additional 2-3 of these would have improved with an H2RA

Cochrane Library CD003244

A simple A fib table

	Patient's ANNUAL risk (%) of ischemic stroke			Difference in benefit between ASA and OAC
$CHADS_2$ Score	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

Primary Prevention Statins & Mortality

Study	Risk Estimate	Authors Conclusion
Arch Intern Med 2005;165:725-730	0.86 (0.76 -0.99)	Decreases mortality
Arch Intern Med 2006;166:2307-2313	0.92 (0.84-1.01)	∅
J Am Coll Cardiol 2008;52:1769-81	0.93 (0.87-0.99)	Decreases mortality
BMJ 2009;338:b2376	0.88 (0.81-0.96)	Decreases mortality
Arch Intern Med 2010;170:1024-1031	0.91 (0.83-1.01)	∅

G. Michael Allan and J. McCormack

Torcetrapib

The Lipid King: HDL up 72% and LDL down 25%

Unfortunately:

- CVD events ↑ sign 25%, AR = 1.2%, NNH 84
- Mortality ↑ sign 58%, AR = 0.45%, NNH 222

Withdrawn

Good Lesson about Surrogates and Targets

N Engl J Med 2007;357:2109-22

examples of Drugs that lower CRP

Rosiglitazone-40%

Rofecoxib-50%

Fibrates-50%

Vitamin E-50%

Niacin-25%

Ezetimibe-10%

Statins-50%

Prednisone-60%

= clear evidence of harm or no benefit

= no evidence

= clear evidence of benefit

Fibrates - BIP, FIELD; Glitazone meta-analysis, Vitamin E meta-analysis; ezetimibe ENHANCE; Niacin Coronary Drug Project; Statins Meta-analysis

Activity

additional benefits not seen with BP/chol/diabetes meds

Lots of studies on positive surrogates BP, lipids, etc

Exercise seems to improve sleep quality & fatigue

Cochrane Database Syst Rev. 2002;(4):CD003404. J Gerontol A Biol Sci Med Sci. 2008 Sep;63(9):997-1004. J Sports Med Phys Fitness. 2007 Dec;47(4):462-7

Improves depression

Cochrane Database Syst Rev. 2008 Oct 8;(4):CD004366

Improves OA pain and function

Cochrane Database Syst Rev. 2008 Oct 8;(4):CD004376

etc

Calcium and risk of MI - meta-analysis

Patients

11,921 receiving at least 500mg a day of elemental calcium, >40 y/o, no vitamin D, average age 74, 78% female, 10% smokers, 8% CHD, 97% white - 15 studies

Treatment

placebo or calcium

Duration

4 years

BMJ 2010;341:c3691 doi:10.1136/bmj.c3691

Results

	MI (%)	MI, stroke, sudden death (%)	Stroke (%)	Mortality (%)
Calcium	2.7	5.9	3.5	9.1
Placebo	2.2	5.5	3.3	9.2
Relative risk increase	23	NSS	NSS	NSS
Absolute risk increase	0.5			
Number needed to harm	200			

Quality of life comparisons

	QOL utilities
Mild stroke	0.70
Angina	0.64
Diabetic neuropathy	0.66

Comprehensive diabetes care	0.64

Diabetes Care 2007;30:2478-83

G. Michael Allan and J. McCormack

So what's left?

1. When there is evidence, don't be afraid to use it
2. Very high is bad but aggressive lowering rarely seems to do much
3. Guidelines are not the gospel
4. Shared informed decision-making is more rewarding
5. Don't sell 'dis-ease'
6. Prevention vs symptoms
7. Sometimes just do an "n-of-1" trial
8. Don't use new drugs until they've been on the market for 5 years
9. Old drugs can often be good drugs
10. Start with very low doses

Martin Dawes

Trust no one - Just the evidence

Martin Dawes

20 minutes

1. The methodology
2. The Pharmaceutical Industry

Declaration of Interest

- **I have advised two pharmaceutical companies about trial design in the last 2 years. No paid talks.**
- **I am a scientist**

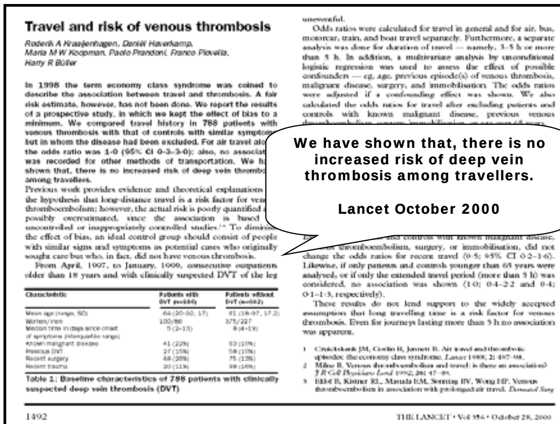
Increasing Medical Knowledge

27Kg of Guidelines

New scientific papers per day
- 3,000

Medline New articles
- 1,000

Randomised controlled trials
- 46



Travel and risk of venous thrombosis

Roderik A Kraaijenhagen, Daniël Haverkamp, Maria M W Koopman, Paolo Prandoni, Franco Piovella, Harry R Büller

In 1998 the term economy class syndrome was coined to describe the association between travel and thrombosis. A fair risk estimate, however, has not been done. We report the results of a prospective study, in which we kept the effect of bias to a minimum. We compared travel history in 788 patients with venous thrombosis with that of controls with similar symptoms but in whom the disease had been excluded. For air travel alo[ne] the odds ratio was 1·0 (95% CI 0·3–3·0); also, no associat[ion] was recorded for other methods of transportation. We ha[ve] shown that, there is no increased risk of deep vein thrombo[sis] among travellers.

Table 1: Baseline characteristics of 788 patients with clinically suspected deep vein thrombosis (DVT)

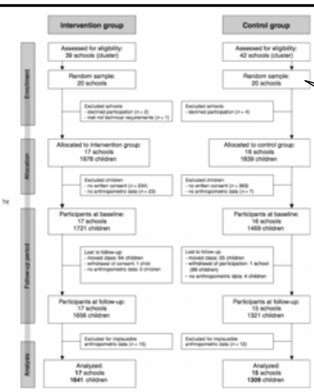
1492 THE LANCET • Vol 356 • October 28, 2000

6 months later

Interpretation We conclude that symptomless DVT might occur in up to 10% of long-haul airline travellers. Wearing of elastic compression stockings during long-haul air travel is associated with a reduction in symptomless DVT.

Lancet 2001; **357**: 1485–89

See Commentary page 1461



Randomization was performed at the city level to minimize contamination between neigh-boring schools in 1 city.

Martin Dawes

1: N Engl J Med. 2004 Jan 8;350(2):105-13.

Comment in:
ACP J Club. 2004 Jul-Aug;141(1):2.
N Engl J Med. 2004 Jan 8;350(2):179-81.
N Engl J Med. 2004 May 20;350(21):2206-9; author reply 2206-9.
N Engl J Med. 2004 May 20;350(21):2206-9; author reply 2206-9.
N Engl J Med. 2004 May 20;350(21):2206-9; author reply 2206-9.

A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation.

Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH; European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group.

Department of Anesthesiology and Critical Care Medicine, Leopold-Franzens U

BACKGROUND: Vasopressin is an alternative to
cardiopulmonary resuscitation, but clinical exp
randomly assigned adults who had had a
40 IU of vasopressin or 1 mg of epineph
The primary end point was survival to
hospital discharge. RESULTS: A total of 1
of missing study-drug codes. Among the
vasopressin and 597 to receive epinephri
were no significant differences in the rates of hospital
epinephrine group either among patients with ventricular
P=0.48) or among those with pulseless electrical activity
patients with asystole, however, vasopressin use was as
admission (29.0 percent, vs. 20.3 percent in the epinephrine group; P=0.02) and hospital discharge (4.7 percent vs. 1.5 percent, P=0.04). Among 732 patients in whom spontaneous circulation was not restored with the two injections of the study drug, additional treatment with epinephrine resulted in significant improvement in the rates of survival to hospital admission and hospital discharge in the vasopressin group, but not in the epinephrine group (hospital admission rate, 25.7 percent vs. 16.4 percent; P=0.002; hospital discharge rate, 6.2 percent vs. 1.7 percent; P=0.002). Cerebral performance was similar in the two groups. CONCLUSIONS: The effects of vasopressin were similar to those of epinephrine in the management of ventricular fibrillation and pulseless electrical activity, but vasopressin was superior to epinephrine in patients with asystole. Vasopressin followed by epinephrine may be more effective than epinephrine alone in the treatment of refractory cardiac arrest. Copyright 2004 Massachusetts Medical Society

PMID: 14711909 [PubMed - indexed for MEDLINE]

Vasopressin followed by epinephrine may be more effective than epi alone in the treatment of refractory cardiac arrest

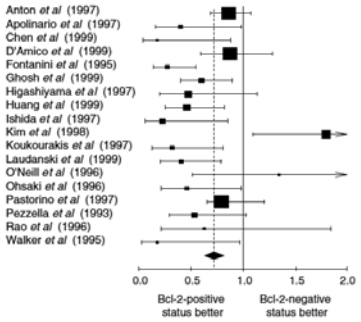


Figure 3 Hazard ratio and 95% CI of mortality in studies incorporating NSCLC whatever the threshold of positivity chosen by the authors. The meaning of the symbols is described in Figure 1.

Martin et al British Journal of Cancer (2003) 89, 55 – 64

Publication bias?

Does the way the trial is performed matter?

No Randomisation
- Overestimates effectiveness by 20%

No Allocation concealment
- Overestimates effectiveness by 30%

No Blinding
- Overestimates effectiveness by 15%

Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001;323(7303):42-6.

Selective reporting of outcomes

1. reporting of some of the set of study outcomes
2. selective reporting of a specific outcome (ie week 6 but not week 12);
3. incomplete reporting of a specific outcome (difference of means but not standard error)

- 40-62% of trials changed, introduced, or omitted at least one primary outcome

Cochrane Trials

- ~20% of statistically significant meta-analyses of the review primary outcome affected by outcome reporting bias
- a quarter would have overestimated the treatment effect by 20% or more
- BMJ 2010 Kirkham et al

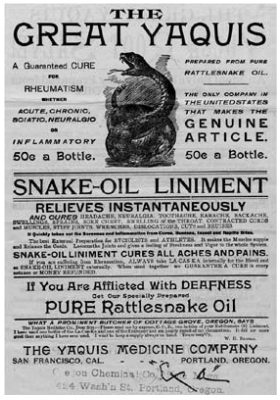
Inclusion & Exclusion Criteria in Trials

- Only 2.1% of subjects in trials of NSAIDs were 65yrs+, even though these drugs are more often used, and have a higher incidence of SEs, in the elderly. CMAJ 1998;159:1373-1374
- Hypertensive trials: ALLHAT Excluded heart failure patients (Fortin 2006 Annals Fam Med)

Martin Dawes

What does this show?

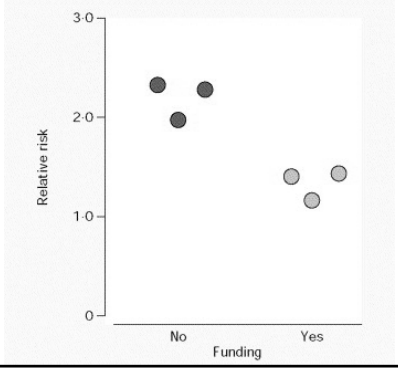
- Trial design is more important than anything else
- Poor trial design often overestimates the effect
- To interpret research we should be aware of the weaknesses of a trial
- Critical appraisal is necessary
- Stick to pre-appraised articles



Be critical

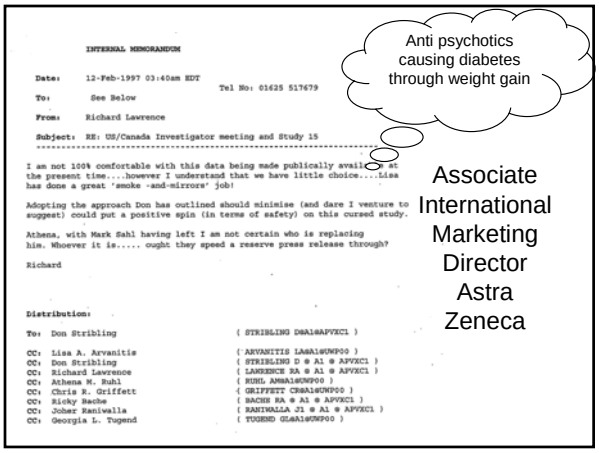
- Deafness
- Headache
- Neuralgia
- Cures all aches and pains

Competing interests and controversy about third generation oral contraceptives higher risk of venous thrombosis



Industry funding of trials

- Analysis of 107 controlled trials
- Two questions :
  - Did authors favor new or old drug?
  - Did authors have industry support or not?
- Trials funded by manufacturer of new drug were significantly more likely to favor new drug
- J Gen Intern Med 1986;1:155-8



INTERNAL MEMORANDUM

Date: 12-Feb-1997 03:40am EDT
Tel No: 01625 517679
To: See Below
From: Richard Lawrence
Subject: RE: US/Canada Investigator meeting and Study 15

I am not 100% comfortable with this data being made publically avail... at the present time....however I understand that we have little choice....Lisa has done a great 'smoke -and-mirrors' job!

Adopting the approach Don has outlined should minimise (and dare I venture to suggest) could put a positive spin (in terms of safety) on this cursed study.

Athena, with Mark Sahl having left I am not certain who is replacing him. Whoever it is..... ought they speed a reserve press release through?

Richard

Distribution:

To: Don Stribling (STRIBLING DA@A1@APVXC1)

CC: Lisa A. Arvanitis (ARVANITIS LA@A1@UNP00)
CC: Don Stribling (STRIBLING D @ A1 @ APVXC1)
CC: Richard Lawrence (LAWRENCE RA @ A1 @ APVXC1)
CC: Athena M. Ruhl (RUHL AM@A1@UNP00)
CC: Chris R. Griffett (GRIFFETT CR@A1@UNP00)
CC: Ricky Sachs (SACHS RA @ A1 @ APVXC1)
CC: Jober Raniwalla (RANIWALLA J1 @ A1 @ APVXC1)
CC: Georgia L. Tugend (TUGEND GL@A1@UNP00)

Anti psychotics causing diabetes through weight gain

Associate International Marketing Director Astra Zeneca

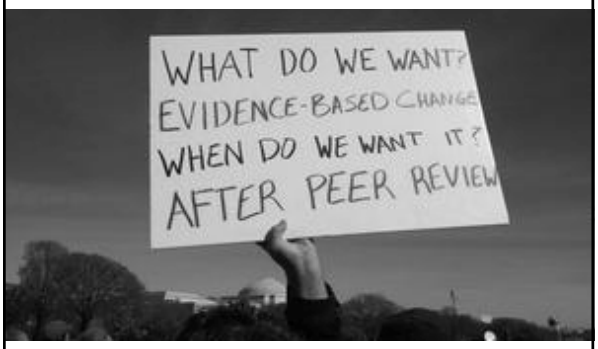
Drug samples

- Industry gave out $7.2 billion worth of free samples in 2000
- Pharmaceutical companies' "generosity" to provide drug samples has a specific purpose: to change physician behavior to write more prescriptions for their particular drug.

Martin Dawes

Influence over guidelines

- Survey of 192 authors of 44 clinical practice guidelines: 87% of authors had some form of interaction with the pharmaceutical industry
- BUT in published versions of the guidelines, specific declarations about the personal financial interactions of authors with industry were made in only 2 cases
- JAMA 2002;287:612–7



Thank You

Drugs for and against female sexual function

Tina Korownyk

"Except for 75% of the women, everyone in the whole world wants to have sex." — Ellyn Mustard

The Problem

- Betty Apathy comes in to see you to discuss serious concerns regarding her decreased libido. She is 45, has been married for 15 years, works full time and has three children. She denies any relational concerns. She does however report that her decreased libido is starting to impact the relationship and begs you to help her…

Betty Apathy

What can you do for Betty?

1) Relationship counseling – it's always the underlying problem
2) Bring in her husband and ask him to lower his expectations
3) Consider off label use of testosterone patches (more is better)
4) Viagra for women?
5) Do nothing and change the topic quickly

What are we talking about?

- Female Sexual Disorder (FSD)
- Further categorized into
  - Hypoactive sexual desire disorder (HSDD)
  - Female orgasmic disorder (FOD)
  - Dyspareunia
  - Female sexual arousal disorder (FSAD)
    - the persistent or recurring inability to attain or maintain sufficient sexual excitement, causing personal distress. This may be expressed as lack of subjective excitement or genital lubrication/swelling or other somatic responses

1) 4th edition DSM-IV. Washington, DC: American Psychiatric Press, 1994

Theory 1: Simple Circulation (Sildenafil)

- 2002 RCT[1]
- 781pts, FSAD, 4 wk run-in, PP analysis
- Pre & postmenopausal women
- No difference for any end point
  - (two GEQ, sexual event log, the LSC, and the SFQ)
- Main AE were headache, flushing, rhinitis, nausea, visual disturbances, and dyspepsia

1) J Womens Health Gend Based Med. 2002;11(4):367-77.

Theory 1: Simple Circulation Sildenafil for Specific Subgroups?

- 53 **premenopausal** women, FSAD: improvement in all outcomes including frequency of sexual fantasies?[1]
- 202 postmenopausal women: Sildenafil was effective in women with FSAD **without concomitant HSDD or contributory emotional, relationship or historical abuse issues** (NNT 7)[2]
- Some Benefit seen in pts with MS[3] , Spinal cord injury[4], DM 1[5], or those on SNRI/SSRIs[6].
  - All studies had significant limitations, <100 tts

1) Br J Obstet Gynaecol 2001; 108:62381. 2)J Urol 2003;170:2333-8. 3) Urology 2000;55:812-5 4) J Urol 2004;171:1189-93. 5) Fertil Steril 2006;85: 1496-501. 6) JAMA 2008;300:395- 404. *Ann Pharmacother 2009;43:1275-85*

Theory 2 – Hormonal Glitch

- Testosterone deficiency – particularly in postmenopausal women could be the cause
- Various formulations studied: Oral, spray, patch, topical preparations…

.

Testosterone Media Blitz*

5 articles published 2005/06, 4 journals, one consistent author [1-5]
- Multicenter, 24 weeks duration, surgical or natural menopause: mild benefit with 300mcg patch (not 150mcg or 450mcg)[1]
- stat ↑ satisfying sexual activity- 2.1 vs 0.98 / 4 wk
  - 1.11 episodes/4 wk.[3]
  - (total sexual activity ↑ 0.84 episodes/4wk)
- Stat ↑ sexual desire – difficult to find numbers, clinical sign?

- Similar trials published between 2000[6] & 2010 (pts with & w/o estrogen)[7,8] all industry sponsored.

*Courtesy of Proctor and Gamble

1) Arch Intern Med 2005;165(14):1582-1589 2) Obstet Gynecol 2005;105(5 Pt 1):944-952. 3) J Clin Endocrinol Metab 2005;90(9): 5226-5233 4) Menopause 2006;13(3)387-396
5) Menopause 2006;13(5)770-779 6) NEJM 2000;343(10):682-8. 7) NEJM 2008;359(19):2005-2017. 8) Climacteric. 2010;13(2):121-31.

Testosterone & The Hyposexuality Crisis

- Variable incidence of sexual dysfunction cited
  - 9-43%[1]
  - Highest values from paper[2] including author with significant conflicts of interest (Pfizer)[3]
- Paper authored by Rodenberg (P&G) in 2009 reported incidence of low sexual desire to be 35-44% in menopausal women[4]
- The market for a drug that enhances female sexual desire has been estimated by some to be worth up to $2bn in the U.S alone.[5]

1) NEJM 2008;359(19):2005-2017. 2) JAMA. 1999;281(6):537-44) 3) Spinal Cord. 2011;49(2): 273-9. 4) J Sex Med. 2009;8:2143-53. 5) *BMJ 2010;341:c5701*

Testosterone & Breast Ca

- 2008 review[1], 5 observational studies
  - inconsistent results, ++ methodological limitations
  - One small restrospective study suggested benefit with addition of T to HRT[2]
- Largest - prospective cohort, Nurses Health Study, 1978-2002. 24 yrs f/u (1 359 323 person yrs)[3]
  - RR Breast Ca with E + T = 2.48 (CI 1.53-4.04)
  - ↑risk compared to E only
  - HRT + T = 17.2% ↑ risk breast ca / year

1) Maturitas 2008;59(3):209-218. 2) Menopause. 2004;11:531-535 3) Arch Intern Med 2006;166 (July (14)):1483–9.

Relative Risk of Invasive Breast Cancer Nurses Health Study 1978-2002[1]

Participants	Person-Years	Cases, No.	RR (95% CI) Adjusted*	RR (95% CI) Adjusted†
Never users	381 797	1181	1.00	1.00
Past users	163 299	543	0.97 (0.87-1.08)	0.94 (0.85-1.05)
Current users‡				
Estrogen only§	45 993	191	1.26 (1.08-1.47)	1.23 (1.05-1.44)
Estrogen and testosterone	2066	17	2.65 (1.63-4.30)	2.48 (1.53-4.04)
Testosterone only	179	1	2.15 (0.30-15.50)	2.10 (0.29-15.18)

Weaknesses: Did not take into account prior hormone use; For E + T users, 97.6% had received ERT/HRT previously. No clear-cut exposure data for current T use (2-yr f/u intervals)

1) Arch Intern Med 2006;166(July (14)):1483–9.

Testosterone & Breast Ca

- 2008 RCT[1] – All women had mammogram in last 12 mo.
  - 4/534 (T) vs 0/277 (P) developed breast Ca at 4,7,12 & 27 mo.
- 2011[2] – 4 yr open label extension of 2 RCTs
  - All women taking E+T, no control group
  - 7 new cases breast Ca, authors argue this is consistent with age appropriate rates

1) NEJM 2008;359(19):2005-2017. 2) Gynecol Endocrinol 2011;27(1):39-48.

Adverse Events: Testosterone 0-12 months[1]	N=967 (%)
All	706 (73)
Unwanted hair growth	167 (17.3)
Acne	89 (9.2)
Alopecia	61 (6.3)
Voice deepening	39 (4.0)
Stroke	1
Angina	2
Clitoral enlargement	4

*Not mentioned but listed in previous trials: headache, breast pain
2005 Cochrane Review reported significant reduction in HDL[2]

1) Gynecol Endocrinol 2011;27(1):39-48 2) Cochrane Database Syst Rev. 2005;(4):CD004509

Theory 3: All in the mind (Flibanserin)

- Marginal benefit in number of satisfactory sexual encounters:
  - ↑from 2.7 to 4.5/mo among women taking flibanserin. The number rose to 3.7/mo in the placebo group.
- No benefit sexual desire
- A/Es: dizziness, nausea, fatigue, somnolence, sedation
- Almost 15% of women discontinued due to increased frequency of significant a/es - depression, accidental injury, syncope/ fainting.
- Rejected by FDA June 2010

1) BMJ 2010;341:c5701

Success in obtaining FDA approval for HSDD Medication[1]

- 1994 efforts for sildenafil abandoned
- 2004 testosterone patch failed to win approval due to safety concerns.
- 2010 flibanserin withdrawn from development

- "The shape shifting of the hunt for a 'pink Viagra'—from vascular drug to male hormone to a central nervous system drug—is a case study of marketing in search of medicine. It couldn't be a better example if industry critics had written it themselves."

Leonore Tiefer, associate clinical professor of psychiatry at New York University School of Medicine and Albert Einstein College of Medicine
BMJ 2010;341:c5701

Korean Red Ginseng

- Crossover, 32 postmenopausal women, 1g tid
- ¼ pts excluded from analysis
  - 4 dropped out due to lack of subjective improvement
  - 4 excluded due to absence of intercourse
- Analyzed: 24
- FSFI (19 questions, each 6pts, 6 domains)
- Stat sign improvement 1 domain (arousal)
  - ↑ from 3.1 ± 0.87 to 3.5 ± 0.72 on 6 pt scale
  - No improvement in desire, lubrication, orgasm, pain or satisfaction
- 12 reported a/es, 2 vaginal bleeding

J Sex Med 2010;7:1469-1477

Diamond in the Rough?

232 women, 29 yrs, HSDD. All failed at least one other tx
- Buproprion SR 150mg/d vs placebo x 12 weeks.

Findings: Significant improvement with buproprion
- 65.3% buproprion responded 'Definitely yes' to Global efficacy question vs 4.3% placebo (p=0.001)
- 71.8% in buproprion were definitely satisfied with tx vs 3.7% placebo (p=0.001)

Limits: One "specialty" site in Iran, + exclusion criteria

Comments: Impressive numbers, however definite limitations. Most common A/E was headache.

Improvement in some outcomes supported by other trials[2]
Side efffects of buproprion may outweigh benefits.

1) BJU Int. 2010 Feb 11. [Epub ahead of print] 2) (J Clin Psychopharmacol 2004;24:339–342)

In bed with pharma…

- Gerpirone-ER – recent 2° analysis of 3 RCTs & depression tx
  - 161 women with MDD & HSDD
    - 63% Gerpirone-ER vs 40% placebo reversed diagnosis of HSDD after 8 weeks (p=0.007)
  - A/Es include dizziness & nausea

1) J Sex Med. 2011 Feb 16. doi: 10.1111/j.1743-6109.2011.02216.x. [Epub ahead of print]

OTC Options

- There are no published controlled trials to demonstrate the effectiveness of the majority of over- the-counter (or on the web) products

Do you have chest pain because you love me or is it GERD from my mom's chilli?
(or all you need to know about GERD in 15 minutes)

Mike Kolber

DTC April 1, 2011

Decision Making 101

Evidence
+ experience
+ patient values (and expectations)
= **decision**

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

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

A) Reach for Esomeprazole from the cabinet (MD)
B) Sell him some OTC Ranitidine (pharm)
C) Tell him to loose weight, elevate head of the bed
D) Give him a double dose PPI off the hop (he is big)
E) Give him a PPI during the day, H2Ant at night

Is this GERD?

- Diagnosis by history
  - Heartburn
  - acid taste (waterbrash) / regurgitation
- How accurate?
  - HB and regurg = 69% sensitivity / 62% specificity[1]
  - FPs are as accurate as GIs[1]
- Better sensitivity then endoscopy!

[1] *Dent Gut 2010;59:714*

Non-pharm interventions in GERD

- Although spicy foods, late meals, bending after eating, smoking, ETOH…are <u>associated</u> with GERD
- Evidence for non-pharm treatment → ↓ GERD
  - Weight loss
  - Elevating head of bed

Arch Intern Med. 2006;166:965-971

How well do the meds work?

Heartburn example

Patients who respond in the PPI group
≈ 65% at 4 weeks, 85% at 8 weeks
Patients who respond to H2RA
≈ 40% at 4 weeks, 55% at 8 weeks
Patients who respond in the placebo group
≈ 15% at 4 weeks, 30% at 8 weeks

8-9/10 patients will respond to a PPI
3 of these improved not because of a drug
an additional 2-3 of these would have improved with an H2RA

Cochrane Library CD003244

Are PPIs equally effective?

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

Khan, Cochrane Systematic Reviews 2007, CD003244
Cadeth

Use the cheapest PPI
100 days of acid suppression: AB 2010

- Omeprazole 20mg: $125
- Rabeprazole 20mg: $93
- Pantoprazole 40mg: $137
- Lansoprazole 30mg: $127
- Nexium 40mg: **$248**
- Ranitidine 150mg: $49
- Tecta $96

What about BID PPI?

- Depends on who takes you golfing!
- No difference c/w OD PPI[1]
- 25% Nova Scotians started on BID PPI[2]
- Reserve BID PPI for your patient with significant classic GERD still having sx on OD PPI

[1] *Khan, Cochrane Systematic Reviews 2007, CD003244*
[2] *Zacny Gastroenterology 2004 April; 126(4) Suppl 2: W1277, A-603*

How long initial treatment?
Earn your Long Term PPI!

- Try ~ 8 weeks and re-evalute[1]
- If better → dc
- If symptoms recurrence → restart
  - daily or less frequent
  - On demand
- Many may not have good reason for LT PPI[2,3]
- LT PPI: GERD, gastroprotection

[1] *Armstrong Can J Gastro 2004 (19): 15*
[2] *van Soest* Aliment Pharm 2006; 24: 377
[3] *Forgacs, BMJ 2008;336:2*

Can patients stop PPIs?

- 27% of PPI users x 4 years → successfully dc

[1] *Bjornsson Aliment Pharm 2006 ;24: 945*

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![3]

[1] *Bjornsson Aliment Pharm 2006 ;24: 945*
[2] *Reimer, Gastroenterology 2009;137:80*
[3] *Kolber, personal communication April 1, 2010*

On Demand PPIs

- Equal to continuous PPIs: patients w/o visible esophagitis[1]
- Most GERDs are NERDs
  - do NOT have esophagitis on endoscopy[2]
  - On demand should work in most patients
- GERD patients: followed LT[3]
  - 80% PPIs
    - 50% daily PPIs
    - 30% on demand PPIs

[1]*Pace,* Aliment Pharm 2007; 26: 195–204
[2]*Armstrong Can J Gastro 2004 (19): 15*
[3]*Nocon, Aliment Pharm 2007; 25: 715–722*

NERDs do well with on demand PPI

Do pro-motility agents work in GERD?

- No!
- Metoclopromide: FDA 2009: Tardive dyskinesia

Khan, Cochrane Reviews 2007, CD003244
Van Pinxteren, Cochrane Reviews 2010, CD002095

Nighttime H2 ant + PPI

- 8 short term studies
- ST (days to weeks): improved sx
- LT study (6 weeks): no difference
- Reserve for early AM sx breakthrough

Wang, Cochrane Systematic Reviews 2009, CD004275

PPI Side Effects:

- Gastrointestinal
  - Nuisance diarhea: 8% (reference)
  - C. diff. and c. diff recurrence[1,2]
  - lymphocytic colitis
- Pneumonia
  - 1 case /100 person years[3,4]
- Osteoporosis and hip #[5]
- VB12 deficiency, Hypomagnesemia

[1]*Dial et all JAMA 2005;294:2989-2995,* [2]*Dial et all CMAJ 2004;171(1): 33-8*
[3]*Laheij et all JAMA 2004;292:1955,* [4]*Eom, CMAJ 2011. DOI:10.1503*
[5]*Yang et all JAMA 2006;296:2947-2953*

Plavix - PPI Interaction: The Last word

- Observational studies: PPIs interact with clopidogrel → ↓ clopidogrel's anti-platelet effect → ? ↑ CV events[1,2,3]
- COGENT: RCT Clopidegrol + omeprazole 20 mg or Clopidegrol alone[4]
- No diff in CV events
- ↓GI events w omeprazole

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

Plavix - PPI: Mar. 2011

- Determine if truly need PPI
  - If not good reason → tapper and D/C
  - If need 'some' acid suppression (mild GERD) → H2Ant
  - Gastroprotection, H2ANT fail: → Panto or (? Rabeprazole)
  - Separate timing of PPI and Plavix?
- Determine if truly need Plavix (how long?)

Who should you scope with GERD?

- Barrett's screen: GERD > 10 years, > 50 yo Caucasian males
- Alarm features: (VBAD) vomiting, bleeding, anemia, dysphagia, wt. loss, atypical chest pain

Can Consensus Conf on Management of GERD Can J Gastro 2005(19): 15-35

GERD / PPI Summary 2011

- Encourage GERDs to ↓ weight, ↑ head of bed
- Earn your long term PPI
- Cheapest and lowest dose
- Clean up the:
  - "I am not sure why I take PPIs", weak indications
- Tapper then dc
- On demand works for most
- Plavix – PPI interaction likely not a big deal
- Scope: alarm features or Barrett's screen

ARE YOU WHAT YOU

EAT?

- Canada's Food Guide
- The World Health Organization
- The American Heart Association
- The American Institute for Cancer Research
- HealthLinkBC
- The British Nutrition Foundation
- ETCETERA???

WHO TELL US:

- **Limit FAT especially TRANS and saturated**
- **Reduce salt**
- **Eat more whole grains, vegetables, and fruit**
- **Avoid high-sugar foods and beverages**
- **Shun "junk": highly processed foods**
- **ETCETERA???**

What if it was all

BS?

Could I eat

WHATEVER I WANT?

WHAT WORRIES US

Fat
Salt
Sugar (and glycemic index/load)
Fiber
Antioxidants
Small frequent meals
Hydration
Junk food

SEARCH STRATEGY

- College Library
- Total 153 articles (mostly metaanalyses) pulled

I THREW OUT:

Bad studies (opinion, nothing measured, etc.)
Unsupported guidelines
Surrogate endpoints
Secondary prevention
Use of supplements
Ridiculously tiny claimed benefit

WHAT WAS LEFT (mostly):

- Meta-analyses, some HUGE
- Mostly cohort and case-control
- "Quantile Magnification"
- Food recall is the intervention
- Contradiction
- Confounders (other diets, socioeconomic)

ON THREE OF THE TOPICS

Junk Food
Small Frequent Meals
Hydration

THERE WAS NOTHING TO CRITICIZE

FAT

20 articles

FOUR DIET ISSUES
THREE OUTCOMES

- Total fat
- Saturation
- TRANS
- n-3 PUFA (fish)

- Events
- Morbidity
- Death

OUTCOMES

(main references 1, 2, 3)

TOTAL: no association

SATURATION and TRANS:

- cohort = association
- RCT = no association

FISH:

- cohort and RCT = association
- BUT supplements in one trial, secondary prevention in the other.

FAT BOTTOM LINE

"…the evidence doesn't support dietary fat reduction or modification."

- Cochrane Collaboration (ref 1)

SALT

15 articles

IN GENERAL

Surrogate endpoints (only one trial examined morbidity itself)

BIG ATTITUDE!

OUTCOMES

(main references 4, 5, 6)

Asthma, renal failure, pre-eclampsia, gastric metaplasia NO DIFFERENCE

BP (surrogate endpoint remember) MINUTE change: 1.1mm Hg systolic only

Cook N et al ref 6 (only one with a real endpoint)

- NO mortality difference
- CARDIOVASCULAR EVENTS: 1000 years of salt restriction prevents one.

SALT BOTTOM LINE

Pass the shaker

SUGAR

(really glycemic index and load)

24 articles

OVERALL

- Obesity is a confounder
- Links claimed to eight conditions
- Main measures are GI and GL
- One standout meta-analysis (ref 9), several technical problems

OUTCOMES

(main references 7-13)

- Surrogate outcomes (obesity, diabetes, lack of micronutrients, metabolic syndrome) NO RELATIONSHIP
- DENTAL CARIES, ADHD, DEMENTIA, DEPRESSION, CARDIOVASCULAR DISEASE all NO RELATIONSHIP

OUTCOMES 2

- **CANCER: of 5 articles, 4 found no relationship except endometrial CA**
- **Relationship (GI/GL) to endometrial CA in 3 articles**
  - **relied on obese tertile**
  - **significance disappeared without case-control studies.**

OUTCOMES ODDBALL

- Barclay et al (ref 9) found relationship of GI +/or GL to almost EVERYTHING.
- Diabetes, cardiovascular disease, gallbladder disease, endometrial cancer, breast cancer, all diseases combined.
- PROBLEMS
  - conflicts with everybody else
  - confounded by obesity
  - huge and variable quantile magnification
  - no raw numbers

SUGAR BOTTOM LINE

How Sweet It Is

FIBER

22 articles

OUTCOMES

(main references 14-19)

- CANCER: prostate, colon, polyps NO RELATIONSHIP, endometrial prospective study NO RELATIONSHIP.
- CARDIOVASCULAR DISEASE:
  - mostly surrogate endpoints
  - big meta-analysis (18) showed better
    - CVD outcomes with fiber

Pereira et al (18) details:

- **good analysis**
- **RRR 12%**
- **ARR 0.02% (2 per 10000)**

Using a huge extrapolation, 96% of men and 97% of women who ate fiber aggressively through their whole lives would experience NO EFFECT

DIABETES AND IMMUNE FUNCTION

- Surrogate endpoints
- Minimal association with diabetes
- Cochrane conclusion:
  - "effect insufficient to make dietary recommendations"

FIBER BOTTOM LINE

Leave It To Its Natural Consumers

ANTIOXIDANTS

40 articles

MAIN POINTS

- Mostly supplements (not diet)
- Antioxidant-poor diets strongly correlated with social deprivation
- Effects examined
  - CANCER
  - ASTHMA/ATOPY
  - CARDIOVASCULAR DISEASES
  - DEMENTIA

OUTCOMES

(main references 20-29)

- CANCER (20,21,22)
  - several analyses claimed relationship
  - endometrial: prospective no effect
  - cervical intraepithelial neoplasia: secondary, 1 of 15 +ve
  - esophageal: small effect, but huge quantile magnification, supplements included

OUTCOMES (continued)

- Asthma: two analyses (24,25) directly conflict. No raw numbers for the positive one.
- Dementia: again conflict (26,27). Positive one: one dementia postponed for 1250 years of very heavy D; beta carotene, flavinoids, and C deleterious.
- Cardiovascular Disease: no quantitative conclusions.

MEDITERRANEAN DIET

Great quality studies
(prospective and randomized, 28 & 29)

STRICTLY SECONDARY
(post-MI)

ANTIOXIDANTS BOTTOM LINE

Just Fine In Theory

CHANGES IN DIET HAVE *NO MEANINGFUL EFFECT* ON REAL HEALTH OUTCOMES IN HEALTHY PEOPLE

WHY DO WE BELIEVE?

Dunno…
No downside?
We're hardwired that way?

TAKE HOME MESSAGE

ENJOY…

DIET AND HEALTH BIBLIOGRAPHY: MAIN REFERENCES
JOHN SLOAN April 2011

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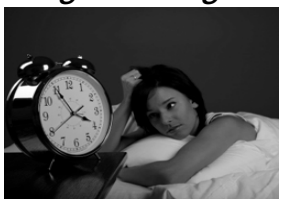
Insomnia: Help me make it though the night…



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Disclosure

- I have no financial relationships with any pharmaceutical companies
- I receive honoraria for work related to rational drug use from the:
  - Therapeutics Initiative
  - Canadian Agency for Drugs and Technologies (CADTH)
  - Patented Medicines Price Review Board (PMPRB)

2

Learning Objectives

- List 4 potential causes of chronic insomnia
- List 4 drugs that can worsen or cause insomnia
- Be familiar with 'proper' sleep hygiene techniques
- List the goals of therapy for insomnia
- Describe the short and long term benefits and risks associated with benzodiazepines
- Be familiar with the benefits and risks associated with the use of zopiclone and other medications used for treating chronic insomnia

Case 1. Ms. Jitters

- ID: 31 year old female with difficulty falling asleep (takes over 60 min) for the last month. She complains of daytime fatigue and takes naps
- PMHx:
  - Generalized Anxiety Disorder x 2 years
  - Asthma x 15 yrs
- Meds: Takes fluoxetine 40 mg daily x 1 year which is helpful for reducing GAD symptoms by about 60%
- Salbutamol and betamethasone inhalers – helpful in controlling asthma

How would you treat Ms. Jitters?

Case 2: Mr. Ian Somnia

- ID: 63 year old with fatigue, difficulty sleeping, poor concentration for 6 weeks
- HPI: otherwise healthy, no sleep apnea, no psychiatric conditions, etc.
- Social: occasional ethanol and caffeine; married; retired engineer
- Medications: occasional ibuprofen for pain, nicotine 14 mg patch (been on a patch x 7 wks)
- Physical exam and labs unremarkable

How would you treat Ian?

Goals of Therapy

1) Promote sound and restorative sleep
2) Minimize external (stress, noise, environment) and internal (anxiety, mood, pain) factors
3) Reduce daytime impairment (fatigue, poor concentration) and complications of lack of sleep
4) Improve the effectiveness of behavioural interventions in managing patients with primary, chronic insomnia

Treatment of Insomnia

Step 1: Get a good history, consider a sleep diary, look for potential underlying causes

Step 2: Nonpharmacological therapy

Step 3: Pharmacological options

What information do you need for both these cases?

Sleep History

- Time data
  - Napping, bed time, lights, how long to fall asleep, how many times awoken, longest awake period, time out of bed, hours of sleep
- Questions about the sleep period
  - Physical symptoms preventing sleep (pain), mental or emotional symptoms (worry, anxiety), what awakens during the night (snoring, gasping for air, nightmares), symptoms when you wake up (headache, confusion, sleepiness)
- Questions for the patient's bed partner
  - Snoring, gasping, breathing; leg twitching, jerking, kicking; alcohol, nicotine, caffeine, other drugs; change in mood or emotional state

Medications that can Cause or Worsen Insomnia

- Antidepressants
  - bupropion, fluoxetine, SNRIs, MAOIs, TCAs
- Antihypertensives
  - beta blockers, methyldopa
- Nicotine
- Sympathomimetic Amines
  - amphetamines, methylphenidate, caffeine, cocaine, decongestants, appetite suppressants, bronchodilators (e.g., salbutamol),
- Miscellaneous
  - corticosteroids, anticonvulsants (e.g., phenytoin, valproic acid), levodopa, quinidine, hormones (e.g., thyroid supplements, estrogen)

Nonpharmacological Options

- Proper sleep hygiene *(see slide in handout)*
- Relaxation exercises and tapes
- Stimulus control
- Sleep restriction
- Sleep diary *(see sample in handout)*
- Increase aerobic exercise earlier in the day (~45 minutes and should induce sweating)
- Cognitive behavioural therapy for insomnia (CBTi)

Sleep Hygiene

1. Keep a regular sleep/wake schedule 7 days a week
2. Limit daily "in-bed" time to average sleep time prior to the sleep disturbance
3. Avoid sleeping in or daytime naps
4. Stop offending medications/substances (caffeine, nicotine, alcohol, stimulants)
5. Avoid evening stimulation
6. Try a warm, 20 minute bath near bedtime
7. Eat regularly during the day and avoid large meals near bedtime
8. Use bedroom only for sleep and intimacy – not for TV or something that keeps you too alert

Pharmacological Options

- Antihistamines
- ⇨ Benzodiazepines
- ⇨ Zopiclone
- Eszopiclone*
- Zaleplon*/Indiplon*
- Zolpidem*
- ⇨ Antidepressants (e.g., trazodone, doxapin)
- Alcohol?
- Melatonin
- Ramelteon* (melatonin receptor agonist)
- Chloral Hydrate
- Antipsychotics ⇦
- L-Tryptophan
- Herbs (valerian, chamomile)

*Not available in Canada

6 Basic Principles

- Use lowest effective dose
- Intermittent dosing (PRN) – e.g., <4/week
- Short term treatment (2-4 weeks) depending on presentation
- Need for medication tapering if longer term
- Select and monitor medications by assessing daytime functioning and adverse effects
- Patient plays an active role in treatment

Benzodiazepines

- Effective in promoting sleep onset and maintaining sleep
- Consider half-life and metabolites
  - Particularly for the elderly
    - Increased risk of higher cortical impairment
      - Confusion and falls
    - Reduced Phase I metabolism
    - Reduced GFR and hepatic blood flow
    - "LOT" – lorazepam, oxazepam, temazepam

Benzodiazepines

- Bind to gamma sub-unit of GABA-A receptor, resulting in an increase in GABA-A receptor activity

Improve insomnia by:

- Reducing REM sleep
- Decreasing sleep latency
- Decrease nocturnal awakenings
- Tolerance develops with repeated administration

Problems with Benzodiazepines

- Short-term
  - Adverse effects
  - Carry-over effects
  - Cognition
  - Anterograde amnesia
- Long-term
  - Tolerance
  - Withdrawal
  - Rebound
  - Dependence

Adverse Effects of BDZs

- Daytime drowsiness/tiredness
- Cognitive impairment
- Rebound insomnia (even after 2 wks)
- Anterograde amnesia
- Incoordination and falls
- Paradoxical effects
- Respiratory depression
- Dependence/tolerance
- Sleep walking?

Physical Dependence vs. Abuse

- Physical Dependence:
  - Down regulation of benzodiazepine receptor sensitivity
  - Need to continue to use a drug to relieve or avoid physical withdrawal symptoms
- Abuse
  - Recreational use
  - Continued use despite negative consequences
  - Dose escalation
  - Loss of control over use

Zopiclone

- Acts at the benzodiazepine receptor
  - Not a benzodiazepine
- Compared to benzodiazepines, zopiclone appears to have less or no:
  - Rebound insomnia
  - Tolerance and dependence
  - Amnesic effects
  - Morning hang-over (short half life)

Zopiclone Pharmacokinetics

- Absorption: Elderly: 75% to 94%
- Protein binding: ~45%
- Metabolism: Extensively hepatic
- $T_{1/2}$: 5 hours; Elderly: 7 hours; Hepatic impairment: 11.9 hours
- Time to peak, serum: <2 hours; Hepatic impairment: 3.5 hours
- Excretion: Urine (75%); feces (16%)

Zopiclone

- Drug interactions:
  - CNS depressants
  - CYP2C9 and CYP3A4 drugs (inducers and inhibitors)
- Adverse effects: bitter taste, dry mouth, headache, somnolence
- Serious AEs: suicidal ideation, aggression, worsening of depression
- Eszopiclone (Lunesta) available in the US

Zolpidem (Ambien or Sublinox)*

- Non-benzodiazepine, binds to the omega -1 (BZ-1) receptor subtype of the GABA-A receptor complex.
- Rapid onset of action; sleep onset/duration
- $T_{1/2}$: 2.5 - 3 h
- 5 – 10 mg Sublingual (sublinox), 6.25 mg CR (Ambien) before bedtime
- Common SE: nausea, dizziness, drowsiness, rebound insomnia
- Serious SE: suicidal ideation, worsening of depression, aggressive behaviour
- Contraindications: severe hepatic impairment, respiratory insufficiency

*Not currently sold in Canada

Trazodone

- Limited data in primary insomnia (only 2 studies)
- Lack of objective efficacy measures
- Short duration of trials (longest is 6 weeks)
- Consideration for side effects (sedation, dizziness, orthostasis, psychomotor impairment, priapism, etc.)

Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry. 2005 Apr;66(4):469-76.

Trazodone vs. zolpidem

- 14 day, placebo controlled, primary insomnia
- Subjective sleep latency and duration showed significant improvement with both trazodone and zolpidem vs. placebo
- Effect was greater with zolpidem

Silber MH. Clinical practice. Chronic insomnia. N Engl J Med. 2005 Aug 25;353(8):803-10.

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Doxepin

- Limited data in elderly primary insomnia
- Dose = 1-3 mg!
- 12 week RCT, DB, Dox 1 mg (n = 77) or Dox 3 mg (n = 82), or placebo (n = 81)
- Outcomes: Polysomnography (PSG), patient and clinician ratings, CGI at nights 1, 29, and 85
- **Results:**
- DXP 3 mg > placebo for all measures and 1mg > placebo for some outcomes

Krystal AD et al. Efficacy and safety of doxepin 1 mg and 3 mg in a 12-week sleep laboratory and outpatient trial of elderly subjects with chronic primary insomnia. *SLEEP* 2010;33(11):1553-1561

Antipsychotics

- Not FDA approved for insomnia
- When used, doses are usually lower than those for treating psychosis
- Can be helpful, but associated with weight gain, increased risk for diabetes, high blood pressure, restless leg syndrome, muscle spasm or parkinson-like symptoms
- Quetiapine and ziprasidone have been studied in clinical trials and were shown to increase total sleep time as well as sleep efficiency

Adil's Comparison of First Line Drugs in Canada for Insomnia

Drug	Night-time Dose (mg)	Half-life (hours)	Metabolites	Comments
Lorazepam	Initial 0.5 Maximum 1	10 to 20	Inactive metabolite	No "hangover" effects; may cause more rebound insomnia on withdrawal than temazepam or oxazepam; may cause amnesia with higher doses
Oxazepam	Initial 15 Maximum 30	5 to 10	Inactive metabolite	Slowly absorbed – delayed onset of action; take 60-90 minutes before retiring; no "hangover" effects
Temazepam	Initial 7.5 Maximum 30	10 to 12	Inactive metabolite	Short duration of action limits morning sedation. Does not accumulate.
Triazolam	Initial 0.125 Maximum 0.25	2 to 3	Inactive metabolite	Anterograde amnesia (esp. with ↑ dose, concomitant alcohol); other dose-related side effects (rebound insomnia, daytime anxiety) have limited its use. Absence of "hangover" effects is major advantage.
Zopiclone	Initial 3.75 Maximum 7.5	5 to 10	N-Desmethyl (has activity) N-Oxide (has weak activity)	Does not accumulate; free of cognitive effects; major adverse effect is bitter/metallic taste; may cause less rebound on withdrawal; minimal additive effects with low doses of alcohol

First-line Pharmacotherapy: Highest level of evidence supporting efficacy and safety

Agents	Recommended Dose	Comments
Zopiclone	3.75-7.5 mg	• Short half-life provides lower risk of morning hang-over effect • Metallic after-taste most common adverse reaction
Temazepam	15-30 mg	• Intermediate half-life carries a low-moderate risk of morning hang-over effect

Second-line Pharmacotherapy: Moderate level of formal evidence. Extent of current use and favorable tolerability support use as second-line agents

Agents	Recommended Dose	Comments
Trazodone	25-50 mg	• Shorter half-life carries lower risk of morning hang-over effect

Variable Evidence

Agents	Recommended Dose	Comments
L'Tryptophan	500 mg-2 gm	• Evidence supporting efficacy is variable and insufficient. May be requested by individual patients looking for a "natural source" agent.
Melatonin	0.3-5 mg	
Valerian	400-900 mg	Taken 60 minutes before bedtime

Other Non-Prescription Products

Agents	Usual Dose	Comments
Diphenhydramine - Benadryl® - Sleep Eze - Simply Sleep - Nytol® - Unisom®	25-50 mg hs	Potential for serious side effects arising from anticholinergic properties (especially in elderly); residual daytime sleepiness, diminished cognitive function, dry mouth, blurred vision, constipation, urinary retention, etc. These products are not intended for long term use and tolerance to sedative effects likely develops rapidly (3 days) Gravol not approved in Canada as a sleep aid
Dimenhydrinate - Gravol	25-50 mg hs	
Doxylamine - Unisom 2	25-50 mg hs	

Toward Optimized Practice Program. Guideline for adult primary insomnia. 2010 Feb

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3. Toward Optimized Practice Program. Guideline for adult primary insomnia. 2010 Feb. Available from: http://topalbertadoctors.org/informed_practice/clinical_practice_guidelines/complete%20set/Insomnia/insomnia_management_guideline.pdf

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5. Wilson SJ, Nutt DJ, Alford C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. J Psychopharmacol. 2010 Nov;24(11):1577-601.

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8. Passarella S, Duong MT. Diagnosis and treatment of insomnia. Am J Health Syst Pharm. 2008 May 15;65(10):927-34.

9. NIH state-of-the-science conference on manifestations and management of chronic insomnia in adults. 2005 Jun. Available from: http://consensus.nih.gov/2005/insomniastatement.pdf

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Alzheimer's Treatment – Who are we fooling?

G. Michael Allan
Associate Professor, University of Alberta,
Director, Evidence & CPD, ACFP

Objectives

- Cursory Review of Options (research or practiced)
- Discussion of Evidence for Anti-cholinesterases.
- Discussion of Concerns with the above.
- Prevention of Dementia: Treating "Mild Cognitive Impairment"

Therapies for Dementia

- Most of us think of Anti-cholinterases
  - Some remember Memantine
- How many others are there?
- 40 & counting,...
- Clioquinol, Omega 3 fatty acids, Melatonin, Alpha lipoic acid, Folic acid, Vinpocetine (herbal), Thiamine, D-cycloserine, Vitamin E, Nicotine, Vitamin B6, Vitamin B12, Lecithin, Ibuprofen, Acetyl-L-carnitine, Statins, Selegiline, HRT, Indomethacin, Physostigmine, Piracetam, Nicergoline, Hydergine, Propentofylline, Nimodipine, Metrifonate, Velnacrine, Reminiscence Therapy, Music Therapy, Respite Care, Light therapy, Transcutaneous electrical nerve stimulation (TENS), Snoezelen (stimulatory therapy), Homeopathy, Aroma therapy for dementia, Validation therapy

Comments from studies

- There are tons of measuring tools used (over 40 types) in these studies. Makes combining hard AND when the trial uses multiple, they don't correct for multiple comparisons.
- Also, define dementia and stages of dementia differently (mild vs mod, etc). For example one study used 27 MMSE as mild. This makes consistency troubled (and more heterogeneity).
-
- Behavior, function rarely ever studied (and never found different).

Scales: studies

- CIBIC is clinician – based impression of change scale. May suffer from the bias of using clinicians to rate differences are they usually exaggerate differences.
- ADAS scale = 0-70 with 4 being a clinically important change
- MMSE and most scales do not have a MICD
- Others Cholinesterase Inhibitors to Donepezil but less robust evidence and less finding of statistical (and clinical significance).

Drugs with Potential: Memantine

- Mild to Moderate Dementia & Vascular Dementia
  - 1.4% - 2.6% ADAS score benefit
  - Most other scales change undetectable or of No detectable clinical benefit.
- Moderate - Severe Dementia (best of bad evidence)
  - Cognition: 3% > Placebo
  - ADL score: 2.4% > Placebo
  - Possibly < agitation (NNT= 63)
  - Well Tolerated

Cochrane Database Syst Rev. 2006 Apr 19;(2):CD003154

Pharmaceutical Leader of Dementia: Anti-Cholinesterases

Separating the drugs: Donepezil for Dementia

- NNT =10 for ↑ in Global Clinical State
  - (Dr rated)
- NNH =27 (Drop-out with AE),
  - Only 12% of trials report mortality
- Truth: 3% less ↓ in cognition
- Truth: Quality of Life scores unchanged & No other hard data.

Cochrane Database Syst Rev. 2006 Jan 25;(1):CD001190

Separating the drugs: Galantamine for Dementia

- NNT=6 for same or ↑ Global Clinical State
  - (Dr rated)
- NNT =6 for ↑ ADAS>4
- NNH = 12 (Drop-out with AE),
- Truth: When ITT, Global Clinical State Not significant.
- Truth: ADAS average= 3.1 or 4% less ↓ in cognition & No hard data.

Cochrane Database Syst Rev. 2006 Jan 25;(1):CD001747

Separating the drugs: Rivastigmine for Dementia

- NNT = 14 for 4pt ↑ ADAS
- NNT = 15 for Global Clinical State
  - (Dr rated)
- NNH = 7 to Drop-out due to AE.
- Truth: ADAS average= 2.1 or 3% less ↓ in cognition & No hard data.
- Up date (2008): 9 RCT, 4775 pts, outcomes at 26 weeks,…
  - Mean 2.15 Prog Deterioration Scale (ADLs) 3.16 to 1.13
  - Mean 1.99 ADAS change (2.49 to 1.50)

Cochrane 2000, Issue 4. Art. No.: CD001191. Cochrane 2009;(2):CD001191.

Cholinesterase Inhibitors: Summary

- Cholinesterase trials vs Placebo
  - Poor reporting (e.g. 12% of Donepezil report mortality)
  - ADAS-cog diff of 4 (5.7%) clinical significant
  - Quality of Life scores unchanged & No other hard data.
-

	Donepezil	Galantamine	Rivastigmine	All
ADAS - Cog	3% less Decline	4% less Decline	3% less Decline	3.9% less Decline
ADAS – Cog of 4		NNT 6	NNT 14	
Glob Clin State	NNT 10	NNT 6*	NNT 15	NNT 12
AE Drop-out	NNH 27	NNH 12	NNH 7	NNH 9

* Not significant if ITT analysis

Cochrane. 2006;(1):CD001190. Cochrane 2000;(4):CD001191. Cochrane 2009(2):CD001191. CMAJ 2003; 169: 557-64.

Anti-cholinesterase Together

- Global Responders: NNT = 12 (for stabilization or improvement)
- After Tx for 6 months: ADAS score 2.7 (3.9%) better in Treatment group
- Adverse Events (GI #1) lead people to stop the Treatment NNH = 9

CMAJ 2003; 169: 557-64. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD005593.

Is one better than another?

- 3 Trials compare Head to Head[1]
- Multiple Flaws (54% CONSORT items inadequate)
  - No Allocation concealment or blinding,
  - Too short (3 months),
  - Small n (for drugs that barely work),
  - Funding (better dosing for sponsor, etc),
  - Subgroup analysis (with recommendations based on it),
- Industry funded, Employee written, results favoring sponsor. (Therefore, no difference)
- In Meta-analysis : "There is no evidence of any difference between them"[2]

1) Lancet Neurol 2004; 3: 622:26. Therapeutics Letter 2005; 56:1-4. 2) Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005593

Meta-analysis of Dementia RCTs

- What is the scientific evidence for Cholinesterase Inhibitors in the treatment of Alzheimer's disease.
- 22 Trials: 12 Donepezil, 5 Rivastigmine, 5 Galantamine: 27 to 978 pt/trial, 6 wks-3yrs long
- **Findings:** 1.5-3.9 (ADAS-cog & Min clinical sign ≥ 4)
- **Limitations:** Numerous
  - ITT flaws (pt exclusion after randomization)= 15/22 (68%),
  - Last Observation Carried Forward (declining illness)
  - Use of Means (in scales),
  - No correction for multiple comparison
  - Funding (often authored by employees)

BMJ 2005; 331: 321-27

Are there any good studies?

- 3 yr, non-profit funded UK community RCT[2]
  - More representative: more co-morbid patients (50%).
  - Seemed to have some benefit in 1st year (but not significant) for institutionalization + progression of disability.
  - No benefit at all by 3 years.
  - Possible Harms (63 Tx deaths, vs 50) but not significant.
  - ++ flawed: $<^1/_5$ of intended enrolment & 40% lost f/u in 1st yr

Lancet 2004; 363: 2105-15.

Treatment of Dementia: Bottomline

- Bad or Biased Trials
- Little benefit: some in scores
- Nothing yet in hard outcomes (long-term etc)
- Side-effects and Cost

What about Prevention

- Mild Cognitive Impairment may be a sign of inevitable decline to dementia.
- Perhaps the best use of these agents is prevention:
  - Giving AChI before Dementia and stopping it from ever occurring.

Prevention of Dementia:

- Vitamin E : No help
- Meta-analysis Donepezil:
  - In 1 of 2 trials, 1 of 5 scores had a 3% less decline
  - Stopping due to adverse events: NNH 7.
- Meta-analysis Galantamine:
  - Marginal to no clinical Benefit
  - ++ Harms: NNH (for death) = 94.

1) NEJM 2005; 352:2379-88. 2) Cochrane Database Syst Rev. 2006;3:CD006104. 3) Cochrane Database Syst Rev. 2006;(1):CD001747. Therapeutics Letter 2005; 56:1-4.

Prevention of Dementia: Bottom-line

- Donepezil:
  - "There is no evidence to support the use of donepezil for patients with MCI. Benefits are minor, short lived and associated with significant side effects."
- Galantamine:
  - "Galantamine use in MCI is not recommended"

1) Cochrane Database Syst Rev. 2006 Jul 19;3:CD006104. 2) Cochrane Database Syst Rev. 2006 Jan 25;(1):CD001747.

Summary: Anti-cholinesterases

- Biased Research
- Multiple Flaws
- Little Benefit
- ? Any Clinical Important Benefit
- Cost and Side-effects
- If patients and care-givers are considering, frank discussion about expectations.

What about Agitation

- Medicaitons most researched:
  - Cholinesterase inhibitors
  - Antipsychotics

What about Anti-Cholinesterases?

- Meta-analysis of behavioral and psychological symptoms of Dementia: 12 studies (9 with enough data for analysis)
- ChEIs as a class had a beneficial effects on reducing BPSD:
  - BPSD = Behavioral and Psychiatric Symptoms of Dementia
  - SMD of -0.10 (CI; -0.18, -0.01) and
  - WMD of-1.38 neuropsychiatry inventory point (CI; -2.30, -0.46).
  - In mild AD patients, the WMD was -1.92 (CI; -3.18, -0.66);
  - In severe AD patients, the WMD was -0.06 (CI; -2.12, +0.57).
- "Clinical Relevance of this effect remains unclear"

Clin Interv Aging. 2008;3(4):719-28.

What about the Anti-Psychotics?

- Atypical Antipsychotic for Behavioral problems in Dementia[1]
  - Mean effect size for 7 placebo-controlled studies:
    - 0.45 (95% CI = 0.16-0.74) for atypical antipsychotics,
    - 0.32 (95% CI = 0.10-0.53) for placebo. (No difference)
- Cochrane Meta-analysis[2] (16 placebo RCT, 31% full published)
  1. Improved aggression with risperidone and olanzapine treatment vs placebo.
  2. Risperidone and olanzapine: increased serious adverse (such as cerebrovascular events).
  3. Increase in drop-outs in risperidone (2 mg) and olanzapine (5-10 mg)
- Mortality up (FDA data: 1.7 OR)

1) Psychother Psychosom. 2007;76(4):213-8. 2) Cochrane Database Syst Rev. 2006 Jan 25;(1):CD003476. (similar found: Int J Geriatr Psychiatry. 2007 May;22(5):475-84.)

Anti-psychotics

- DART-AD: 165 pts, mean 85, 76% female, long-term care (ITT, AC, blind everyone)
- Withdraw antipsychotic (placebo) or continue
- Outcomes
  - Behavior: NPI behavior score worsened by by 1.7% (2.4 /144). Not stat sign.
  - Mortality: at 2 years, 71% continued anti-psychotic vs 46% placebo, (Diff = 25%, NNT 4)
- Patients on anti-psychotics deserve a break

Lancet Neurol 2009; 8:151–57. *PLoS Med 5(4): e76.doi:10.1371/journal.pmed.0050076*

Questions?

Adil Virani

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Overview

- Case
- Treatment Options
- Treatment Guidelines
  - CADDRA 2011
- Adverse effects
- Monitoring Parameters

Case: Oliver DePlace

- ID: 7 year old boy with combined type of ADHD
- HPI: Oliver is easily distracted, constantly interrupts others and talks excessively. He consistently fidgets with his hands and runs around the house often yelling at the top of his lungs. He currently has difficulty concentrating and following instructions.

3

Epidemiology of ADHD

- Among the most prevalent chronic health conditions affecting children and adolescents[1]
  - Most common psychiatric disorder in children in NA[2]
- Prevalence: 3-7 %[3]
- Usual age of onset is 3 yrs old
- Boys > girls 3:1 to 9:1[3,6]
- 30-70% of children have ADHD symptoms last into adulthood

1. Amer Acad Ped. *Pediatr* 2000; 2. Stubbe DE. Psych. Clin NA July 2000; 3. APA. *DSM-IV-TR* 2000 4. Wolraich et al. *J Dev Behav Pediatr* 1998; 5. Barbaresi et al. *Acta Paediatr Suppl* 2004; 6. Gaub, Carlson. *JAACAP* 1997

Goals of Therapy

- Eliminate or decrease symptoms
- Shift in 'focus' from improving ADHD symptoms to restoring normal functioning
- Improve concentration time
- Build self-esteem
- Prevent the development of other psychiatric disorders
- Prevent/minimize side effects
- Education

Treatment Options in ADHD

- Behaviour Management
- Stimulants
  - Methylphenidate (MPH, Concerta® Novo-MPH-ER-C)
  - Amphetamines (Dexadrine, Vyvanse®, Adderall XR®)
  - Dexmethylphenidate** (Focalin®)
- Nonstimulants
  - Atomoxetine
- Antidepressants
  - TCA's, Bupropion, Venlafaxine
- Alpha-2 Agonists
  - Clonidine, Guanfacine (Intuitiv)**
- Other agents
  - Atypical antipsychotics, modafinil, herbals, mood stabilizers

Probability that there will be a 50% reduction in CORE symptoms

- Behaviour Management **40-60%**
- Stimulants **65-80%**
  - Methylphenidate (MPH, Concerta®)
  - Amphetamines (Dexadrine, Vyvanse®, Adderall XR®)
  - Dexmethylphenidate** (Focalin®)
- Nonstimulants **50-60%**
  - Atomoxetine
- Antidepressants **~50%**
  - TCA's, Bupropion, Venlafaxine
- Alpha-2 Agonists **~40%**
  - Clonidine, Guanfacine**
- Other agents
  - Atypical antipsychotics, modafinil, herbals, mood stabilizers

Stimulants: What You Should Know…

- Overall 'response' rate of ~ 75%[1-4]
- No large clinical trials comparing stimulants
- Effective on day 1 and continue over the following months
- Side effects (sleep disruption, weight loss) are common
- Immediate release preparation should be dosed 2-3 times /day
- 'Non-addictive' in ADHD pts
- Cardiac concerns

1. Stein *Pediatr* 2003; 2. Pelham *Pediatr* 2001; 3. Greenhill *APA* 2004; 4. Kemner *APA* 2004

8

Psychostimulants

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Benefits of stimulants include:

- Decreased aggression, Improved social interaction & academic performance (parent & teacher rating)

Stimulants do not improve:

- Anxiety, academic performance (testing), delinquency/substance abuse at 3 years

Not studied:

- QOL, school completion, employment, future health

Stimulants associated with ↓ ht/wt at 3 yrs

Therapeutics Initiative Newsletter 69. March-May 2008.

9

Stimulant Adverse Effects

- adverse effects fairly well characterized
- CNS: insomnia, anxiety, activation, irritability (rebound), worsening tics, psychosis/mania
- HEENT: xerostomia, mydriasis
- CVS: ↑HR, ↑BP, palpitations, Sudden Cardiac Death
- RESP: URTI, sinusitis, cough
- GI: Anorexia, nausea, abdominal pain, wt loss
- GU: urinary retention, sexual dysfunction
- LAB/MSK/EXTR: growth delay (ht & wt), rash, leukopenia, anemia

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2011 CADDRA GUIDELINES

Table 1. MEDICAL TREATMENT FOR ADHD UNCOMPLICATED – CHILDREN

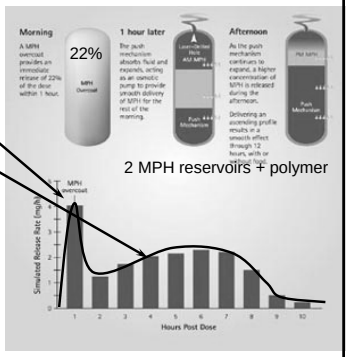
Alphabetically Listed – Refer to product monographs for complete prescribing information.

Would you agree that these are the only first line agents or that all should be first line agents?

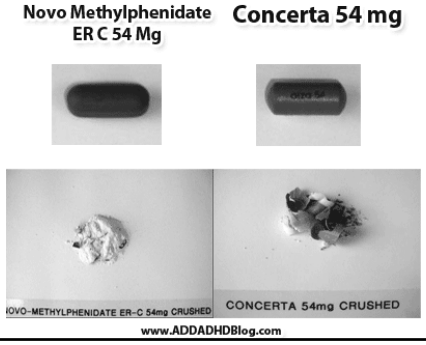
Adderall XR® *(amphetamine mixed salts)*	5, 10, 15, 20, 25, 30 mg cap	5-10 mg q.d. a.m.	* 5-10 mg	* 5-10 mg	30 mg	30 mg
Biphentin® *(methylphenidate HCl)*	10, 15, 20, 30, 40 50, 60, 80 mg cap	10-20 mg q.d. a.m.	* 10 mg	* 10 mg	60 mg	60 mg
Concerta® *(methylphenidate HCl)*	18, 27, 36, 54 mg tab	18 mg q.d. a.m.	* 18 mg	* 18 mg	54 mg	72 mg
Strattera® *(atomoxetine)*	10, 18, 25, 40, 60, 80, 100 mg cap	0.5 mg/kg/day	Maintain Dose for a min. of 7-14 days before adjusting to 0.8 mg/kg/day then 1.2 mg/kg/day	Maintain Dose for a min. of 7-14 days before adjusting to 0.8 mg/kg/day then 1.2 mg/kg/day	lesser of 1.4 mg/kg/day or 60 mg/day	lesser of 1.4 mg/kg/day or 60 mg/day
Vyvanse® *(lisdexamfetamine dimesylate)*	20, 30, 40, 50, 60 mg cap	20-30 mg q.d. a.m.	By clinical discretion	* 10 mg	60 mg	60 mg

OROS-Methylphenidate (Concerta®)

- Controlled release
  - Initial bolus
  - ↑ conc'n during the day
- Non-absorbable tablet shell is eliminated in stool
- Crush-resistant
  - Deters abuse
- 18 mg, 27 mg, 36 mg, 54 mg 'tablets'

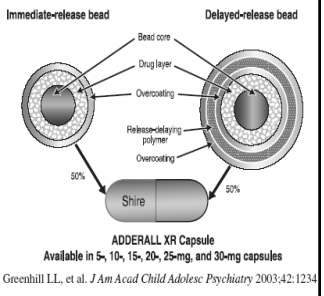


Generic Concerta – but is it really?



Mixed Amphetamine Salts (Adderall XR®)

- 50:50 ratio of immediate to delayed release beads
- 4 salts: 75% d-amphet. & 25% l-amphet.
- Don't chew
- OK to sprinkle
- 10-12 hr DoA
- Well tolerated
- Controlled trials support the efficacy of MAS over placebo in >3000 pts
  - None looking at remission



Greenhill LL, et al. *J Am Acad Child Adolesc Psychiatry* 2003;42:1234

McCracken, et al. JAACAP 2003;42(6):673-683; Biederman et al. *Pediatrics* 2002;110(2):258

Lisdexamfetamine (Vyvanse)

- Prodrug converted to dextroamphetamine by erythrocytes
- Can dissolve in water or sprinkle on food
- 20-30 mg once daily; increase by 10 mg at weekly intervals (70 mg max)
- Capsules: 20mg, 30mg, 40mg, 50mg, 60mg

Benefits of Once Daily Agents

- Adherence
- Coverage during evening and early morning
  - Homework, extracurricular activities, social interactions
- Decreased abuse potential
- Problems with in-school dosing
  - Privacy issues
    - Decreased embarrassment
  - Storage of controlled medications
    - Less drug diversion ("sharing")
- Ascending schedule decreases acute tolerance

Atomoxetine

- "Selective" presynaptic NE reuptake inhibitor
- Nonstimulant agent indicated for ADHD in children (≥6 years old), adolescents & adults
- Marketed in Canada Dec 2004
- Non-controlled substance
- Leads to increases in PFC NE/DA
- Metabolized by CYP2D6 (90% Extensive/10% Poor)
- Half-life of 5 hrs, however duration of action is significantly longer (18-21 hrs)
- 10mg, 18 mg, 25 mg, 40 mg, 60 mg capsules

Atomoxetine Side Effects

- Decreased Appetite
- Nausea
- Dyspepsia (7%)
- Vomiting*
- Somnolence(15%)*
- Fatigue
- Dizziness
- Hepatic (2/3,400,000)
- Mood Swings
- Transient Weight Loss (0.5 kg)
- Increased:
  - HR (8 bpm)
  - SBP (3 mmHg)
  - DBP (2 mmHg)
- Sexual Dysfunction
- Suicidal ideation?

*Occurred significantly more frequently in atomox. vs MPH patients

Wernicke JF, et al. *J Clin Psychiatry.* 2002;63 (suppl 12):50-5.; Kratochvil CJ, et al. *JAACAP* 2002;41:776-84.
Kelsey DK, et al. Pediatrics. 2004 Jul;114(1):e1-8.

Atomoxetine Safety data

- Meta-analysis of PC trials in children (ages 7-12)
  - 5/1357 (0.37%) atom vs. (0/851) PLB grp
- "No events" in those >12 yrs old (25% of study pop, in meta-analysis)
- Analysis of adult data did not indicate an increased risk of "suicide related events"
- Slight "increase in risk of side-effects such as suicidal thoughts, hostility, and mood swings"
- Need to inform patient/caregiver & document
- Need for monitoring

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/strattera_hpc-cps_e.pdf

Atomoxetine's Role

- Stimulant non-responder
- Stimulants not tolerated
- Concern over using stimulants (e.g., abuse)
- Inattentive type of ADHD?
- Comorbid anxiety/depression?

Kratochvil CJ et al. Atomox mono vs. Atomox/Fluox. JAACAP. 2005 Sep;44(9):915-24.

Thanks for your 'Attention'!

Val Montessori

Traveler's Diarrhea

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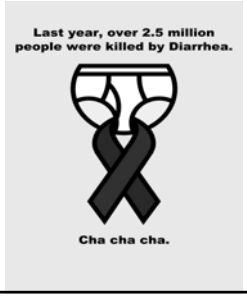
University of British Columbia

Traveler's Diarrhea

- 50% of travelers affected in some areas



CDC Health Information for International Travel 2008. Found at http://wwwn.cdc.gov/travel/YellowBookListofMaps.aspx.

Traveler's Diarrhea

- 80% bacterial, 15% viral, 5% other
- Bacterial
  - Enterotoxogenic *E. coli* – gastroenteritis
  - Salmonella – gastroenteritis
  - Shigella – dysentery, small volume mucopurulent
  - Camplyobacter – dysentery
  - *S. aureus* – acute vomiting
- Viruses
  - Norovirus
- Parasitic

Current Medical Diagnosis and Treatment, 2007.

Other Enteric Pathogens

- **Vibrio spp.**
  - *Vibrio parahaemolyticus & Vibrio cholerae*
    - associated with eating raw/partially cooked seafood
- **Other**
  - *Aeromonas hydrophila, Plesiomonas shigelloides, Yersinia enterocolitica*

Val Montessori

General Features

- Benign, self-limited disease
- One week into travel
- Prophylaxis recommended
  - For inflammatory bowel, HIV, IBS, immunosuppression: give prophylaxis
- In others: treat symptomatically

Current Medical Diagnosis and Treatment, 2007.

E coli induced Diarrhea

- **Enterotoxigenic *E. coli***
  - Express two plasmid-encoded toxins: heat labile (LT) and heat stable (ST)
- **Enteroadherent *E. coli***
  - Defined by their adherence properties to cells in culture
- **Enteroinvasive *E. coli***
  - Have plasmids that encode "invasive proteins"
  - Proteins are necessary for virulence and bacterial invasion into gut mucosa
- **Enteropathogenic *E. coli***
  - Mechanisms are not defined; uncommon in the US
- **Shiga toxin–producing *E. coli***
  - Produce Shiga-like toxins that are cytotoxic for cells in culture
  - Genes for these toxins are located on bacteriophages
  - Known causes of HUS/TTP

E coli Pathogens

- **Enterotoxigenic Escherichia coli (ETEC)**
  - most common cause of TD worldwide
  - large inoculum necessary to produce disease
  - watery diarrhea associated with cramps
  - fever may be low grade or absent
- **Enteroaggregative E. coli (EAEC)**
  - up to 25% of cases
  - resemble ETEC in presentation & response to abx

Preventive Measures

- For travelers to high-risk areas, several approaches may be recommended that can reduce but never completely eliminate the risk for TD. These include—
- Instruction regarding food and beverage selection
- Use of agents other than antimicrobial drugs for prophylaxis
- Use of prophylactic antibiotics for select high risk patients
- Carrying small containers of hand-sanitizing solutions or gels (containing at least 60% alcohol) may make it easier for travelers to clean their hands before eating

Food and Beverage Selection

- freshly cooked and served piping hot are
- avoid beverages diluted with nonpotable water and foods washed in nonpotable water, such as salads.

- Other risky foods include raw or undercooked meat and seafood, and unpeeled raw fruits and vegetables.
- Safe beverages include those that are bottled and sealed, or carbonated.
- Boiled beverages and those appropriately treated with iodine or chlorine may also be safely consumed.

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Nonantimicrobial Drugs for Prophylaxis

- Bismuth subsalicylate (BSS) (Pepto-Bismol).
- Studies from Mexico have shown this agent (taken daily as either 2 oz of liquid or two chewable tablets four times per day) reduces the incidence of TD from 40% to 14%.
- BSS commonly causes blackening of the tongue and stool and may cause nausea, constipation, and rarely tinnitus.
- BSS should be avoided by travelers with aspirin allergy, renal insufficiency, and gout, and by those taking anticoagulants, probenecid, or methotrexate.

Nonantibiotic Prophylaxis

- Caution should be used in administering BSS to children with viral infections, such as varicella or influenza (Reye syndrome).
- BSS is not recommended for children <3 years of age. Studies have not established the safety of BSS use for periods >3 weeks.
- The use of probiotics, such as Lactobacillus GG and *Saccharomyces boulardii*, has been studied in the prevention of TD in limited numbers of subjects. Results are inconclusive
  - ?partially because standardized preparations of these bacteria are not reliably available.

Antibiotic Prophylaxis

- For high risk patients (eg immunosuppressed)
- Increasing resistance is problematic with Septra, doxycyline, quinolones
  - Rifaximin 200 BID with lunch / dinner
  - Cipro 250 BID

DuPont H. Bacterial Diarrhea. *NEJM* 2009;361:1560-1569

Travelers' Diarrhea - Vaccine

- New oral,inactivated cholera vaccine, Dukoral approved in Canada in 2003
- Killed whole cell Vibrio cholerae and non-toxic, recombinant toxin B-subunit
  - Toxin B subunit gives moderate protection against diarrhea from ETEC

Cholera and ETEC

- Overall efficacy approx. 60 - 80% against cholera
- Many ETEC strains produce toxin similar to cholera toxin so some protection with Dukoral
  - Approx. 50% effective against ETEC and as ETEC do not cause all travelers' diarrhea overall protection of 25%

Dukoral

- Not widely recommended
- Most travelers' diarrhea self-limited
- Might lead to false sense of security
- Consider in:
  - Chronic illness
  - Increased risk for TD (gastric hypochlorydria, young children >2)
  - immunosuppressed

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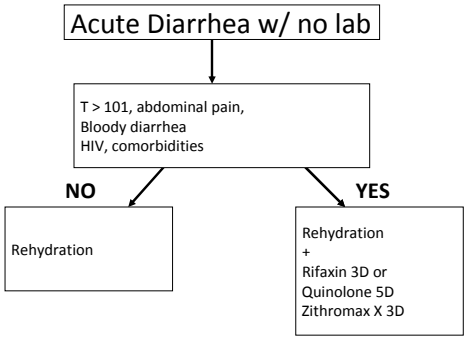
DUKORAL



Adapted from: Figure 14-1 and 14-6, 559. Current Medical Diagnosis and Treatment, 2008

Therapy for Diarrhea

- With sugar and salt (raw sugar or molasses can be used instead of sugar)
  - 1 liter (.3 gallon) of clean water
  - 1/2 tsp SALT
  - 8 level tsps sugar or substitute
  - Need 3 L/ D, drink q5 min
  - BRAT diet: Bananas, rice, applesauce, toast

Werner D. Where There is No Doctor: A Village Healthcare Handbook for Africa, p161.

DuPont H. Bacterial Diarrhea. *NEJM* 2009;361:1560-1569

Persistent Diarrhea

- Suggest protozoan parasites as the etiology.
- Parasites as a group are the pathogens most likely to be isolated from patients with persistent diarrhea
- Parasites may also be the cause of persistent diarrhea in those already appropriately treated for a bacterial pathogen.
- Intestinal parasites include *Giardia* (most common) as well as *Cryptosporidium parvum*, *Entamoeba histolytica*, *Isospora belli*, *Microsporidia*, and *Dientamoeba fragilis*, as well as *Cyclospora cayetanensis*.

Giardia

- Suspicion for giardiasis should be particularly high when upper gastrointestinal symptoms predominate.
- Untreated, symptoms may last for months even in the immunocompetent host.
- The diagnosis can often be made through stool microscopy.
- Given the high prevalence of *Giardia* in persistent travelers diarrhea, empiric therapy is a reasonable option in the appropriate clinical setting after negative stool microscopy and in lieu of duodenal sampling

CDC Yellow Book 2010

Persistent Diarrhea

- C. difficile
- Tropical sprue
- Brainerd diarrhea

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Postinfectious Phenomena

- At least 3 months of symptoms, with an onset of symptoms at least 6 months previously.
- Recurrent abdominal pain or discomfort associated with two or more of the following features:
  - Improvement with defecation
  - Onset associated with a change in the frequency of stool
  - Onset associated with a change in form (appearance) of stool

Conclusion

- Acute Travelers Diarrhea
  - Common - bacterial
  - Avoidance is key
  - Supportive care
  - Self initiated antibiotics
- Persistent Diarrhea
  - Parasitic
  - Postinfectious

Cutting the Crap on CAP

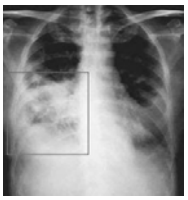
Natasha Press
April 1, 2011.

Community Acquired Pneumonia (CAP)

∗Adults

∗Outpatient setting

∗Walk-in pneumonia



Objectives:

∗Review the IDSA guidelines

∗Choice of empiric therapy

∗Drug resistance

∗Duration of therapy

IDSA guideline: a brief review

- For outpatients:
- no risk factors ➔
  - macrolide (doxycycline)
- comorbidity ➔
  - flouroquinolone
  - beta-lactam + macrolide

IDSA 2007. www.idsociety.org

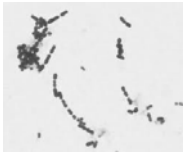
IDSA guideline: a brief review

- Inpatients:
  - flouroquinolone
  - beta-lactam + macrolide
- ICU:
  - beta-lactam + quinolone (or azithromycin)

IDSA 2007.

Walk-in pneumonia

- Common etiologies:
- *Streptococcus pneumonia*
- *Mycoplasma pneumoniae*
- *Haemophilus influenzae*
- *Chlamydophila pneumoniae*
- Respiratory viruses



IDSA 2007

Natasha Press

Walk-in pneumonia

- BTS guidelines:
- Recommend amoxicillin because:
- low rates of mycoplasma pneumonia (low mortality rate and affects mostly younger patients)

Thorax 2009; 64 (suppl III)

Do the guidelines work?

∗Observational study

∗N = 55,000

∗65% treated according to guidelines

∗↓hospital mortality (OR 0.7)

∗↓ length of stay (OR 0.6)

∗Conclusion: results "support compliance with guidelines"

Arch Intern Med. 2009:169.

Following guidelines

∗Improvement of a clinical parameter:

∗↓ mortality

∗↓ hospitalization

∗↓ length of stay

∗NNT: 3-20 (depends on the study)

Guidelines aren't perfect

∗1998→ sparfloxacin, grepafloxacin

∗2000→ trovafloxacin

∗2003→ gatifloxacin

∗2007 ....

Even when the guidelines work...

- Macrolides + Calcium channel blockers (CCB) → hypotension/shock
- 7000 patients > 65 years old
- On a CCB and admitted to hospital with ↓BP
- Erythromycin OR 5.8
- Clarithromycin OR 3.7
- Azithromycin (no inhibition of cytochrome P450)

CMAJ Jan 17, 2011.

Drug resistance

∗Penicillin-resistant SP:

∗Age > 65

∗Recent Abx use

∗EtOH

∗Medical comorbidities

∗Day care

∗Macrolide-resistant SP

∗Previous use of a macrolide

∗Azithromycin OR 9.9

∗Clarithromycin OR 3.9

∗Non-macrolide OR 2

Clin Infect Dis 2005.

Natasha Press

Local Resistance

Providence Health (Hospital, 2010)	BC BIO (Community, 2007)
Strep pneumo:	Strep pneumo:
R to penicillin 14%	5%
R to moxifloxicin 0%	2%
R to macrolides 42%	27%
H. flu: R to amp 11%	16%
Moraxella: R to amp 95%	All

Personal communication, Dr Marc Romney

Discordant therapy

- What is the impact of *in vitro* resistance on clinical outcomes of CAP?
- Resistance to macrolides ➔ clinical failure
- Resistance to cipro/levo ➔ clinical failure
- Beta-lactams – not as straightforward
- If appropriate drugs & doses are used ➔ doesn't lead to treatment failure

NEJM 2002. Clin Infect Dis 2006.

Discordant Therapy

- A lot of azithromycin use
- Shouldn't there be more clinical failures?
- Underreporting?
- Higher concentrations of macrolides within tissues overcome the *in vitro* resistance?
- Anti-inflammatory effect of macrolides?

Duration of antibiotic therapy

- IDSA guidelines:
- Minimum of 5 days
- Afebrile for 48-72 hours
- ≤ 1 CAP-associated sign of clinical instability

Duration of Abx: 5-14 days

- Meta-analysis 15 RCTs
- Mild-moderate CAP
- ≤ 7 days versus longer
- 4 antibiotic classes:
- macrolide, quinolone, beta-lactam, ketolide
- No difference in clinical outcome
- No difference in bacteriologic eradication

American Journal of Medicine. Sept 2007.

Duration of Abx: < 5 days?

- Netherlands
- Amoxicillin x 3 days ➔
- 2/3 of patients improved
- In those patients, no benefit to taking additional abx

BMJ 2006:332.

Natasha Press

Persistence of Symptoms

- N=134 ambulatory patients with CAP
- 3-14 days: Resolution of cough and fatigue
- 28 days: 1/3 of patients still had one symptoms (cough, fatigue, dyspnea)
- Not an indication to extend abx

Respir Med. 1998.

Abx duration: azithromycin

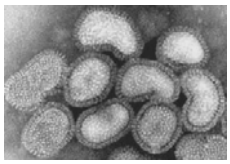
- Azithromycin x 5 days
- Azithromycin x 3 days = clarithromycin x 10 days
- Azithromycin 2g single dose (microspheres)
  = clarithromycin x 7 days
  = levofloxacin x 7 days

Abx duration

- Azithromycin 2 g x one dose
- Azithromycin 3-5 days
- Other abx 5 days minimum

Pneumonia isn't only bacteria

- Influenza
- Other respiratory viruses



Prevention

- Flu shots
- Pneumovax
- Smoking cessation
- Hand/respiratory hygiene (for viral)

Conclusion: CAP

- Guidelines are good, but not perfect
- Antibiotic choice depends on:
- Individual e.g. concurrent medications
- Population e.g. local resistance rates
- Duration of therapy: 5 days
- Discordant therapy: still figuring it out, but avoid abx reported as resistant
- Consider viral causes

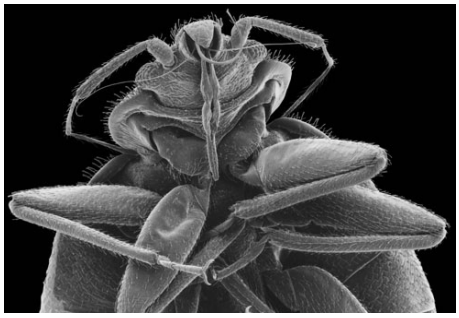
Bedbugs - More than Just a Nuisance?

V. Montessori MD, FRCPC
Division of Infectious Diseases
St. Paul's Hospital/
University of British Columbia

Bedbugs

- What is a bedbug?
- Bedbug bites
- Bedbug avoidance and control
- Medical complications of bedbugs

What is a Bedbug?



What is a Bedbug?

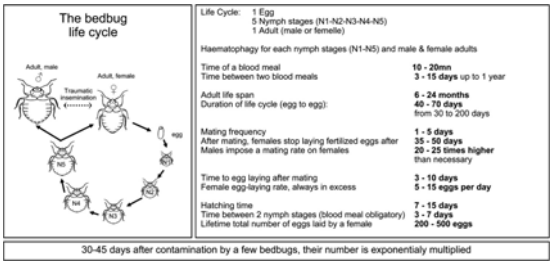
What is a Bedbug?

- Bedbugs are brown and flat hematophagous insects
- Two main species: Cimex lectularius and Cimex hemipterus
- Feed on humans and/or domestic animals, and recent outbreaks have been reported in occidental countries.

What is a Bedbug?

- Bedbugs fear light and are generally active in the dark.
- They hide in any small dark place, such as bedclothes, mattresses, springs, bed frames, cracks, crevices, and wallpaper.
- They emit an easily recognized, offensive odor caused by an oily secretion produced by special glands

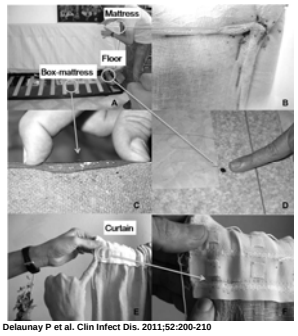
Life cycle of the bedbug (Cimex lecturarius or Cimex hemipterus).



Delaunay P et al. Clin Infect Dis. 2011;52:200-210

Clinical Infectious Diseases

Hiding places of Bedbugs (Cimex lecturarius or Cimex hemipterus).

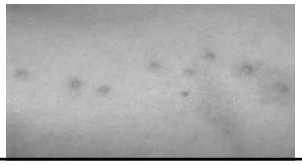


Delaunay P et al. Clin Infect Dis. 2011;52:200-210

Clinical Infectious Diseases

Bedbug Bites

- The common dermatological presentation of bites is an itchy maculopapular wheal
- Urticarial reactions and anaphylaxis can also occur.

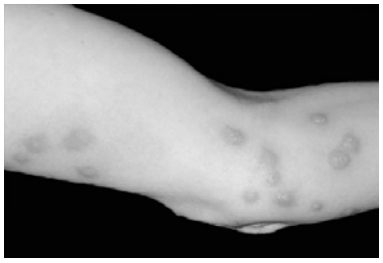


Bedbug Bites

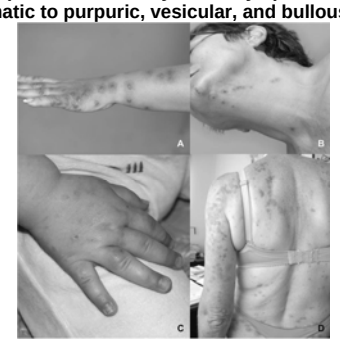
- Hosts are usually bitten at night.
- Because bedbug saliva contains anesthetic compounds, bites are painless and usually not felt until several hours later.
- Other compounds are also injected: anticoagulant factors (eg, factor-X inhibitor), vasodilatory compounds (such as nitric oxide), and proteolytic enzymes (eg, apyrase) lead to local hypersensitivity reactions

Bedbug Bites

- Bites may also become infected



Presentation of bedbug (Cimex lecturarius or Cimex hemipterus) bites: forms vary from asymptomatic or pauci-symptomatic to purpuric, vesicular, and bullous lesions.



Delaunay P et al. Clin Infect Dis. 2011;52:200-210

Clinical Infectious Diseases

Bedbug Avoidance

- Before a Trip
- During a Trip
- After a Trip

Before a Trip

1. Learn about bed bugs and their behaviour. Bedbugger.com
2. Consult The Bed Bug Registry or Trip Advisor re bed bug infestations where you will be staying

   may not be reliable since they are not corroborated by an independent third party
3. Bring clear or opaque plastic bags that can be properly sealed for worn clothing / laundry and to wrap your luggage

During a Trip

1. Inspect your room.

   Check for feces and eggs in the following: mattress and box spring seams, creases, and folds, headboard, cushions side table drawers, chairs, furniture, picture frames, radios, TVs, phones, clocks, baseboards, window and door casings, cracks and crevices
2. Don't unpack your clothes from your suitcase. Place your luggage in the bathtub or shower stall. If there is no washroom adjacent to your room, place your luggage in a large clear plastic bag and keep it away from the bed and the floor.

During a Trip

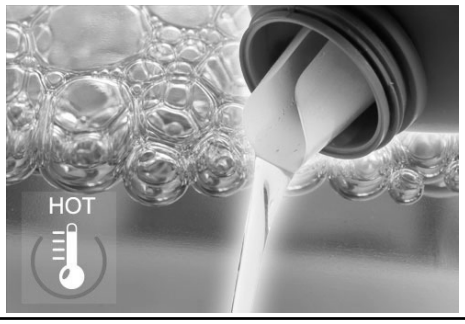
During a Trip

3. Place all clothes for laundry (including your pajamas) in a tightly sealed plastic bag to contain potentially affected clothing. To avoid escaping bed bugs back home, sort laundry in colours and place in separate plastic bags so it's easy to load the washing machine.

After a Trip

1. Place your luggage in an isolated part of the house, such as your garage or porch. Thoroughly inspect the suitcase and all articles of clothing that are not sealed in a plastic bag.
2. Wash your clothes using the hottest machine setting (washing at high temperatures will kill the eggs). Some fabrics will not be able to withstand hot water, so dry-cleaning may be an option. Don't forget to warn the dry cleaner about a possible bed bug problem.
3. Dry your clothes at the hottest setting for at least 45 minutes.

After a Trip



After a Trip

- Items that can't be washed can be heated or frozen.
  - If using extreme heat, the item has to be exposed to a minimum of 45ºC for at least two hours.
  - If you freeze the item, it should be at a minimum of -5ºC for at least 5 days
- If you suspect that you brought back bed bugs with you, contact a pest control company for a consultation.

Bedbugs - Vectors of Infectious Disease?

- Bedbugs have been suspected of transmitting infectious agents
- Over 40 microorganisms have frequently been considered strong candidates
- Literature evidence level for disease transmission by bedbugs is very heterogeneous and sometimes incomplete.

Possible Bedbug Transmissions

- Coxiella burnetti (Q fever)
- Trypanosoma cruzi
- Hepatitis B

Clin Infect Dis. (2011) 52 (2): 200-210.

Bedbugs and MRSA

- Recent report of Vancomycin Resistant Enterococci and CA-MRSA isolated from several bedbugs from patients admitted to St. Paul's
- No evidence of transmission of bacteria to patient

Lowe C and Romney M. EID 2011 (in press)

Anemia and Bedbugs

- 60 year old man with severe anemia (Hgb 52)
- Extensive investigation for blood loss negative
- Severe infestation with bedbugs
- Concluded that bedbugs cause of anemia

Pritchard and Hwang CMAJ 181 (5): 287. (2009)

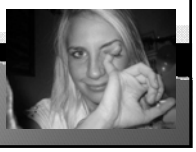
Conclusion

- Bedbugs common and difficult to avoid
- Literature supporting bedbugs as vectors of infectious diseases is incomplete
- Severe infestations cause significant dermatitis, possibly anemia

Natasha Press

Otitis and Conjunctivitis – "Ears looking at you, Kid"

Natasha Press
April 1, 2011.



Acute Conjunctivitis: Objectives

- When to swab
- When to treat
- What to treat with
- When to call ID

The average family doctor

- Swabs them if it's goopy icky and there's a reason (infants, immunosuppressed, hx of eye disease)
- Gives a prescription and tells them not to fill it unless he calls
- Treats contact lens wearers with poor hygiene (e.g. leave lenses in for 3 days)
- Gentamicin drops qid
- Fucithalmic (fucidin) drops bid
- Infants: erythromycin ointment

When to swab

- Red flags for red eye: pain, photophobia, blurred vision, contact lens wearer
- Conjunctivitis: infectious vs. non-infectious
- Infectious: viral vs. bacterial
- Hard to tell the difference

(wrong more than half the time)

Rietveld RP. BMJ 2004; 329: 206-10.

When to swab

- Viral
- Adenovirus
- +/- URTI
- +/- 2nd eye involvement within 48 hours
- Gritty, watery
- Highly contagious

- Bacterial
- Staph aureus
- (kids: pneumococcus, H. flu, Moraxella)
- May be unilateral
- Purulent discharge
- Highly contagious

When to swab

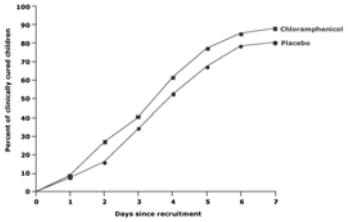
- Most cases diagnosed on history/physical
- Not done routinely

- In unusual host (e.g. neonate, STI)
- Or unusual symptoms (e.g. severe)

Natasha Press

When to treat

- Placebo-controlled trial, children, UK
- Placebo-group: 80% better within 7 days
- Chloramphenicol group: 85%
- NNT: 22



Rose P et al. Lancet 2005; 366: 41

Antibiotic eye drops

- Bugs and Drugs:
- Adults:
- Polymyxin B gramicidin eye drops (lysporin)
- Gentamicin 0.3%
- Kids:
- Bacitracin-Polymyxin B eye drops
- Erythromycin 0.5% eye ointment
- Sanford:
- Gatifloxacin 0.3%
- Levofloxacin 0.5%
- Moxifloxacin 0.5%
- Polymixin B-TMP (Polytrim)

www.bugsanddrugs.ca

What's usually prescribed?

- Popular eyedrops:
- Garasone (gentamicin 0.3% + betamethasone)
- Pentamycetin (chloramphenicol 0.25%) +/- HC

Antibiotic eye drops

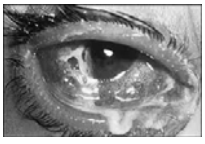
- Avoid topical glucocorticoids
- For viral conjunctivitis: artificial tears, topical antihistamines

When to call ID

- I received a phone call …
- Unilateral conjunctivitis
- Swabbed because of concern of ?MRSA
- Swab – *Neisseria meningitides*

When to call ID

- Usually never
- Hyperacute bacterial conjunctivitis
- Due to Neisseria species
- Immediate ophthalmologic referral
- Needs systemic and topical therapy



Natasha Press

The Case

- Conjunctivitis had resolved
- Further history: recent headache
- Lumbar puncture, blood C&S
- IV ceftriaxone x 1 dose followed by po cipro x 5 days

Acute conjunctivitis: summary

- Viral more common than bacterial
- Swab if unusual host or eye sx
- Antibiotic eye drops shorten duration of sx (NNT 22)
- Eye drop choice: inexpensive and least toxic
- When to call ID: systemic therapy required (e.g. Neisseria, chlamydia)

Acute Otitis Externa: Objectives

- 1. When to swab
- 2. When to treat
- 3. What to treat with
- 4. When to call ID

Acute Otitis Externa (AOE)

- 1. Assess and treat the pain (RCT)
- 2. Rule out other causes of otalgia (Observational)
- 3. Assess for factors that modify management (Observational)
- 4. Use topical preparations for uncomplicated AOE

American Academy of Otolaryngology guidelines 2007.

When to swab

- Empiric treatment
- Almost all bacterial
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*

When to treat

- Antibiotic drops (RCT, meta-analysis)
- NNT = 2

Natasha Press

What to treat with

- Antiseptic? Antibiotic? Corticosteroid? Combination?

Systematic Review of 20 Randomized Trials

- No difference in clinical outcomes for:
- Antiseptic vs. abx
- Quinolone vs. non-quinolone
- Steroid/abx vs. abx alone
- In general 65-90% had resolution within 7-10 days

Topical treatment

- High concentration of abx >100x
- May result in less selective pressure for resistant organisms

Which drops to choose

- Mild: acetic acid/steroid
  - 2.0% acetic acid (Vosol) +/- steroid qid
- Moderate: abx/steroid
- *S. aureus* and *P. aeruginosa* coverage
- Limited allergic reaction
- Easy dosing

www.uptodate.com Grade 2B (weak, RCT with limitations)

Which drops to choose

- $$$Cipro HC bid
  - ciprofloxacin + hydrocortisone + alcohol
- $$$Ofloxacin 0.3% bid
  - ofloxacin
- $$Aminoglycoside qid
  - ophthalmic preparation
- $Cortisporin Otic qid
  - polymixin B + neomycin + hydrocortisone + sulfuric +alcohol

www.uptodate.com Grade 2B (weak, RCT with limitations)

Other recommendations

- Aural toilet
- Abstain from water sports
- Limit ear devices

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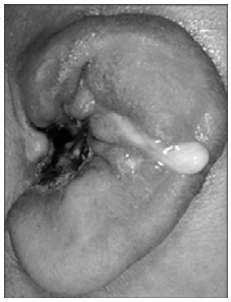
When to call ID

- Malignant otitis externa
- Osteomyelitis



American Family Physician 2006 Nov 1.

Conclusion: Acute Otitis Externa

Recommendation	Evidence	Comments
Clear debris/cerumen Check tympanic membrane	Standard of care	
Relieve pain with analgesics	Randomized controlled trial	Acetaminophen, NSAIDS
Mild: acidifying drops Moderate: abx drops	Standard of care	
Counsel patient about prevention	Standard of care	Dry canals after swimming Avoid cotton swabs
Systemic therapy if severe disease/immunocompromise	Expert opinion	Consider malignant otitis externa

Practical Advise for the use of Systemic steroids from a dude that uses steroids

Mike Kolber

DTC April 1, 2011

Steroids Overview

- Indications
- Oral vs. IV
- Dosages
- Short term uses
- Long term uses
- Risks

What do the following patients have in common?

- 30 yo with asthma attack not improving with ↑B AGO and ↑inhaled steroids
- 82 yo female with proximal muscle weakness, headache "hurts to wear my hat" and ESR = 88
- 78 yo w COPD with 5 days of progressive dyspnea despite increasing inhalers
- 23 yo with crohn's presenting with 1 week history of abd pain, diarrhea, abdominal distention
- 3 year old boy with barky cough that was "much worse before we drove to the ED"

What do all these dudes have in common?

Practical Steroid Tips for primary care providers

Evidence

+ experience

+ Common sense

+ patient education

= steroid use

Use them if you need them!

- Good evidence for systemic steroids:
  - Asthma exacerbation
  - AECOPD
  - IBD
  - PMR / Temperal Arteritis
  - Croup
  - Bells palsy
  - Many others: derm, renal, MS, ICH, ITP, AIHA
- Sometimes we use but w/o great evidence:
  - Anaphylaxsis

Rule #1 Oral steroids rule!

- Use oral unless…
  - Your patient's GI tract does not work, NPO or vomiting
  - Your patient is too busy yapping on the phone to your MLA about how long you waited in ER
- No difference in MS flares[1], AECOPD[2]

[1] *Burton, Cochrane Reviews 2009,CD006921*
[2] *de Jong, Chest 2007;132;1741-1747*

Please: start with one 50 mg pill

- If I'm sick and get 12 x 5 mg pills, I will:
  - Spit them back and tell you to shove it
- They are not feeling well → minimize additional insults

Kolber, personal communication Apr. 1, 2011

Rule # 2
Acute diseases = short term steroids

- Acute asthma: 3-14 days
- AECOPD: 5 – 10 days
- Bell's: 5-10 days
- Croup: 1 dose

No tapering if use < 2 weeks

- Remember rule #2
  - acute diseases or flares = short term steroids

Myth #1
IBD flare is a short term disease

- Do not treat for one week and stop!
- No RCTs of steroid taper regimens in IBD
- *"Further info required to determine optimal duration of treatment and tapering protocol to maximize the efficacy of treatment with corticosteroids"*
- What I do: 50 mg x 1-2 weeks (until better) then ↓ to 40 mg then 5 mg / week until ~10 - 20 mg, then ↓ by 2.5 mg / week

Steroid Prescribing in IBD
Bonus point

- Hand that writes Rx for steroids in IBD flare checks off the req for stool C & S, O & P, C. DIFF

Temperal arteritis / PMR ≠≠ a short term disease

- Once well, taper by 5 mg until 10 mg and then 1 mg per month
- Median treatment duration = 2 years

Too rapid taper…

1) Disease worsens
2) Adrenal insufficiency
   - nausea, vomiting, abdominal pain, weakness, confusion or coma, hypotension

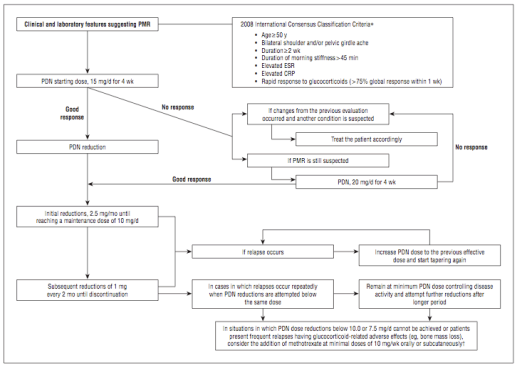


Figure 2. Proposed therapeutic algorithm for the treatment of polymyalgia rheumatica (PMR). PDN indicates prednisone. *The 2008 International Consensus Classification Criteria[47] are awaiting prospective validation. †This recommendation is not based on the data analyzed in the present review; rather, it relies on evidence that methotrexate administered at PMR onset can reduce glucocorticoid-related adverse effects, especially bone mass loss,[48] and suggestions and reports from experienced investigators.[1,49] Glucocorticoid-related adverse effects, including bone mass loss, should be managed according to local policies and guidelines. CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate.

Croup and Steroids

- Give croup kids steroids[1,2]
  - No need for 2nd dose of dexa
  - Oral = IM[2]

[1] *NEJM 2004; 351(13): 1306*
[2] *Cochrane Reviews 2011 : CD001955*

Risk of short term steroids

Risks of LT Steroids

- Depends on the three Ds:
  - **D**isease: IBD > others[1]
  - **D**ose
  - **D**uration

[1] *Ann Rheum Dis 2009;68:1833*

Major side effects associated with corticosteroid therapy

Dermatologic and soft tissue	**Renal**
Skin thinning and purpura	Hypokalemia
Cushingoid appearance	Fluid volume shifts
Alopecia	**Genitourinary and reproductive**
Acne	Amenorrhea/infertility
Hirsutism	Intrauterine growth retardation
Striae	**Bone**
Hypertrichosis	Osteoporosis
Eye	Avascular necrosis
Posterior subcapsular cataract	**Muscle**
Elevated intraocular pressure/glaucoma	Myopathy
Exophthalmos	**Neuropsychiatric**
Cardiovascular	Euphoria
Hypertension	Dysphoria/depression
Perturbations of serum lipoproteins	Insomnia/akathisia
Premature atherosclerotic disease	Psychosis
Arrhythmias with pulse infusions	Pseudo tumor cerebri
Gastrointestinal	**Endocrine**
Gastritis	Diabetes mellitus
Peptic ulcer disease	Hypothalamic-pituitary-adrenal insufficiency
Pancreatitis	**Infectious disease**
Steatohepatitis	Heightened risk of typical infections
Visceral perforation	Opportunistic infections
	Herpes zoster

UpToDate

Long term steroids

- Advise before
- Visit:
  - Check BP
  - Weight
  - Ask: infections, vision (sugar or cataracts), GI upset, acne
- Labs:
  - CBC, Lytes, creatinine
  - FBS
- Adjuvant Therapy:
  - Calcium, Vit D, bisphosphonates
  - PPI for gastroprotection if needed

Steroid induced osteoporosis

- IBD patients have ↑bone disease
- Guidelines: BMD if steroids > 3/12 at > 7.5 mg / day *and* start bisphosponates[1]
- Bisphosphonates: ↑BMD, but no ↓ fractures[2]

[1] *CMAJ 2010. DOI:10.1503/cmaj.100771*
[2] *J Crohn's Colitis 2008; 2:202*

Steroid Summary

- Use them if you need them
- Use oral
- Prednisone = 50 mg and 5 mg tablets
- Short term diseases = ST steroids
- No tapering if treatment < 2 weeks
- IBD, PMR / TA are not short term diseases
- Educate about potential adverse events

Steroid Success!

Bill Honer

Antipsychotics as antidepressants - anti-intuitive?

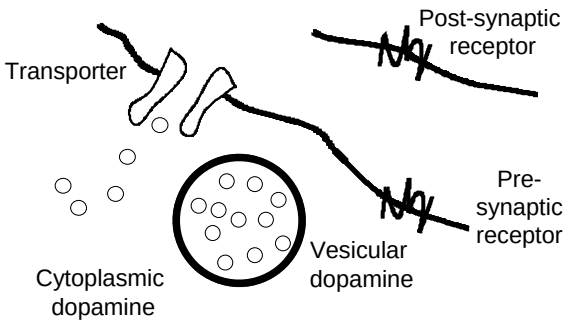
Disclosure 2010-2011

- Consultation/Advisory Boards: In-Silico (unpaid), Canadian Agency for Drugs and Technology in Health, Fasken Martineau DuMoulin LLP
- Grants: Canadian Institutes of Health Research
- Honoraria/travel: Canadian/European College of Neuropsychopharmacology, National Institute of Mental Health, Rush University, Hong Kong College of Psychiatrists, U Calgary, Cdn Academy of Psychiatry & Law, IoP-Chinese Academy Sciences, BC Psychiatric Association

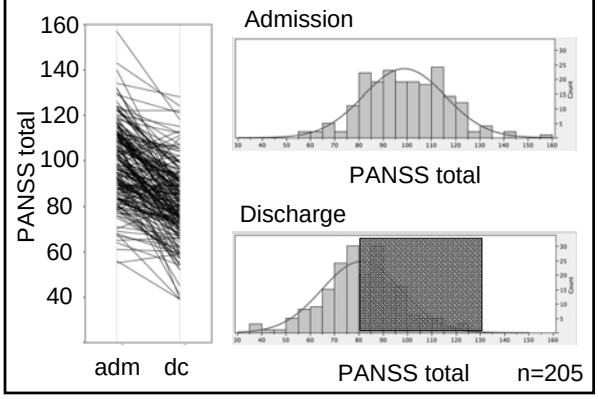
Objectives

- Review the mechanism of illness in schizophrenia
- Discuss antipsychotic drug effects in the context of mechanism
- Describe the goals and effectiveness of antipsychotic drug treatment
- Consider a rationale for broader effecs of antipsychotic drugs
- Review evidence for using antipsychotic drugs in mood disorders

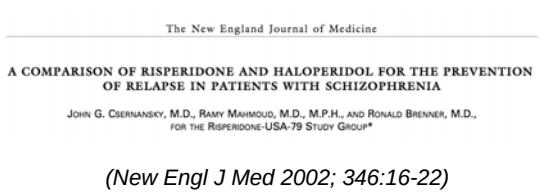
Synaptic terminal and dopamine



Clozapine: limitations



Relapse in chronic schizophrenia


The New England Journal of Medicine

A COMPARISON OF RISPERIDONE AND HALOPERIDOL FOR THE PREVENTION OF RELAPSE IN PATIENTS WITH SCHIZOPHRENIA

JOHN G. CSERNANSKY, M.D., RAMY MAHMOUD, M.D., M.P.H., AND RONALD BRENNER, M.D., FOR THE RISPERIDONE-USA-79 STUDY GROUP*

(New Engl J Med 2002; 346:16-22)

Bill Honer

Relapse in chronic schizophrenia

- Relapse
- Hospitalization
- Increase in level of psychiatric care
- Increase in total PANSS score of 25%
- Deliberate self injury
- Suicidal or homicidal ideation
- Violent behaviour
- Substantial clinical deterioration (“Much worse”)

BMJ

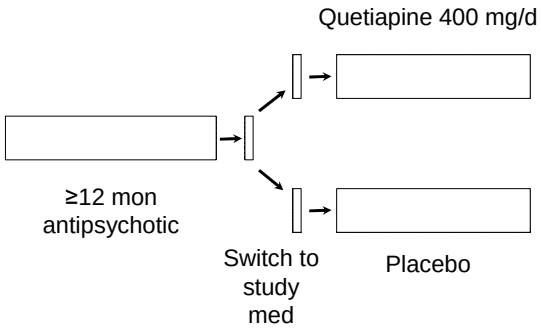
RESEARCH

Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial

Eric Y H Chen, professor,[1] Christy L M Hui, research fellow,[1] May M L Lam, clinical assistant professor,[1] Cindy P Y Chiu, clinical assistant professor,[1] C W Law, associate consultant,[2] Dicky W S Chung, consultant,[3] Steve Tso, associate consultant,[4] Edwin P F Pang, associate consultant,[1] K T Chan, medical officer,[1] Y C Wong, associate consultant,[5] Flora Y M Mo, associate consultant,[1] Kathy P M Chan, associate consultant,[1] T J Yao, associate professor,[6] S F Hung, consultant,[1] William G Honer, professor[7]

Cite this as: *BMJ* 2010;341:c4024

Relapse in first episode psychosis



Conclusions: antipsychotic drugs

- The acute phase of illness in schizophrenia is related to increased dopaminergic neurotransmission
- Antipsychotic drugs are effective in reducing the severity of positive symptoms of psychosis
  - A full remission of psychotic symptoms can be obtained in first episode psychosis
- Antipsychotic drugs are effective in reducing the likelihood of relapse

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Atypical antipsychotics and bipolar?

REVIEW

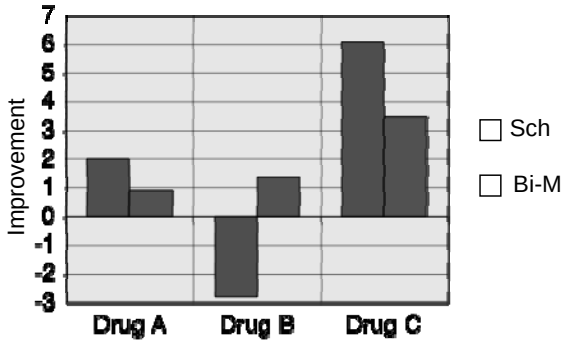
Toward Convergence in the Medication Treatment of Bipolar Disorder and Schizophrenia

Leslie Citrome, MD, MPH, Joseph F. Goldberg, MD, and Stephen M. Stahl, MD, PhD

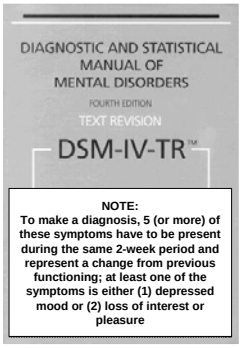
The introduction of SGAs has led to the observation that they have not only a lower propensity toward extrapyramidal side effects and a lower risk of tardive dyskinesia, but also a wider spectrum of action compared to FGAs.[4]

(Harv Rev Psychiatry 2005;13:28–42.)

Medications: Schizophrenia-mania



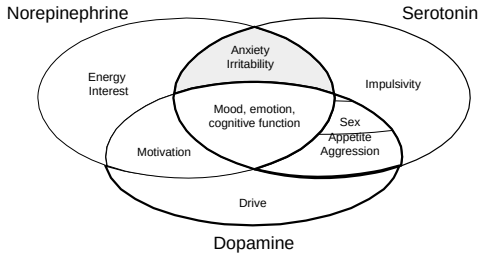
Core Symptoms of Depression



- Depressed mood
- Apathy/loss of interest/pleasure
- Weight/appetite changes
- Sleep disturbance
- Psychomotor agitation/retardation
- Fatigue
- Guilt/worthlessness
- Concentration/ decision making
- Suicidal ideation

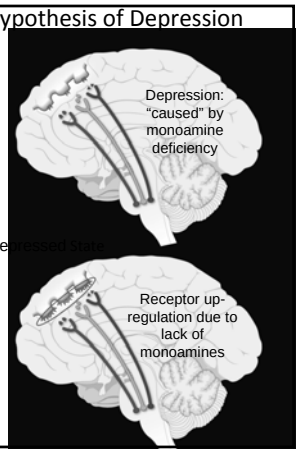
(DSM-IV TR, 2000)

Neurotransmitters Involved in Regulating Mood



(Adapted from Stahl SM. Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 2000:152)

Monoamine Receptor Hypothesis of Depression



(Adapted from S. Stahl, Essential Psychopharmacology, 2005)

Review of Antidepressant Pharmacology

- Inhibition of monoamine oxidase (A +/- B)
  - MAOIs & RIMA (moclobemide)
- Presynaptic inhibition of NT transporters
  - TCAs, SSRIs, SNRIs, NDRI (bupropion)
- Inhibition of serotonin transporters + antagonism of postsynaptic serotonin receptor(s)
  - SARI (Trazodone)
- Antagonism of α_2 autoreceptors and antagonism of postsynaptic $5HT_{2A}$ receptors
  - Mirtazapine

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Receptor Binding Profiles

Receptor	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
D1	387	189	58	712	61	30
D2	0.95	431	72	567	5	4
D3	1.0	473	49	839	14.1	7.3
5HT1A	5.6 ☼	105 ☼	2063	431 ☼	427	76 ☼
5HT2A	8.7	5.4	2.0	101	0.17	0.3
5HT2C	22.4	17	6.8	2502	35	13
α1	25	1.6	109	22	5	18
H1	29.7	1.2	2	11	15	43
M1	6776	14	24	858	>10,000	>10,000
5HTT	1082	1624	3676	>10,000	>10,000	112
NET	2093	3168	>10,000	>10,000	>10,000	44

☐ Antidepressant pharmacology properties ☼ Partial agonist

Data represented as K_i (nM)

NIMH Psychoactive Drug Screening Program: http://pdsp.med.unc.edu/indexR.html

Receptor Binding Profiles

Receptor	Aripiprazole (Dehydro)	Clozapine (N-desmethyl)	Olanzapine (N-desmethyl)	Quetiapine (N-desalkyl)	Risperidone (9-hydroxy)	Ziprasidone (S-methyldihydro)
D1	--	14.3	203	--	41	--
D2	--	115.2	32	489	9.4	--
D3	--	153	>300	--	0.1	--
5HT1A	--	105 ☼	--	191 ☼	637	--
5HT2A	--	10.9	--	2.9	1.9	--
5HT2C	--	11.9	--	18.5	100	--
α1	--	105	--	37.5	2.5	--
H1	--	3.4	22	1.15	5.6	--
M1	--	67.6	--	38.3	>10,000	--
5HTT	--	317	--	>10,000	3717	--
NET	--	494	--	34.8	10,000	--

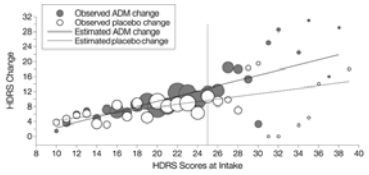
☐ Antidepressant pharmacology properties ☼ Partial agonist

Data represented as K_i (nM)

NIMH Psychoactive Drug Screening Program: http://pdsp.med.unc.edu/indexR.html

Antidepressant Drug Effects: Severity of Depression

- Objective: To estimate the relative benefit of medication vs placebo across a wide range of initial symptom severity in patients diagnosed with depression



ADM: Antidepressant medication; HDRS: Hamilton Depression Rating Scale

- Conclusion: The magnitude of benefit of antidepressant medication compared with placebo increases with severity of depression.

Fournier JC, et al., JAMA 2010:303:47-53

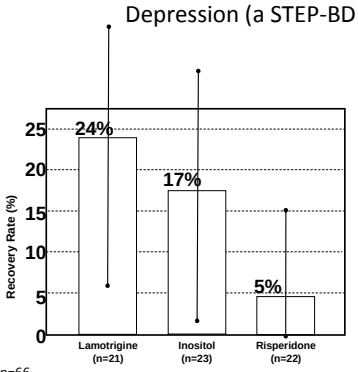
STAR*D: Current Antidepressant Treatments May be Inadequate

Level	Interventions	Remission Rate+	Cumulative Remission
Step 1 N=3,671	• CITALOPRAM	36.8%	36.8%
Step 2 N=1,439	• Switch: VEN / BUP / SER • Combine: BUP / BUS • Switch / Combine: CT	30.6%	56.1%
Step 3 N=390	• Switch: NOR / MIR • Augment: LI / T3	13.7%	62.1%
Step 4 N=123	• Switch: TCA / MIR+VEN	13.0%	67.0%

+ Quick Inventory of Depressive Symptomatology-Self Report ($QIDS\text{-}SR_{16}$) ≤ 5

(Rush AJ et al. Am J Psychiatry 2006;163:1905-17)

Lamotrigine, Inositol, or Risperidone for Bipolar Depression (a STEP-BD study)



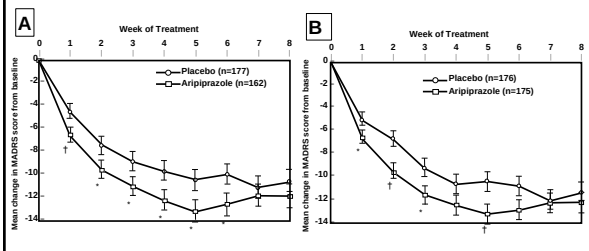
RCT, 16 weeks
Demonstrated failures to standard treatment
Primary outcome: durable 8 wk recovery

Symptoms and Functioning:
LTG superior to RSP
- Depression score
- CGI
- GAF

n=66

(Nierenberg A et al., Am J Psychiatry 2006;163:1519-1530)

Aripiprazole NOT for Bipolar Depression

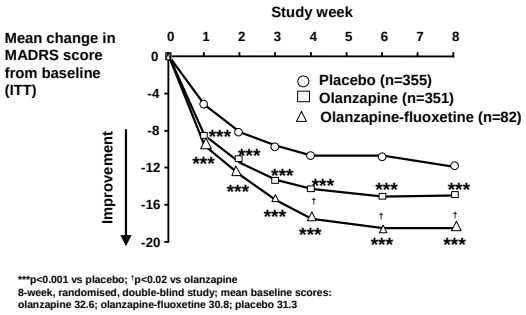


100 week extension: no protection against depressive relapse
Keck et al. J Clin Psychiatry 2007

(Thase et al. , J Clin Psychopharmacol. 2006;26:600-9)

Bill Honer

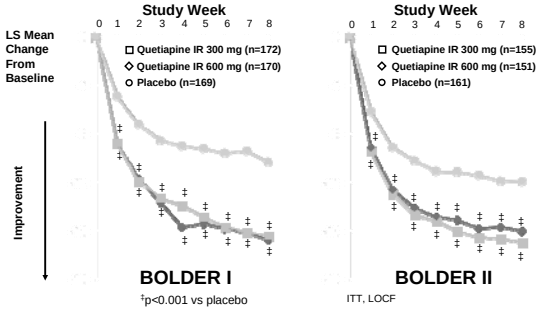
Olanzapine or OFC for Bipolar Depression



***p<0.001 vs placebo; †p<0.02 vs olanzapine
8-week, randomised, double-blind study; mean baseline scores: olanzapine 32.6; olanzapine-fluoxetine 30.8; placebo 31.3

(Tohen et al., Arch Gen Psychiatry. 2003;60:1079-88)

Quetiapine IR in Patients with Bipolar Depression: BOLDER I vs BOLDER II (MADRS total score)



‡p<0.001 vs placebo
ITT, LOCF

(Calabrese et al., Am J Psychiatry. 2005;162(7):1351-60; Thase et al, J Clin Psychopharmacol. 2006 ;26:600-9)

From Clinical Evidence to Clinical Guidelines

CANMAT/ISBD Guidelines for the management of bipolar disorder … 2009

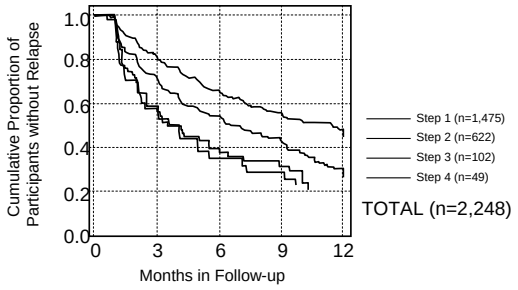
Bipolar Disorders
Volume 11, 225-255.

Recommendations for Pharmacological Treatment of Acute Bipolar I Depression

1st line	Lithium, lamotrigine, quetiapine (IR & XR), lithium or divalproex + SSRI, olanzapine + SSRI, lithium + divalproex, lithium or divalproex + bupropion
2nd line	Quetiapine + SSRI, divalproex, lithium or divalproex + lamotrigine, adjunctive modafinil
3rd line	Long list (no antipsychotics)
Not recommended	Gabapentin monotherapy, aripiprazole monotherapy

(Yatham et al., Bipolar Disorders 2009: 11: 225-255)

STAR*D: Relapse is Common in Antidepressant Responders



Relapse definition: QIDS-SR$_{16}$ ≥ 11 (corresponding to an HRSD17 ≥14)

(Rush AJ et al. Am J Psychiatry 2006;163:1905-17)

CANMAT Depression Guidelines 2009

SECTION I
Classification, Burden and Principles of Management

SECTION II
Psychotherapy alone or in combination

SECTION III
Pharmacotherapy

SECTION IV
Neurostimulation therapies

SECTION V
Complementary & Alternative Medicine Treatments

- Levels of evidence / treatment recommendations
- Question-Answer format
- Printed supplement of Journal of Affective Disorders, October 2009

(Patten et al. J Affect Disord 2009;117:S5-S14)

Bill Honer

Choosing an Antidepressant (monotherapy)

1st Line Monotherapy	▪ **Bupropion** ▪ **Citalopram** ▪ **Desvenlafaxine** ▪ **Duloxetine** ▪ **Escitalopram** ▪ **Fluoxetine** ▪ **Fluvoxamine** ▪ **Mirtazapine** ▪ **Moclobemide** ▪ **Paroxetine** ▪ **Sertraline** ▪ **Venlafaxine**
2nd Line	▪ **Quetiapine Extended Release** ▪ **Tricyclic Antidepressants**
3rd Line	▪ **Monoamine Oxidase Inhibitors**

*Other agents not available in Canada are omitted from this table.

(Lam et al J Affect Disord 2009;117:S26-S43)

Choosing an Add-on Strategy

1st Line	**Level 1 Evidence** • Lithium • Aripiprazole • Olanzapine • Quetiapine XR*	**Level 2 Evidence** • Risperidone
2nd Line	**Level 2 Evidence** ▪ Bupropion ▪ Mirtazapine/mianserin** ▪ Quetiapine IR ▪ Triiodothyronine	**Level 3 Evidence** • Other antidepressant
3rd Line	**Level 2 Evidence** ▪ Buspirone ▪ Modafinil	**Level 3 Evidence** • Stimulants

* Recently published data not included in the 2009 CANMAT MDD guidelines

**Not available in Canada (November, 2009).

(Lam et al. J Affect Disord 2009;117:S26-S43;
**Bauer et al. J Clin Psychiatry 2009;70:540; Nelson & Papakostas. Am J Psychiatry 2009;166:980-91)*

Summary

- Specific pharmacologic mechanisms targeting the mechanism of depression remain elusive.
- Standard antidepressants are frequently unsatisfactory
- Several atypical antipsychotics demonstrate receptor-based antidepressant effects
- Clinical trials in bipolar depression and major depressive disorder suggest a role for some atypical antipsychotics
- Treatment may be limited by high rates of non-persistence, related only in part to adverse effects

Overall conclusions

- Psychopharmacology aims to reduce the severity of target symptoms, and prevent relapses
- If response is poor, or relapse is frequent, reconsider the diagnosis, and extent of treatment adherence
- Always seek the best fit between patient, medication response and side effect profile
- In general, avoid polypharmacy where possible

Osteoporosis

The real skinny on brittle bones

Tina Korownyk, MD
DTC 2011

What we really care about…

- Who to screen?
- Who to treat?
- How to treat?

"Randomly" selecting who to screen?

- Multiple scores proposed for screening
- ORAI[1], SCORE, OST, BW, OSIRIS, ABONE,
- Roulette wheel decision tool
- Xray goggles
- What do Osteoporosis Canada Guidelines 2010 suggest?

1. CMAJ 2000;162(9):1289-1294.

2010 Guidelines
Indications for Measuring Bone Density

Older adults (age ≥ 50 yr)	Younger adults (age < 50 yr)
Age ≥ 65 yr (both women and men)	Fragility fracture
Clinical risk factors for fracture (menopausal women, men age 50–64 yr)	Prolonged use of glucocorticoids*
Fragility fracture after age 40 yr	Use of other high-risk medications†
Prolonged use of glucocorticoids*	Hypogonadism or premature menopause (age < 45 yr)
Use of other high-risk medications†	Malabsorption syndrome
Parental hip fracture	Primary hyperparathyroidism
Vertebral fracture or osteopenia identified on radiography	Other disorders strongly associated with rapid bone loss and/or fracture
Current smoking	
High alcohol intake	
Low body weight (< 60 kg) or major weight loss (> 10% of body weight at age 25 yr)	
Rheumatoid arthritis	
Other disorders strongly associated with osteoporosis	

*At least three months cumulative therapy in the previous year at a prednisone-equivalent dose ≥ 7.5 mg daily.
†For example, aromatase inhibitors or androgen deprivation therapy.

CMAJ. 2010 Nov 23;182(17):1864-73. Epub 2010 Oct 1 (**JAMA. 2007 Nov 28;298:2389-98)**

The Evidence

- 860 ♀, mean 62yrs, 59% Chinese, avg 13.6 yrs postmenopausal
- **Primary Outcome:** Risk factors that best predict osteoporosis in menopausal women
- **Findings:** An index based only on age and weight performs as good as, or better than other published indices based on larger numbers of risk
- Sens 91%, spec 45%

Osteoporos Int 2001;12: 699–705 .

The Evidence

- **Comments:** Subsequently, 4 systematic reviews from 2007-2010, with 36 studies and 72,315 postmenopausal women have supported these findings.[1-4]

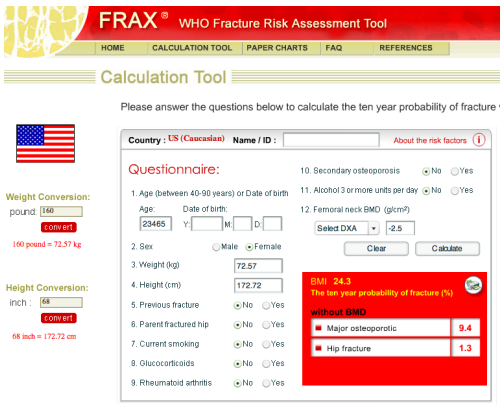
  Age - Weight (kg)
  - If > -5, increased risk of osteoporosis and BMD is warranted

  60 yrs – 60kg = 0 High Risk
  60 yrs – 100kg = -40 Low Risk

1) Osteoporos Int 2007;18:1177-1187. 2)Nelson HD, Haney EM, Chou R, et al. Rockville (MD): Agency for Healthcare Research and Quality (US); 2010 Jul. 3) Ann Intern Med. 2010;153 :99-111. 4) Osteoporos Int 2009;20:599-607.

Determining who to Treat

Mrs. Brittle is an 80 year old female with a T score of -2.0 (Osteopenia). She is also high risk for falling. She has 13 cats at home and finds she is tripping quite often. You have heard that looking at other factors than BMD might be the best predictor of who will benefit from treatment…



Facts and FRAX…

In older women, do simple models predict 10-year fracture risk as accurately as more complex models?

Prospective Cohort, 10 yrs follow up, 6252 ♀ ≥ 65 yrs

- **Primary Outcome:** Fractures
- **Findings:** Simple models (age + BMD) were as accurate as more complex FRAX models
  - No difference between FRAX with BMD and simple models with age and BMD alone in discriminating hip (P = .26), major osteoporotic (P = .51), and clinical fracture (P = .16).

Arch Intern Med. 2009;169(22):2087-94

10 Year Probability of a Fracture

SD	1	0	-1	-2	-2.5	-3	-4
Women							
AGE							
50	2	4	6	9	11	14	21
55	3	4	7	11	13	17	26
60	3	5	8	13	16	20	31
65	4	6	10	16	19	24	36
70	4	7	12	18	23	28	42
75	4	7	12	19	25	31	46
80	5	8	13	21	26	32	46
85	5	7	12	19	24	30	43

CMAJ 2002; 167: S1-S34

Ca – Friend or Foe?

- Ca+ (88% with Vitamin D) decreased fracture (any type) NNT 63 x 3.5 yrs[1]
- Ca+ alone just failed to reach statistical significance.
- Other studies suggest Ca+ alone does not decrease non-vertebral fracture and may actually increase hip fracture.[2,3]
- NNH for one MI 135 to 211 over 4 years. [4,5]

1) Lancet 2007;370:657-66. 2) Am J Clin Nutr 2007;86:1780–90. 3) Osteoporos Int 2008;19:1119–1123. 4) Ann Intern Med.2010;152:315-323. 5) BMJ. 2010;341:c3691.

Vitamin D – A Bright Light in a Dark Place?

- Fracture (19 trials)[1]: High dose (>400IU/day) Vitamin D reduced
  - Non-vertebral fractures 1.1%, NNT 93
  - Hip fractures by 0.6%, NNT 168
- Falls (5 trials)[2]: Reduced 7%, NNT 15
  - Proposed mechanism is improved muscle strength and postural stability.
- Study[1-3] doses varied but the most common was 800IU.

1)Arch Intern Med. 2009;169(6):551-561. 2) JAMA. 2004;291(16):1999-2006. 3) Arch Intern Med. 2007;167(16):1730-1737

Absolute (and relative) benefits of Bisphosphonate therapy over 5 years.

	Vertebral Fractures		Non-Vertebral		Hip Fracture	
	1º	2º	1º	2º	1º	2º
Alendronate[1]	2% (45%)	6% (45%)	ns	2% (23%)	ns	1% (53%)
Risedronate[2]	ns	5% (39%)	ns	2% (20%)	ns	1% (26%)
Etidronate[3]	ns	5% (47%)	ns	ns	ns	ns

1) Cochrane 2008; 1: CD001155. 2) Cochrane 2008; 1: CD004523. 3) *Cochrane Database Syst Rev. 2008(1):003376.*

10 Year Fracture Risk & Bisphosphonate Benefits (T-score = -2.5)

Age	All Fracture Risk[1]	Risk on Meds (30% RRR)[2,3]	Hip Fracture Risk (FRAX)*	Risk on Meds (50% RRR)[3]
50	11	8	1.2	0.6
60	16	11	1.7	0.9
70	23	16	3.5	1.8

Approximate values
*60kg women, No other risk factors

1) CMAJ 2002; 167: S1-S34 2) Cochrane 2008; 1: CD001155. 3) Cochrane 2008; 1: CD004523.

Do we have other options?

Zoledronic Acid[1]

- Effective in reducing the risk of hip, spine and other fractures, no evidence that it is clinically superior to oral bisphosphonates
  - 2º prevention: Hip Fracture ARR 1%, Vertebral ARR 8%
  - cost, coverage, side effects

Potential Side Effects of all bisphosphonates…

1) N Engl J Med.2007;356(18):1809-1822.

Other options?

Strontium[1]

- Cochrane review 4 RCTs, approx 7000 women
  - ARR 8% vertebral fractures, 2% non-vertebral fractures
  - Non-significant difference in hip fractures
  - 2% increase in diarrhea
  - vascular and nervous system s/es

Denosumab, Raloxifene, HRT, Calcitonin, Lifestyle, Fall Prevention, Hip protectors…

1) Cochrane Database Syst Rev. 2006 Jul 19;3:CD005326

Time to not Test

- Secondary analysis of RCT[1]
  - 97.5% of people reach the "effective" increase.
  - Individuals' BMD readings more variable than readings between people.
- 535 pts scanned 2x over 2-4 wks
  - variability at hip 2.4% to 5%.[2]
- Most treatments increase BMD 1-6% over 3 yrs.
- Decreased fracture risk has been reported in those who lost bone density during treatment.[3]

BottomLine: Ask patients is they are taking it and don't monitor (at least 3 years).

1)BMJ 2009;338:b2266 2) JBoneMinerRes.1994Jun;9(6):951-60 3) Osteoporos Int 2005;16:842-8

Staying on Bisphosphonates

- Fracture Intervention Trial
  - Women on Bisphosphonates 4-5 yrs, 5 additional yrs
    - alendronate or placebo
  - No difference in clinical fractures or total vertebral fractures.
    - subgroup of clinical vertebral fracture reduced 3% (NNT=36).
- Two smaller flawed studies had similar findings[2,3]
  - lower BMDs with residual fracture protection

1) JAMA 2006; 296; 2927-38. 2. NEnglJMed2004;350:1189-99 3)OsteoporosInt2008;19:365–372

Bottom line on Brittle Bones*…

- Who to screen?
  - Age – Weight (Kg)
- Who to treat?
  - Age & BMD or FRAX
- How to treat?
  - Consider Vitamin D, bisphosphonates first
  - If bisphosphonates, wait 3 yrs to repeat BMD and consider stopping after 5 yrs.

*In the context of physician experience, common sense, patient preference, patient history, environmental & psychosocial factors as well as physician & patient anxiety

Thanks for your questions and discussion.

Thanks for completing your course evaluations.

HAVE A SAFE TRIP HOME

We hope to see you next year!