Ontario Prescribing and Therapeutics Certification Course for Naturopathic Doctors

TRANSITIONAL COUNCIL OF
The College of Naturopaths of Ontario

Agenda

- ❑ Introductions and orientation to webinar tools
- ❑ Course facilitators
- ❑ Course overview
- ❑ Course objectives and expectations
- ❑ Orientation to website
- ❑ Online resources
- ❑ Assessment process
- ❑ Questions

Course Facilitators

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Disclosure

- ❑ Neither of us have any financial relationships with any pharmaceutical companies
- ❑ Adil receives honoraria for work related to rational drug use from the Therapeutics Initiative, the Canadian Agency for Drugs and Technologies (CADTH) & Patented Medicines Price Review Board
- ❑ James receives honoraria for work he does with the Clinical Research Ethics Board & acting as an expert witness in some medicolegal trials

Course Overview

- ❑ Focus on therapeutics
- ❑ 4 days of live instruction (to be recorded for online use)
- ❑ Supplemental webinars
- ❑ Multifaceted website with list of readings and online resource centre
- ❑ Oral and written examination process

http://therapeuticseducation.org/Course-Overview

Objectives & Expectations

After completion of the course, registrants will be able to:

1. Create therapeutic plans and monitor therapy to ensure safe and effective treatment.
2. List factors to consider when critically evaluating medical literature and promotional materials.
3. Appropriately use specific substances that Ontario NDs will have access to (according to the College of Naturopaths of Ontario and the Ontario College of Pharmacists Standards)

Objectives Continued

After completion of the course, registrants will be able to:

4. Engage in informed decision making related to prescription and non-prescription medications.
5. Discuss when prescription medications are appropriate and/or desirable to use for specific conditions.
6. Identify strategies for determining which prescription and over the counter medications are utilized for various medical conditions.
7. Consider factors such as efficacy, safety and cost when selecting a prescription medication.

Objectives Continued

After completion of the course, registrants will be able to:

8. Select appropriate starting doses and titration schedules when initiating selected prescription medications.
9. Identify strategies for determining when a prescription may not be needed or potentially may be harmful. Participants will be able to describe strategies for reducing doses or stopping drug therapy.
10. Appropriately recognize and report situations where an adverse drug reaction may have occurred.

Our Therapeutic "Philosophy"

- Common goal to improve patients' well being through "therapeutics"

It's not important WHO prescribes, but it is important that it's done WELL

We believe in the principles of "EVIDENCE-BASED PRACTICE" - best available evidence, clinical experience, patient preferences/values

Naturopathic Doctors Prescribing Medications?

- ND's provide primary care - focus on the whole person - reducing risk and preventing illness
- ND's use "nature's" healing powers, treat the cause of the illness and teach patients about appropriate health
- Do "no harm"
- ND's utilize many different treatments (e.g., nutritional supplements, botanical and homeopathic medicines, manipulative therapies, hydrotherapy, hormones, therapeutic life changes, etc.)
- Prescription medications are an additional modality to use when consistent with ND's practice principles

Course Disclaimer

- Being able to appropriately prescribe medications requires considerable experience and understanding of pathophysiology, pharmacology and therapeutics.
- The content of the course focuses ONLY on the safe and effective use of prescription medications and those in Schedule 4 to treat common disorders. We don't discuss the many other potential treatments that may be utilized.

Orientation to Website

http://therapeuticseducation.org/content/welcome

EVERYTHING YOU NEED TO KNOW
Getting Started
Course Facilitators
Course Overview and Objectives
Course Content
Course Textbooks
Assessment Process
FAQ
Community Practice - participate in discussions with your fellow students
Free TEC PREMIUM Podcast Subscription
Other Resources

The Assessment Process

- Curriculum developed in conjunction with the CONO and based partly on process used in BC
- Valid Assessment Process tested in BC
- Written and oral components
- Process for those who are not successful

The Assessment: Written Exam

- 100 Multiple Choice Questions (open book)
  - ~60-online questions in preparation area, ~15 will be on the final exam
- 50 from the readings
- 40 from the recorded live sessions and webinars
- ~15 (of the 90) are pharmacology, the rest are therapeutics
- ~5-10 jurisprudence
- Plus 10 prescription sample questions on the exam

The Assessment:Oral Exam

- Open Book preparation - 75 min prep time
- 3 cases/
- 25 min/station (not open book)
- One evaluator/station
- Structured marking sheet
- Identify goals of therapy, therapeutic options and list advantages and disadvantages for each option
- Provide rational prescription(s), monitoring parameters & be able to and justify choice
- Identify monitoring parameters
- List other things you want to do

Evidence Based Practice Primer

Outline

- Evidence Based Practice (EBP)
- EBP overview and process
- Formulating clinical questions (PICO)
- Searching for EB answers
- Trial design
- Critical appraisal
  - Assessing the validity of trial design
- Interpreting results
  - p values and confidence intervals
  - Statistical vs clinical significance
  - Magnitude of effect (ARR, RRR, NNT)

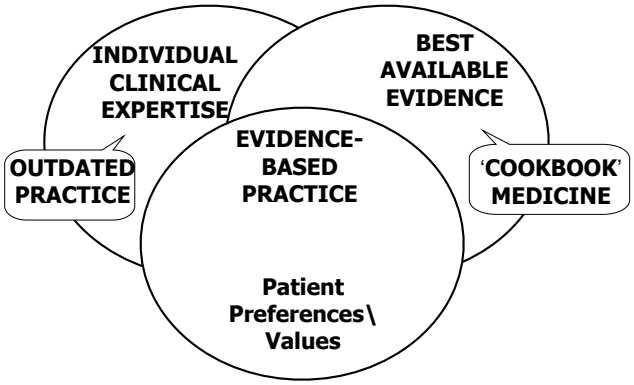
What is Evidence-Based Practice?

"The integration of best research evidence with clinical expertise and patient values"

Sackett et al 2000

When these three elements are integrated, clinicians and patients form a diagnostic and therapeutic alliance with optimized clinical outcomes and quality of life

EVIDENCE-BASED PRACTICE



What EBP is Not:

EBP is not cook-book medicine

- Evidence needs translation to patient's unique features and values

EBP is not cost-cutting practice

- May actually result in increased costs for some patients and/or conditions

Why Sharpen your Critical Appraisal Skills?

- Even highly reputable journals publish poor and/or misleading information
- Improved decision making about the management of patients
- Tool to efficiently stay current with advancing health care knowledge while filtering out studies not worth your time
- A method of managing and utilizing the enormous amount of medical literature
- Help solve clinical problems
- Can even be fun & make your practice more interesting

Knowledge's Half Life:

"My students are dismayed when I say to them, 'Half of what you are taught as medical students will in 10 years have been shown to be wrong. And the trouble is, none of your teachers knows which half.'"

Dr. Burwell, Dean of Medicine, Harvard University

The Process

Clinical Scenario

Clinical Question (PICO)

Search

Critical Appraisal

Integrate & Apply

Barriers to EBP

- Limited awareness/knowledge
- Limited time
- Limited amount of well designed trials in your practice area
- Lack of motivation
  - Lack of skills or resources
  - Lack of financial incentives
- Inadequate literature searching skills
- Abundance of information

Clinical Questions (PICO)

Patient
  Description of the most important characteristics of the patient or target disorder
Intervention
  What do you want to do for the patient? Could include exposure, diagnostic test, prognostic factor, surgery, therapy or patient's perception
Comparator (s)
  Relevant alternative(s) most often considered for this type of patient
Outcome
  Clinical outcome of interest to you and your patient

Why all the fuss about a good clinical question?

With limits on time, it is important to ask questions that by design focus on evidence that is directly relevant to the patient's clinical needs and our knowledge needs

They can suggest high yield search strategies

Questions suggest forms that useful answers might take

PICO: Case 1

A 25 yo male comes into your office with symptoms of Major Depressive Disorder (that meet the criteria in the DSM IV TR. This is his second episode (in 2 yrs) and he has tried citalopram (with little benefit after 6 wks).

Patient
Intervention
Comparison
Outcome

PICO: Case 2

A 56 yo female with 5 year history of Type 2 DM has come to your office. Her family physician gave her metformin 500 mg bid and she says her HbA1C is 8.5% and she wants some natural therapies. What should she do?

Patient
Intervention
Comparison
Outcome

The Question Defines the "Best Evidence"

Therapeutic intervention
- RCT or systematic review/meta-analysis

Rare side effect
- Case control study

Exposure to a potential toxin
- Cohort study

Evaluation of a new drug by Medicare
- Pharmacoeconomic analysis

Trial Designs for Therapy Questions

Randomized controlled trial (RCT)
Systematic review (SR)
- A systematic (and hopefully rigorous) process to identify, synthesis and evaluate the available literature

Studies are:
- Identified according to an explicit search strategy
- Selected by defined inclusion & exclusion criteria
- Evaluated against consistent methodological standards

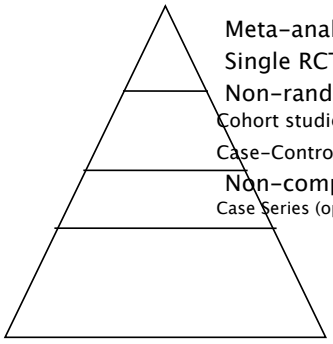
Meta-analysis (MA)
- A statistical process for quantitatively estimating the net benefit/risk from the results of the included studies

Where do you begin?

Textbooks
Journals
Phone a friend
Medline
The Cochrane Library
Evidenced based journals
- ACP Journal Club, EBM

Internet websites
- Drug information websites
- Evidence-based practice websites
- Therapeutic specialty websites
- Healthcare websites

The Hierarchy of Evidence for Therapy Studies



Meta-analysis of RCTs
Single RCTs
Non-randomized comparative studies
Cohort studies
Case-Control studies
Non-comparative studies
Case Series (open trial)
Case reports
Expert opinion

Synopses

Evidence-based journal abstracts and commentaries
Summary of reviews or individual studies
Easy to interpret & digest
Highly efficient
Detailed information readily available

Where Would I Find a Synopses?

Infopoems

Clinical Evidence on line

Bandolier

Evidence-Based Medicine

Therapeutics Initiative

ACP journal club

http://therapeuticseducation.org/useful-links

Efficiently Appraising 'Usable Evidence'

Right patient population (external validity)

Study design (right for the question?)

Internal validity

Results

are they meaningful and useful?

outcome measure?

can they be applied to my CQ?

Top 5 trial design features of prospective controlled trials

1. Randomized
2. Double blind
3. Allocation concealment
4. > 80 % of patients at study completion
5. Important, valid clinical outcomes selected

Why randomize?

Assessing the effectiveness of a treatment requires a comparison

In non-randomized comparisons, other factors may explain any differences observed (confounding)

Randomization controls for both known and unknown confounders

(Confounders ≈ risk factors)

Allocation Concealment

Shields those who admit patients into a trial from knowing future assignments

Happens before and during randomization process

"The decision to accept or reject a patient must be made, and informed consent obtained, without knowledge of the treatment to be assigned"

Schulz, 1995

Blinding

Unlike allocation concealment, this may not always be possible

Happens after randomization

Three main groups to consider:

Patient

Treatment team

Treatment evaluator

p-value

The probability of the data, or more extreme data, occurring in the long run when there is NO treatment effect; i.e. how often this result or one more extreme will occur by chance alone

p-value

The p-value tells us if the difference was due to chance

p=0.013…what does that mean?

1.3% chance the difference was due to just chance (T or F)

98.7 % chance the difference was due to the intervention (T or F)

What can account for the difference?

1. A true difference
2. Bias
3. Confounding factors
4. Random error (chance)
5. All of the above

p-value

The p-value does NOT tell us …

If the difference is valid

If the difference is clinically meaningful

If the difference is real

If the drug works

Etc.

What is a Confidence Interval?

Quantifies the uncertainty in measurement

- A measure of the precession of the "effect estimate" from the study

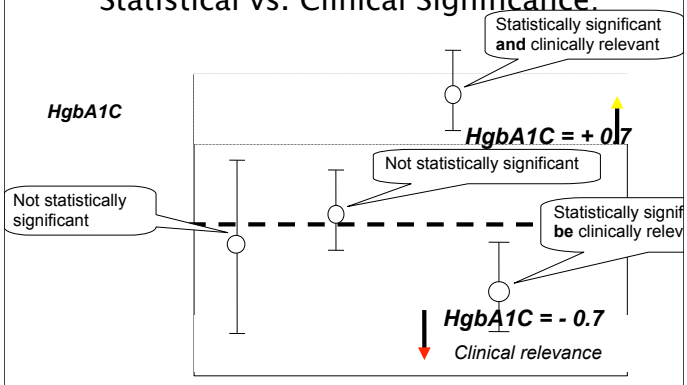
Usually reported as 95% CI

- In a very large number of repetitions of the study, 95% of all CIs obtained will contain the "true" value of the treatment effect in the population studied (assuming random sampling)

Primary Prevention Statins & Mortality

Study	Risk Estimate	Authors Conclusion
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)	∅
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

Statistical vs. Clinical Significance:



Typical Radio, TV, and Newspaper Reports

"Aspirin produces a 30% reduction in heart attacks"

"Treating high blood pressure reduces the chance of strokes by 40%"

"Cholesterol lowering drug decreases chance of heart attacks by 35%"

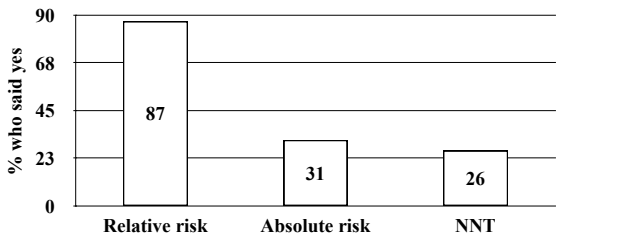
"Vasectomies increase chance of prostate cancer by 40%"

Imagine that you just found out you have a risk factor for cardiovascular disease (e.g., high blood pressure or high cholesterol).
A drug that will treat this risk factor is available and it has no side effects and its cost is covered by a plan.

Consider the following three scenarios. Would you be willing to take this drug every day for the next five years if it had been shown in a clinical trial that:

1) patients treated with this cholesterol pill had been shown to have 33% fewer heart attacks than the non-treated patients; or if
2) it was found that 2% of the patients who took this cholesterol pill had a heart attack, compared to 3% who did not take this pill – a difference of 1%; or if
3) in 100 patients who took this cholesterol pill for five years the medicine would prevent one of the 100 from having a heart attack. There is no way of knowing in advance which person that might be?

Would you take a drug daily for 5 years if it was free with no side effects



RRR = 33% fewer heart attacks
ARR = 2% of patients on this drug had a heart attack compared to 3% on placebo – a difference of 1%
NNT = Drug would prevent 1 of 100 from having a heart attack

A 33% Reduction Can Mean Events Were Reduced From:

	Absolute reduction	NNT
3/million to 2/million	1/million	1,000,000
0.3 % to 0.2 %	0.1%	1000
3 % to 2 %	1%	100
6 % to 4 %	2%	50
30 % to 20 %	10%	10
100 % to 67 %	33%	3

Benefits Must Always Be Expressed Over a Period of Time

NNT (prevent a fatal heart attack) = 300

Chew an aspirin at onset of chest pain – YES

NNT (prevent a fatal heart attack/stroke/cancer) = 1

Chew some poison hemlock now – NO

NNT (prevent a heart attack/stroke) = 50

Take a drug for 5–10 years – side effects and cost – ????

Up to

SALE - 50 % OFF

on selected items

"X" % of WHAT!!!!!!!!!

Up to

SALE - 50 % OFF

on selected items

"X" % of WHAT!!!!!!!!!

Statin results in patients (45-60) without cardiac disease – 5-7 years treatment

	CHD deaths (%)	All deaths (%)	Coronary events (%)
Placebo	1.4	4.1	5.0
Statins	0.9	3.7	3.3
Relative risk reduction	35	NSS	35
Absolute risk reduction	0.5		1.7
Number needed to treat	200		59

(ACAPS,WOSCOPS,AFCAPS/TexCAPS) BMJ 2000;321:983-6

Interpreting Results:

Depression trial: 200 people with MDD x 3 months

Sadex 250 mg daily	Pharmex 200mg daily
68 people/100 are no longer depressed	48 people/100 are no longer depressed

Did this happen by chance or are they statistically different?

Interpreting Results:

Depression trial: 200 people with MDD x 3 months

Sadex 250 mg daily	Pharmex 200mg daily
50 people/100 are no longer depressed	40 people/100 are no longer depressed

p = 0.20

Interpreting Results:

Depression trial: 200 people with MDD x 3 months

Sadex 250 mg daily	Pharmex 200mg daily
50 people/100 are no longer depressed	30 people/100 are no longer depressed

p value = 0.006

RRR, ARR, NNT…

$$RRR = \frac{\text{rate A} - \text{rate B}}{\text{rate A}}$$

ARR = rate A – rate B

NNT = 1/ARR

RRR, ARR, NNT…

$$RRR = \frac{50 - 30}{50} = \frac{20}{50} = 40\%$$

ARR = 50% – 30% = 20%

NNT = 1/ARR = 5

Examining ARR, RRR, and NNT

Event Rate (Treatment vs. Placebo)	RRR	ARR	NNT
1% vs. 2%	50%	**1%**	**100**
10% vs. 20%	50%	**10%**	**10**
40% vs. 80%	50%	**40%**	**2.5**

RRR = relative risk reduction; ARR = absolute risk reduction; NNT = number needed to treat

Important

Only calculate ARR/ARI/NNT/NNH if the result is **statistically significant**!!

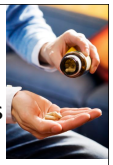
NOTE: NNT and NNH

Studies have shown mixed results in terms of the usefulness of these statistics

Clinicians and patients do not always find it useful to help choose therapy

NNT of 30 may be good or bad depending on the situation

An Example: Hypoglycemia



RCT of 20 patients comparing a new diabetes treatment (drug A) vs. the control

Risk of experiencing hypoglycemia:

Drug A: 2 out of 10 pts 

Risk = 2/10 = 0.2 or 20%

Control: 4 out of 10 pts 

Risk = 4/10 = 0.4 or 40%

Relative Risk (RR) = risk in Drug A / risk in Control = 0.2/0.4 = 0.5

proportion of people having the event in the treatment group compared to the control group

Number Needed to Harm (NNH)

Example

Weight gain (>7kg) with olanzapine =30%

Weight gain with ziprasidone =5%

The Absolute Risk Increase (ARI)

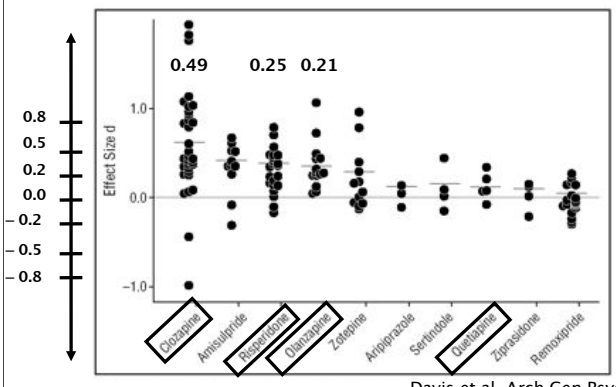
30-5=

25% increased risk with olanzapine

NNH=100/25=4

What is an effect size?

Global Symptom Improvement (Meta-analysis: Atypicals vs. Conventionals)

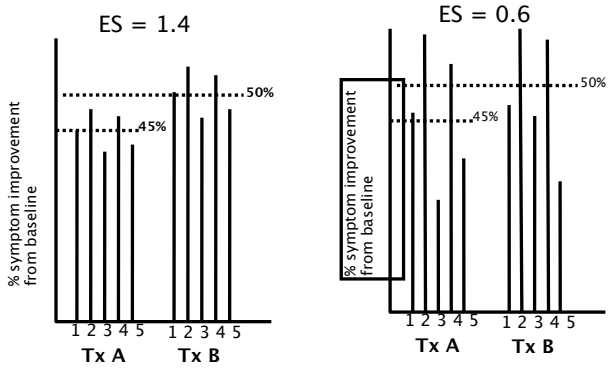


N=124 trials, 18, 272 pts

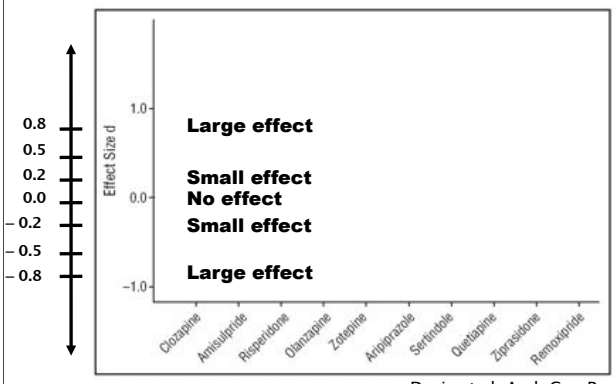
Davis et al. Arch Gen Psych 2003

Effect size $ES = \frac{mean1 - mean2}{SD}$

Illustrating Variability in



Global Symptom Improvement



Davis et al. Arch Gen Psych 2003

What is an Odds Ratio?

Commonly used in systematic reviews and epidemiological studies that list the likelihood of harm an exposure may cause

Calculated as the number of events divided by the number of non-events.

Eg, 51 boys are born in every 100 births

The odds of a randomly chosen delivery being a boy is:
(51 / 49)= 1.04

http://www.jr2.ox.ac.uk/bandolier/band25/b25-6.html

Odds Ratio (and relative risk)

Exposure/Treatment	Disease/Outcome +	Disease/Outcome -
+	a	b
-	c	d

OR = odds in the treated/exposed group divided by the odds in the control group

$$\text{Odds Ratio (OR)} = \frac{\frac{a}{b}}{\frac{c}{d}}$$

$$\text{Relative Risk (RR)} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

RR approximates OR when events are rare!

Risk factor modification
Blood pressure/cholesterol etc

James McCormack, B.Sc. (Pharm), Pharm.D.
Professor
Faculty of Pharmaceutical Sciences

1148 NOVEMBER 26, 1966 THE LANCET

EFFECT OF PROPRANOLOL IN MILD HYPERTENSION

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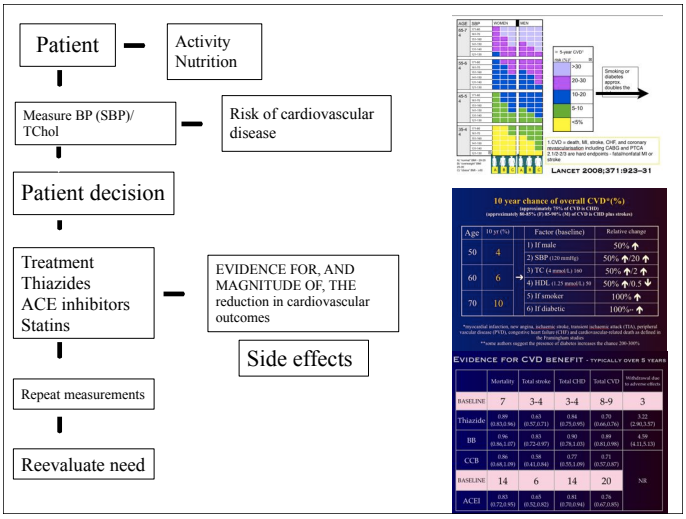
Objectives

To be able to design an effective, safe and cost-effective therapeutic plan for the treatment of patients with high blood pressure/cholesterol



Non-drug measures

Activity
Nutrition
Lose weight
Smoking?
Salt?
Potassium

High Blood Pressure

Measurement

must be determined under relaxed conditions and should be done on at least 3 separate occasions (3 sets of 3 readings with an interval of at least 2 weeks between readings unless the initial level is very high >120 mmHg or target organ damage is present)

patient should sit or lie down quietly for at least five minutes before blood pressure measurement

avoid smoking or eating within the 30 minutes prior to measurement

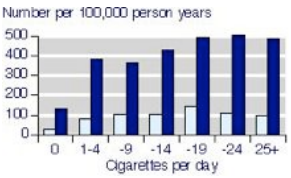
Drug-Induced

Prescription Drugs:
NSAIDs, including coxibs
Corticosteroids and anabolic steroids
Oral contraceptive and sex hormones
Vasoconstricting/sympathomimetic decongestants
Calcineurin inhibitors (cyclosporin, tacrolimus)
Erythropoietin and analogues
Monoamine oxidase inhibitors (MAOIs)
Midodrine
Other substances: Licorice root. Stimulants including cocaine, Salt, Excessive alcohol use

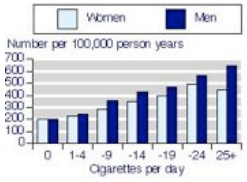
From CHEP 2006

Smoking and risk

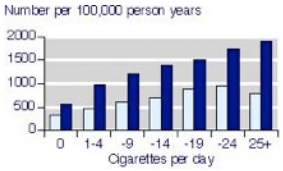
IHD



All Cancer

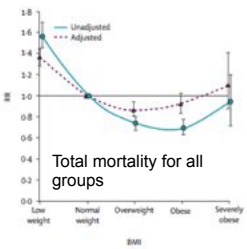


Overall mortality

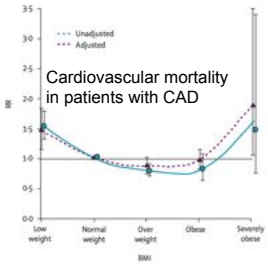


Bandolier

BMI and risk



Total mortality for all groups

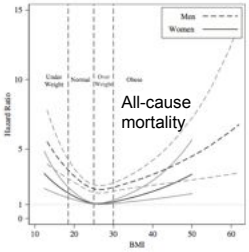


Cardiovascular mortality in patients with CAD

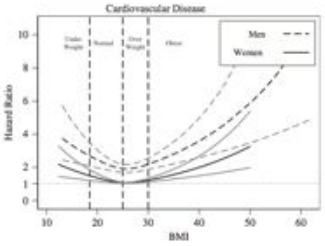
Lancet 2006;368:666–78

BMI and risk

Age 70-75



All-cause mortality



J Am Geriatr Soc 2010;58:234–41

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

Patient values and risk assessment

"As in previous years, it needs to be reiterated that the **CHEP hypertension** management recommendations are based solely on efficacy data. Considerations relating to individual patient/ physician preferences and cost-effectiveness of different drug classes have not been a component of this process and need to be considered by the physician and patient when individualizing therapy"

Describing Benefits

The chance
WITH NO TREATMENT
The chance
WITH TREATMENT

Risk of what and over how long

Definitions

WHAT

CVD is cardiovascular disease

Typically = CHD + cerebrovascular

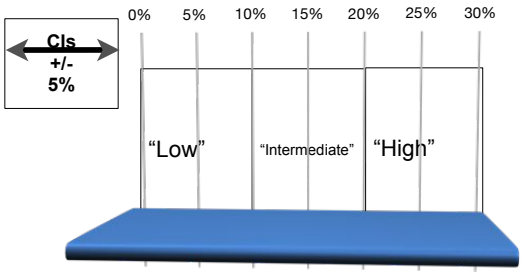
CHD = coronary heart disease = fatal and non-fatal MIs and sometimes angina

Cerebrovascular disease = fatal and non-fatal strokes - and sometimes TIAs

CVD sometimes includes other conditions - heart failure, peripheral vascular disease

HOW LONG - 5 or 10 years

How accurately can we predict risk?



J Cardiovasc Risk 2002;9:183-90

• 10 year CVD risk assessment •

AGE (YR)	BASELINE 10 YEAR CVD*		FACTOR (BASELINE)	RELATIVE CHANGE
50	4%		1) If male	~50% ⬆
			2) SBP (120 mmHg)	~50% ⬆/20 mmHg ⬆
			3) TC (4 mmol/L) 160mg/dL	~50% ⬆/2 mmol/L⬆
60	6%	→	4) HDL (1.25 mmol/L) 50mg/dL	~50%⬆/0.5 mmol/L ⬇
			5) If smoker	~100% ⬆
			6) If diabetic	~100%** ⬆
			7) A1C# (6%)	~33% ⬆/2% ⬆
70	10%		8) Positive Family Hx	~50% ⬆
			9) Negative family HX	~33% ⬇

*CVD = myocardial infarction, new angina, ischemic stroke, transient ischemic attack (TIA), peripheral vascular disease (PVD), congestive heart failure (CHF) and cardiovascular-related death as defined in the Framingham studies
** based on UKPDS which uses A1c categories - Framingham only categorizes diabetes as a yes/no factor
*** positive family history = CHD in parents before age 60
# - changes in A1c only impact CHD risk not CVD
approximately 75% of CVD is CHD

• Impact of A1c on 10-year CHD risk

A1C 7%, SBP 140, TC 6, HDL 1, NONSMOKER	BASELINE 10-YEAR CHD RISK	FOR EVERY 1% ⬆ IN A1C ADD THIS ABSOLUTE RISK TO THE BASELINE CHD RISK
50 y/o F diabetes for 3 years	~10%	~1%
50 y/o M diabetes for 3 years	~15%	~2%
65 y/o F diabetes for 10 years	~20%	~3%
65 y/o M diabetes for 10 years	~35%	~4%

• Lifetime risk of dialysis/blindness -impact of A1c •

AGE	A1C	DIALYSIS	BLINDNESS
65	8	~0.5%	~0.2%
	9	~0.6%	~0.5%
	11	~0.9%	~1.9%
75	8	~0.1%	<0.1%
	9	~0.1%	~0.1%
	11	~0.2%	~0.5%

• One year ischemic stroke risk for atrial fibrillation •

CHADS2 CALCULATION	CHADS2 SCORE	ANNUAL ISCHEMIC STROKE RISK
CHF = 1 point	0	~2%
HTN =1 point	1	~3%
Age> 75 = 1 point	2	~4%
Diabetes = 1 point	3	~6%
Prior Stroke/TIA = 2 points	4	~9%
	5	~18%

How good is the Framingham risk estimate?

UK - overestimates mortality from CHD by 47% and non-fatal CHD by 57%

Germany, Italy, and Denmark - overestimates risk by 50%

BMJ 2003;327:1-6

Lancet 2008;371:923–31

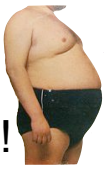
National Health and Nutrition Examination Survey (NHANES) prospective cohort study of 14,407 US participants

non-laboratory-based risk factors predicted cardiovascular events as accurately as one that relied on laboratory-based values

What do you REALLY need to know to make a reasonable estimate of CVD risk????

Eur J Card Prev Rehab May 2009 Similar findings

Age
gender
SBP
Smoker
Diabetes
Obese - just look!!



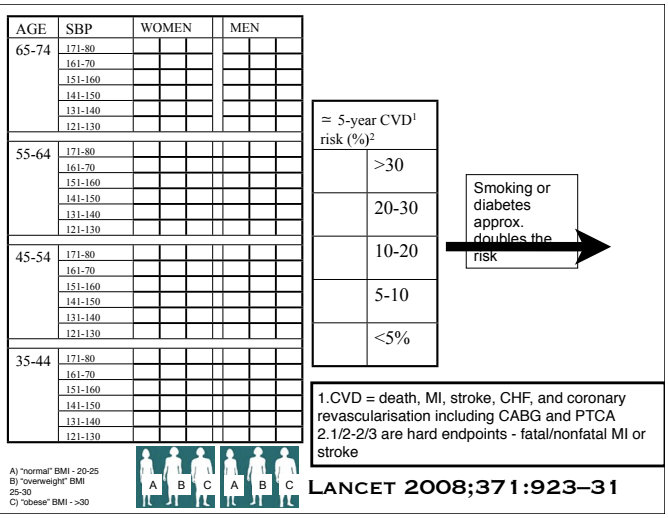
CHOLESTEROL OR CRP really not needed

55 year-old male

non-smoker, Chol 5, HDL 1.25

10 year risk (%)

JNC 6	JNC 7	Systolic mm Hg	Non diabetic		Diabetic	
			CHD	Stroke	CHD	Stroke
Optimal	Normal	110	7	1	9	1
Normal	Prehtn	120	8	1	11	2
Borderline	Prehtn	130	9	2	12	3
Stage 1	Stage 1	140	10	2	13	3
Stage 1	Stage 1	150	11	3	15	4
Stage 2	Stage 2	160	12	4	16	6
Stage 2	Stage 2	180	15	5	19	9



1.CVD = death, MI, stroke, CHF, and coronary revascularisation including CABG and PTCA
2.1/2-2/3 are hard endpoints - fatal/nonfatal MI or stroke

LANCET 2008;371:923–31

Factors to consider when choosing a drug

1. Efficacy at lowering risk of cardiovascular disease
2. Tolerability/allergies
3. Frequency of dosing
4. "2-fers" - for blood pressure
5. Cost

Efficacy at lowering blood pressure

all high blood pressure drugs presently available are equally effective at lowering blood pressure

there is important variability between patients and not every drug will necessarily work in every patient

Lipid-lowering drugs

Table 4: Lipid-lowering Agents—Effect on Lipoproteins

	LDL	HDL	TG
Resins	↓↓	↑	↑
HMG CoA reductase inhibitors	↓↓↓	↑	↓↔↓↓[a]
Niacin	↓↓	↑↑	↓↓
Fibrates	↓↔↓	↑↑	↓↓↓
Ezetimibe	↓↓	↑↔	↓

[a] Atorvastatin and rosuvastatin have the greatest TG-lowering effect.

Primary Prevention Benefit -non-diabetics - 4-8 years

RELATIVE BENEFIT		CVD RISK REDUCTION		MORTALITY
		CHD	CVA	
Blood pressure	(most drugs except alpha blockers and atenolol)	~ 20%	~ 40%	~ 10-15%
Cholesterol	Statins	~ 30%	~ 20%	~ 10-15%
	Fibrates	~ 20?%	~ 0%	~ 0%
	Ezetimibe	~ 0%	~ 0%	~ 0%
ASA		~ 0%	~ 20%	~ 0%

ABSOLUTE BENEFIT		CVD RISK REDUCTION		MORTALITY
		CHD	CVA	
Blood pressure	(most drugs except alpha blockers and atenolol)	~1% (3-4%)		~ 1?%
Cholesterol	Statins	~1-1.5%	~ 0%	~0.5%
	Fibrates	~1%	~ 0%	~ 0%
	Ezetimibe	~ 0%	~ 0%	~ 0%
ASA		~ 0%		~ 0%

* 1% - one drug and BP of 160/98 – 3-4% with higher starting BP, 20/10 change with multiple drugs

• Primary Prevention Benefit -diabetics - 5-11 years •

RELATIVE BENEFIT		CVD REDUCTION	MORTALITY
Blood pressure*		~ 50%	~ 15%
Cholesterol	Statins	~ 20-25%	~ 5-10%
	Fibrates	~ 20% (just non-fatal MI)	~ 0%
	Fibrates (added to statins)	~ 0%	~ 0%
Glucose	All drugs combined**	~ 10-15%	~ 0%
	Metformin	~ 35%	~ 35%
ASA		~ 0%	~ 0%

ABSOLUTE BENEFIT		CVD REDUCTION	MORTALITY
Blood pressure*		~6-7%	~2%
Cholesterol	Statins	~3%	~1%?
	Fibrates	~ 1.5% (just non-fatal MI)	~ 0%
	Fibrates (added to statins)	~ 0%	~ 0%
Glucose	All drugs combined**	~2%	~ 0%
	Metformin	~8%	~7%
ASA		~ 0%	~ 0%

* reducing BP from 155/90 to 140/80 but no benefit when BP 140/90 mmHg reduced to 120/80 mmHg
** pooled data for all hypoglycemic agents – issue of what drugs have not been studied
aggressive glucose lowering below A1c of 7-7.5% no benefit except metformin in UKPDS

Evidence for CVD benefit - typically over 5 years

	Mortality	Total stroke	Total CHD	Total CVD	Withdrawal due to adverse effects
BASELINE (%)	7	3-4	3-4	8-9	3
Thiazide	0.89 (0.83,0.96)	0.63 (0.57,0.71)	0.84 (0.75,0.95)	0.70 (0.66,0.76)	3.22 (2.90,3.57)
BB	0.96 (0.86,1.07)	0.83 (0.72-0.97)	0.90 (0.78,1.03)	0.89 (0.81,0.98)	4.59 (4.11,5.13)
CCB	0.86 (0.68,1.09)	0.58 (0.41,0.84)	0.77 (0.55,1.09)	0.71 (0.57,0.87)	NR
BASELINE (%)	14	6	14	20	
ACEI	0.83 (0.72,0.95)	0.65 (0.52,0.82)	0.81 (0.70,0.94)	0.76 (0.67,0.85)	

Treatment of Hypertension in the Elderly
typically over 5 years - 2-3 years for the over 80

	Mortality	CV mortality and morbidity	Withdrawal due to adverse effects
BASELINE (%)	12	15	7
60 years or older	0.9 (0.84,0.97)	0.72 (0.68,0.77)	1.71 (1.45,2.00)
BASELINE (%)	14	11	NR
80 years or older	0.98 (0.87,1.10)	0.75 (0.65,0.87)	

Cochrane Library

Treatment blood pressure targets for hypertension (Review)

Arguedas JA, Perez MI, Wright JM

Objective:

To determine if lower BP targets (135/85 mmHg) are associated with reduction in mortality and morbidity as compared with standard BP targets (140-160/ 90-100 mmHg)

Arguedas JA, Perez MI, Wright JM. Treatment blood pressure targets for hypertension. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD004349. DOI: 10.1002/14651858.CD004349.pub2.

7 RCTs, N=22,089

Despite a -4/-3 mmHg greater achieved reduction in systolic/diastolic BP, p< 0.001, attempting to achieve "lower targets" instead of "standard targets" did not change

total mortality (RR 0.92, 95% CI 0.86-1.15)
myocardial infarction (RR 0.90, 95% CI 0.74-1.09)
stroke (RR 0.99, 95% CI 0.79-1.25)
heart failure (RR 0.88, 95% CI 0.59-1.32)
major cardiovascular events(RR 0.94, 95% CI 0.83-1.07)
end-stage renal disease (RR 1.01, 95% CI 0.81-1.27)

Arguedas JA, Perez MI, Wright JM. Treatment blood pressure targets for hypertension. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD004349. DOI: 10.1002/14651858.CD004349.pub2.

Pharmacotherapy for mild hypertension (Review)

Diao D, Wright JM, Cundiff DK, Gueyffier F

THE COCHRANE COLLABORATION®

"Antihypertensive drugs used in the treatment of adults (primary prevention) with mild hypertension (systolic BP 140-159 mmHg and/or diastolic BP 90-99 mmHg) have not been shown to reduce mortality or morbidity in RCTs"

"Treatment caused 9% of patients to discontinue treatment due to adverse effects."

August 2012

ALLHAT - **high-risk hypertensive patients randomized to ACE inhibitor or calcium channel blocker vs. diuretic**

Patients

33,357 patients with hypertension and 1 or more risk factors - mean age 67, 47% women, diabetics (36%), history of heart disease (25%), smoker (22%), HDL < 0.9 mmol/L (12%)

Treatment

chlorthalidone, amlodipine or lisinopril – 2nd line therapy allowed was atenolol, clonidine or reserpine

Duration

4.9 years

Results

Blood pressure differences at 5 years compared with chlorthalidone group

Systolic – amlodipine 0.8 mmHg higher, lisinopril 2.0 mmHg higher

Diastolic – amlodipine 0.8 mmHg lower, lisinopril no difference

JAMA 2002;288:2981-97

6 year data

	Fatal CHD or non-fatal MI (%)	Mortality (%)	Combined CHD (%)	Stroke (%)	Combined CVD (%)
Chlorthalidone	11.5	17.3	19.9	5.6	30.9
Amlodipine	11.3	16.8	19.9	5.4	32.0
Lisinopril	11.4	17.2	20.8	6.3	33.3
Relative risk reduction	NSS			11*	7*
Absolute risk reduction				0.7	2.4
NNT				143	42

* p <0.05 lisinopril vs. chlorthalidone

JAMA 2002;288:2981-97

6 year data

	ESRD (%)	Cancer (%)	CHF (%)	Angina (%)	Coronary Revasc (%)	PVD (%)
Chlorthalidone	1.8	9.7	7.7	12.1	9.2	4.1
Amlodipine	2.1	10.0	10.2	12.6	10.0	3.7
Lisinopril	2.0	9.9	8.7	13.6	10.2	4.7
Relative risk reduction	NSS		25**	11*	NSS ***	NSS #
Absolute risk reduction			2.5	1.5		
NNT			40	67		

p <0.05 lisinopril vs. chlorthalidone
** p <0.05 lisinopril vs. amlodipine
*** p = 0.05 lisinopril vs. chlorthalidone, p = 0.06 amlodipine vs. chlorthalidone
# p = 0.06 amlodipine vs. chlorthalidone

JAMA 2002;288:2981-97

Meta-analysis of 4 HTN trials

6,825 patients - atenolol versus placebo/no treatment

	All deaths (%)	CVD death (%)	MIs (%)	Strokes (%)
Atenolol	13.0	7.8	7.2	8.0
Placebo	13.3	8.0	7.3	8.2
RR	NSS			
ARR				
NNT				

Lancet 2004;364:1684–9

Meta-analysis of 5 HTN trials

17,671 patients - atenolol versus other agents

(thiazides,ACEI CCB)

	All deaths (%)	CVD death (%)	MIs (%)	Strokes (%)
Atenolol	8.0	5.1	4.6	5.4
Other	7.1	4.4	4.5	4.2
RR	11	14	NSS	15
ARR	0.9	0.7		0.8
NNT	111	143		125

Lancet 2004;364:1684–9

Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis

Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

13 beta-blocker vs other anti-HTN trials

105,951 patients

No difference for MI or mortality, 16% more strokes in BB group

7 beta-blocker versus placebo or no treatment trials

27,433 patients

No reduction for MI or mortality, 19% decrease in stroke (approx 0.2% ARR?)

No change in any endpoint in either the atenolol or non-atenolol sub-group

Lancet Oct 18 2005

Levels and break points

CHOLESTEROL

There are NO studies that have looked at getting patients to different cholesterol levels

BLOOD PRESSURE

Less than 135/85 "Despite a -4/-3 mmHg greater achieved reduction in systolic/diastolic BP, attempting to achieve "lower targets" instead of "standard targets" did not change total mortality, MI, stroke, CHF, major CV events or ESRD" Cochrane Review 2009;Issue 3:CD004349

DIABETES

three end points - Overall CHD - Strokes, Overall Mortality

5 years - lower HbA1c by 1% - compared to "standard" treatment

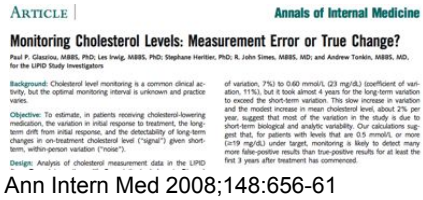
CHD - they state there was a 1.5% ⬇ in CHD one table ⬇ from

Strokes - NSS, Mortality - NSS

Hypoglycemic events

⬆ from 28.6% to 38.1% - Severe -1.2% to 2.3%

Participants gained 2.5 kg more in the intensive group Lancet 2009;373:1765–72



ARTICLE | Annals of Internal Medicine

Monitoring Cholesterol Levels: Measurement Error or True Change?

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

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

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

Design: Analysis of cholesterol measurement data in the LIPID

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

After initial change only measure every 3-5 years

Ann Intern Med 2008;148:656-61

AJH American Journal of Hypertension

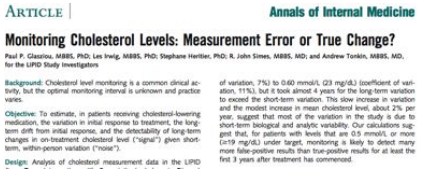
Editorial

Blood Pressure Variability: The Challenge of Variation

Tom P Marshall

Need changes of at least 10/5 mmHg before you can say there has been a change

Am J Hyper 2008;21:3–4



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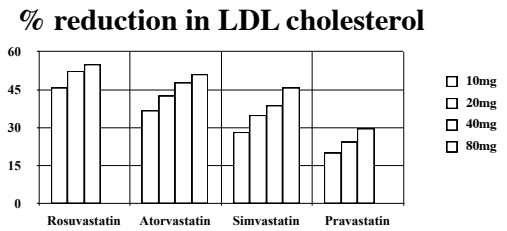
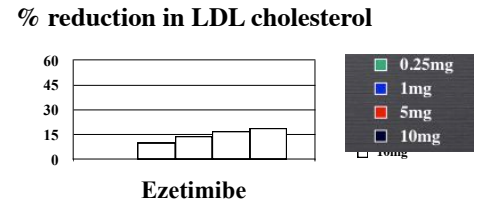
"After initial change only measure every 3-5 years"

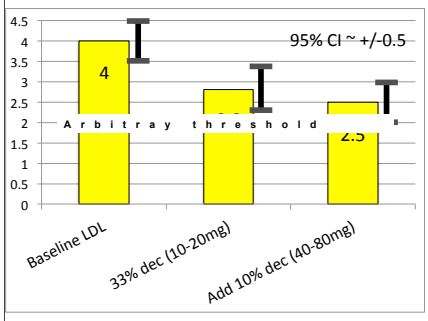
Average increase in chol is 0.5-1%/year

Within-person coefficient of variation is ~7%
Single measurement
95% CI
Total chol ~ -0.80 to 0.80 mmol/L
LDL chol ~ -0.5 to 0.5 mmol/L

Ann Intern Med 2008;148:656-61







Statins in secondary prevention

10-20 mg - 5-6% ARR in MIs and strokes

Inc. dose 4-8X you get an additional 1-2% ARR

short-term variability - a combination of analytic variability and week-to-week biological fluctuation around a stable aver- age

Tolerability

almost all high blood pressure medications produce a similar incidence of side effects and are equally well tolerated however, the types of side effects are different

Examples of "2-fers"

Ischemic heart disease (BB, CCB)
Previous MI (BB, ACEI)
CHF (DIUR, ACEI, BB, A2B)
COPD and asthma (avoid BB for asthma)
Type-2 diabetes (ACEI?, ARB? – avoid CCB?)
Type-1 diabetes (ACEI?)
Hyperlipidemia (avoid anything that would worsen lipids enough to require drug therapy)
Atrial fibrillation (BB, CB)
Migraine (BB, ACEI?)

Remember issue of betablockers

Key point

Start with a LOW!!!!!! dose

Thiazides

TOXICITY (thiazides)
Hypokalemia
Gout
Hypomagnesemia
Hypercalcemia
Hyperlipidemia
Blood dyscrasias
Photosensitivity
Gynecomastia (spironolactone)

Betablockers

acebutolol (Sectral, Monitan)
atenolol (Tenormin, generics)
bisoprolol (Monocor)
carvedilol (Coreg)
nadolol (Corgard, generics)
metoprolol (Lopressor, Betaloc, generics)
oxprenolol (Trasicor, Slow-Trasicor)
propranolol (Inderal, Inderal LA, generics)
sotalol (Sotacor)
pindolol (Visken, generics)

Betablockers

CONTRAINDICATIONS
Asthma or chronic bronchitis with bronchospasm
Raynauds
Intermittent claudication?
Bradycardia, atrio−ventricular conduction defects
TOXICITY
Fatigue
Bradycardia
Asthma
CNS effects
Cold extremities

ACE Inhibitors

benazepril (Lotensin)
captopril (Capoten, generics)
cilazapril (Inhibace)
enalapril (Vasotec, generics)
fosinopril (Monopril)
lisinopril (Prinivil, Zestril, generics)
quinapril (Accupril)
ramipril (Altace)
trandolapril (Mavik)

Thiazides

hydrochlorothiazide (HCTZ, Hydrodiuril, generics)
chlorthalidone (Hygroton, generics)
indapamide (Lozide)
amiloride/HCTZ (Moduret, generics)
spironolactone/HCTZ(Aldactazide, generics)
triamterene/HCTZ(Dyazide, generics)

ACE Inhibitors

CONTRAINDICATIONS
Intolerance or allergic reaction to ACE inhibitors
Pregnancy
Rapidly worsening renal failure
Severe hypotension
Bilateral renal artery stenosis, unilateral renal artery stenosis in a patient with one kidney
TOXICITY
Acute renal failure - esp if volume depleted
Hyperkalemia
Hypotension
Dry cough
Rash, mucosal ulcerations
Angioedema

Angiotensin II receptor antagonists

losartan (Cozaar)
candesartan (Atacand)
irbesartan (Avapro)
telmisartan (Micardis)
valsartan (Diovan)

Angiotensin II receptor antagonists

CONTRAINDICATIONS

Intolerance or allergic reaction to ARBs

Pregnancy

Rapidly worsening renal failure

Severe hypotension

Bilateral renal artery stenosis, unilateral renal artery stenosis in a patient with one kidney

TOXICITY

Acute renal failure - esp if volume depleted

Hyperkalemia

Hypotension

Angioedema - reported??/

Calcium channel blockers

amlodipine (Norvasc)

diltiazem (Cardizem SR, Cardizem CD, generics)

felodipine SR (Plendil, Renedil)

nicardipine (Cardene)

nifedipine (Adalat, Adalat PA, Adalat XL, generics)

verapamil (Isoptin, Isoptin SR, generics)

Calcium channel blockers

CONTRAINDICATIONS

Severe left ventricular dysfunction (EF< 20-30%)

Second- or third-degree AV block or sick sinus syndrome (unless a functioning ventricular pacemaker is in place)

Wolff-Parkinson-White syndrome

Wide-complex ventricular tachycardia

TOXICITY

Hypotension

Headache

Bradycardia (verapamil)

Dizziness or lightheadedness

Exacerbation of congestive heart failure (verapamil)

Constipation

Peripheral edema

Heart burn

Alpha blockers

prazosin (Minipress, generics)

doxazosin (Cardura, generics)

terazosin (Hytrin, generics)

Centrally acting agents

clonidine (Catapres, generics)

methyldopa (Aldomet, generics)

reserpine (Serpasil)

When to stop

Stepped-down therapy should be considered in patients whose blood pressures during the previous few visits have been well controlled

approximately 50% of patients with well-controlled blood pressures successfully undergo either a reduction in dosage or number of drugs and remain normotensive for a time

How to stop

very gradual dosage and drug discontinuation

a precise discussion of why drug reduction is being done

dosage should be reduced by 50%, with reassessment of blood pressure at 2 weeks

if the patient is still normotensive, reduce the dosage by another 50% (i.e., to 25% of the initial dose) and recheck the blood pressure in another 2 weeks

Lipid-lowering drugs

Resins
cholestyramine
colestipol (Colestid)

Cholesterol Absorption Inhibitor
ezetimibe (Ezetrol)

HMG CoA Reductase Inhibitors
atorvastatin
fluvastatin (Lescol)
lovastatin (Mevacor, generics)
pravastatin (Pravachol, generics)
rosuvastatin (Crestor)
simvastatin (Zocor, generics)

Lipid-lowering drugs

Niacin (Nicotinic Acid) derivatives
niacin, immediate release
niacin, slow release (SR)
niacin, extended release (ER)

Fibrates
bezafibrate (Bezalip)
fenofibrate (Generics)
fenofibrate microcoated (Lipidil Supra, generic)
fenofibrate micronized (Lipidil Micro, generics)
fenofibrate nanocrystals (Lipidil EZ, generics)
gemfibrozil (Lopid, generics)

Lipid-lowering drugs

Resins

Common: Constipation (>10%), bloating, abdominal fullness, flatulence, ↑ triglycerides, ↑ transaminases (reversible).

Rare: hyperchloremic acidosis, cholecystitis, cholelithiasis, pancreatitis, malabsorption syndrome, GI bleeding, peptic ulceration.

Cholesterol Absorption Inhibitor

Common: back pain, arthralgia, diarrhea, abdominal pain, fatigue, dizziness, headache.

Rare: myopathy, rhabdomyolysis, hepatitis, acute pancreatitis, thrombocytopenia.

HMG CoA Reductase Inhibitors

Common: ↑ CPK, ↑ transaminases (reversible), mild upper GI disturbances, myalgias (with and without CPK elevation), sleep disturbances, headache, rash.

Lipid-lowering drugs

Niacin (Nicotinic Acid) derivatives

Common: hot flushes and pruritus, dry skin, acanthosis nigricans (reversible), reactivation of peptic ulcer, GI disturbances, ↑ blood glucose, glucose intolerance, uric acid and transaminases.

Rare: torsades de pointes, severe hepatotoxicity (more frequent with slow-release formulation), ↑ blood glucose, uric acid, transaminases.

Fibrates

Upper GI disturbances (nausea, abdominal pain, flatulence), myalgias, ↑ bile lithogenicity, ↑ CK, ↑ creatinine (not representative of renal function deterioration).

Secondary prevention (Post MI, Atrial fibrillation, Heart failure

James McCormack, B.Sc. (Pharm), Pharm.D.
Professor
Faculty of Pharmaceutical Sciences

Post MI

• Secondary Prevention Benefit - 2-5 years •

RELATIVE BENEFIT		CVD RISK REDUCTION		MORTALITY
	Duration	CHD	CVA	
Beta-blockers	~2 years	?	?	~25%
ACEI/ARB - no HF	~4 years	~20%	~20%	~15%
Statins	~5 years	~25%	~20%	~15%
Fibrates	~5 years	~0% ~20% gemfibrozil	~0%	~0%
Niacin	~3 years	~ 0%	~ 0%	~0%
ASA	~2 years	~25%		~15%

ABSOLUTE BENEFIT		CVD RISK REDUCTION		MORTALITY
	Duration	CHD	CVA	
Beta-blockers	~2 years	1%	?	~2%
ACEI/ARB -no HF	~4 years	~1-1.5%	~0.5%	1% ~2% if heart failure
Statins	~5 years	~3-4% higher dose ~1.5% more	~1% higher dose ~0.5% more	~ 2% higher dose no additional benefit
Fibrates	~5 years	~0% ~3% gemfibrozil	~0%	~0%
Niacin	~3 years	~0%	~0%	~0%
ASA	~2 years	~3-4%		~1-2%

Atrial fibrillation

• Atrial Fibrillation Drugs Benefit - 1 year •

RELATIVE BENEFIT	ISCHEMIC STROKE
ASA	~20-25%
Warfarin	~65-70%
Dabigatran (150mg BID), apixaban, rivaroxaban	~75-80%

ABSOLUTE BENEFIT	ANNUAL ISCHEMIC STROKE RISK						ANNUAL BLEED RISK
CHADS2 score	0	1	2	3	4	5	
No therapy	~2%	~3%	~4%	~6%	~9%	~18%	
On ASA	~1.5%	~2%	~3%	~5%	~7%	~14%	~1%
On OAC	~0.5%	~1%	~1%	~2%	~3%	~6%	~2-3%
ASA minus OAC	~1%	~1%	~2%	~3%	~4%	~8%	

Heart failure

Diuretics for heart failure
(some withdrawal trials)
2-12 months

	Mortality (%)	HF worsening (%)
Placebo	12	15
Diuretics	3	0

Cochrane CD003838

Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction (36 months)

	Mortality (%)	Reinfarction (%)	Readmission for HF (%)	Overall (%)
Placebo	26.8	11	18.9	41
ACE inhibitor	23	8.9	13.7	33.8

Lancet 2000;355:1575-81

Beta-blockers in patients with heart failure or left-ventricular dysfunction (3-24 months)

	Mortality (%)	Admission for HF (%)
Placebo	12.8	15.6
Beta-blocker	8.4	10.3

Ann Intern Med 2001;134:550-60

ACE inhibitor issues

Dose issues

NETWORK trial – Eur H J 1998;19:481-9

1,532 patients with class II to IV heart failure randomised to receive either 5,10, or 20 mg of enalapril for 6 months

No difference in deaths, worsening of heart failure or hospitalization for heart failure

ACE inhibitor issues

Dose issues

ATLAS - Circ 1999;100:2312-8

3164 patients with class II to IV heart failure randomised to receive either 2.5 to 5.0 mg daily or 32.5 to 35 mg daily of lisinopril for approx 4 years

No difference in mortality

Mortality plus hospitalization for any cause reduced from 83.8% to 79.7%

Worsening heart failure reduced from 44 to 38%

Dizziness ARI by 7%, hypotension by 4% and worsening renal function by 3%

CHARM Overall – Candesartan in patients with CHF

Patients

7601 patients mean age 66 (32% women) with CHF (NYHA Class II 45%, Class III 52%), a history of MI (53%), stroke (9%), diabetes (29%), smoker (15%), HTN (55%), lipid lowering (42%), aspirin (56%)

Treatment

candesartan started at 4-8 mg PO daily, doubled approximately every 2 weeks up to a maximum of 32 mg PO daily (63% in candesartan group got to this dose) or placebo

Duration

3 years

Results

blood pressure was 5/3 mmHg lower in the candesartan group at 6 months

Lancet 2003;362:759-66

Candesartan results

	CV death or hospitalization for CHF (%)	All deaths (%)	CV deaths (%)	CV death, hospitalizations for CHF, MI, stroke, revascularization (%)
Candesartan	30	23	18	37
Placebo	35	25	20	41
Relative risk reduction	14	P =0.055	10	10
Absolute risk reduction	5		2	4
Number needed to treat	20		50	25

Combined ACEI and ARBs

Admissions for heart failure - RR 0.81 (0.72-0.91)

Overall hospitalizations - RR 0.92 (0.82-1.05)

Mortality - RR 0.97 (0.92-1.03)

Fatal MI - RR 0.97 (0.76-1.22)

Non fatal Mis - RR 0.91 (0.78-1.07)

Worsening renal function RR 1.91 (1.40-2.6)

Symptomatic hypotension RR 1.57 (1.44-1.71)

Hyperkalemia RR 1.95 (0.85-4.48)

ONTARGET trial showed similar results

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0009946

COMET - carvedilol vs metoprolol in CHF

Patients

3029 patients mean age 62 (20% women) with CHF (NYHA Class II 48%, Class III 48%), a history of IHD (53%), cardiomyopathy (44%), diabetes (24%), HTN (36%), ACEI (92%), digoxin (60%), spironolactone (11%), lipid lowering (21%), aspirin (36%)

Treatment

carvedilol started at 3.125 mg PO BID up to 25 mg PO BID (75% got to this dose) or metoprolol started at 5 mg PO BID up to 50 mg PO BID (78% got to this dose)

Duration

5 years

Results

Heart rate was 1.6 BPM lower and systolic blood pressure was 1.8 mmHg lower at 4 months in carvedilol group

Lancet 2003;362:7-13

COMET results

	Mortality and all cause admission (%)	All deaths (%)	CV deaths (%)	Serious adverse events (%)
Carvedilol	74	34	29	75
Metoprolol	76	40	35	77
Relative risk reduction	NSS	15	17	NSS
Absolute risk reduction		6	6	
Number needed to treat		17	17	

Spironolactone and congestive heart failure

Patients

1663 patients with severe heart failure on diuretic and ACE inhibitor

Treatment

placebo or spironolactone 25-50 mg PO daily

Duration

24 months

Results

no differences in side effects overall but 9% (spironolactone) versus 1% (placebo) incidence of gynecomastia

3% more patients withdrew because of side effects in the spironolactone group

no difference in serious hyperkalemia

New Engl J Med 1999;Sept 2

Spironolactone Results

	Hospitalizations due to cardiac causes (%)	Death from cardiac causes (%)	Death from any cause (%)
Placebo	40	37	46
Spironolactone	32	28	35
Relative risk reduction	20	24	24
Absolute risk reduction	8	9	11
Number needed to treat	13	11	9

Nitrates

Stable Angina

Increased exercise duration by 30-50 sec

Attacks/per week - reduced by 2.45 episodes - baseline 5-15 episodes

52% headaches - dizziness, hypotension, skin rashes

Heart failure Int JCard 2011;146:3-12

10 MONTHS	ISDN/hydralazine	Placebo
HF exacerb (%)	8.7	12.8
Mortality (%)	6.2	10.2
HF hosp (%)	16.4	24.4
Dizziness (%)	29.3	12.2
Headache (%)	47.5	19.2

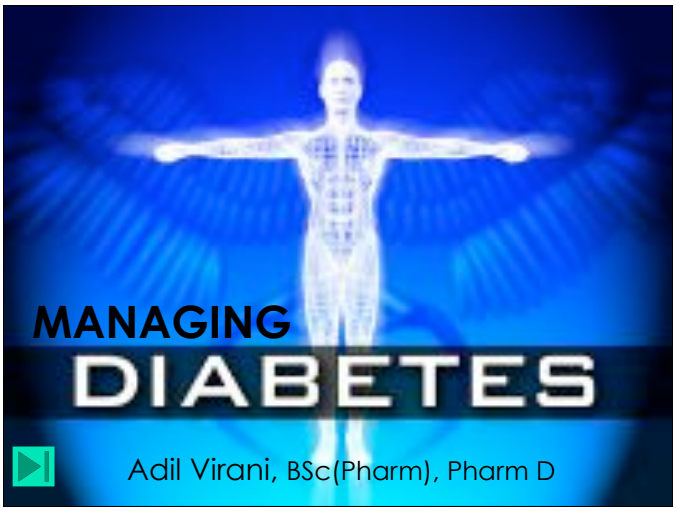
NEJM 2004;351:2049-57

Nitrates (treatment/prevention)

Lingual spray: 1 to 2 sprays (0.4 to 0.8 mg) onto or under the tongue every 3-5 min as needed, up to 3 sprays in 15 minutes

Sublingual tablet: 0.3 to 0.6 mg dissolved under the tongue or in the buccal pouch every 5 minutes as needed, up to 3 doses in 15 minutes

Headache, hypotension, tolerance



Objectives

- Compare and contrast treatment options for Type 2 DM on the basis of efficacy and safety
- Select a patient specific pharmacotherapy regimen for someone diagnosed with Type 2 diabetes
- Describe the importance of lifestyle modification in treating diabetes
- List the monitoring parameters you would use in a person taking either insulin or oral hypoglycemics
- Describe the benefits and drawbacks of patient self monitoring of blood glucose (SMBG)

Diabetes:Additional References:

- Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2008;32(suppl 1):i-S201. Available from: http://www.diabetes.ca/files/cpg2008/cpg-2008.pdf
- CADTH second-line OT draft recommendations: http://www.cadth.ca/media/compus/pdf/C1110-OT-Recs-draft-for-feedback.pdf
- NICE Diabetes guidelines (UK): http://www.nice.org.uk/nicemedia/pdf/CG66FullGuideline0509.pdf

Matt Formin

- Age 60, weight 235lbs (BMI = 33)
- Symptoms: Blurred vision, excess urination, fatigue, pain in knees
- Medical History
  - Hypertension: BP 140/90
  - Osteoarthritis affecting knees (moderate pain)
  - 1 ppd smoker
  - No allergies
- Takes ibuprofen 400 mg 2-3 times a day
- Plasma Glucose = 12.5mmol/L

Discuss how you would approach Simon's treatment with someone sitting beside you…Discuss the goals of therapy and treatment options.

Write a prescription for this person. You must write something but, feel free to write what ever you want.

Goals of Therapy for Simon?

- Control symptoms
- Minimize cardiovascular risks (assess for CVD risk factors and control where possible/applicable)
- Minimize complications from hyperglycemia
- Avoid hypoglycemia
- Establish and maintain glycemic control (HbA1C)
- Education (promote good diet and lifestyle)

Long Term Complications Associated with having Hyperglycemia

- Neuropathy
- Retinopathy (Blindness)
- Renal Dysfunction
- Cardiovascular
  - Dyslipidemia
  - Hypertension
  - Ischemia
- Psychological
- Lower limb amputation
- Sexual
- Risk of hypoglycemia with too aggressive treatment

Effect of intensive BG control with metformin on complications in overweight patients with Type 2 DM (UKPDS 34)

- 4075 patients 15 centres in the UK; Mean age 53 years for UKPDS study
- 753 entered a RCT, median duration 10.7 yrs:
  - conventional (primarily diet alone n=411) vs metformin (n=342)
- A secondary analysis compared the 342 metformin vs. 951 overweight pts given either chlorpropamide (n=265), glibenclamide (n=277)) or insulin (n=409)
- **Primary outcome:** Any DM clinical endpoint, DM death, and all-cause mortality.
- Results: Metformin HbA1c was 7.4% vs 8.0% in the conventional group
- Metformin > chlorpropamide, glibenclamide, or insulin for any diabetes-related endpoint (p=0.0034), all-cause mortality (p=0.021), and stroke (p=0.032)

Lancet. 1998 Sep 12;352(9131):854-65.

Lancet 1998;352:837-53

UKPDS 34 – United Kingdom Prospective Diabetes Study Group

	Deaths related to diabetes (%)	All cause mortality (%)	MI (%)	Stroke (%)
Metformin	8.2*	14.6**	11.4*	3.5#
Conventional	13.4	21.7	17.8	5.6
Intensive (e.g., SU/insulin)	10.8	20.0	14.6	6.3
RRR	39	33	36	38
ARR (metformin vs diet)	5.2	7.1	6.4	2.1#
NNT	19	14	16	48

UKPDS 34 – 10 Year Follow up

N Engl J Med 2008;359:1577-89

	Any diabetes related end-point %	Deaths related to diabetes %	All cause mortality %	MI %	Stroke %
Conventional/ Baseline	52-53	17-19	30-33	20-21	7
Metformin	8↓	5↓	7↓	6↓	NS
Sulfonylurea/ insulin	4↓	3↓	3↓	3↓	NS

↓ - refers to ARR

Rosy Glitazown

- Age 51, weight 190 lbs (BMI = 30)
- Symptoms: Fatigue, dyspnea
- Medical History
  - BP 130/85
  - Asthma
  - HbA1C =9; LDL = 3.1 mmol/L; TC/HDL = 5
- No allergies
- Metformin 1 gm bid
- Ventolin PRN and Qvar 100 ug BID
- SMBG 2 times daily; Most recent Plasma Glucose = 12.5mmol/L

Treatment options for Rosy

How frequently should Rosy monitor his BG?

Type 2 DM Treatment Options

- Drugs that sensitize the body to insulin and/or decrease hepatic glucose production
  - Biguanides, Thiazolidinediones (TZD), Incretins*
- Drugs that stimulate the pancreas to release more insulin (secretagogues)
  - Sulfonylureas, meglitinides (eg, nateglinide, repaglinide)
- Drugs that slow the absorption of starches
  - α-glucosidase inhibitors (eg, acarbose)
- *Incretins delay gastric emptying, decrease glucagon secretion, increase satiety, increase insulin secretion
  - GLP-1 (exenatide – sc administration)
  - DPP4 Inhibitors (sitagliptin, saxagliptin, vagagliptin*)
- Insulin

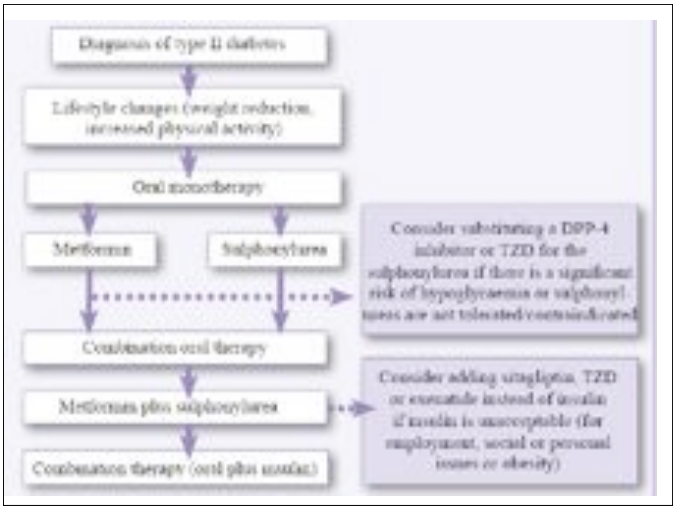
Comparative Efficacy, Safety and Cost of Oral Hypoglycemic Agents

Drug		Death, major CV events	A1c	Weight	Hypo-glycemia	Heart failure and edema	LDL	GI	Cost	Overall
Biguanides (metformin)										
Sulfonylureas										
Glitazones	pioglitazone									
	rosiglitazone									
α-glucosidase inhibitors										
Meglitinides	repaglinide									
	nateglinide									
DPP 4 inhibitors										

Best Outcome | Intermediate | Problem | Unknown

GI=gastrointestinal intolerance; LDL = LDL cholesterol level
For References see Evidence Document; Cost information as per Table 2 (see reverse)

Choudhry NK,et al. *Just a spoonful of medicine helps the sugar go down: Improving the management of type 2 diabetes* [Internet]. Boston (MA): Alosa Foundation; 2009.



Pharmacologic Management of Type 2 Diabetes

- **Add anti-hyperglycemic agents if:**

  Diet & exercise therapy do not achieve targets after 2-3 month trial

  Or

  newly diagnosed and has an A1C of ≥ 9%

A1C	& BMI	Suggested starting agent
< 9%	BMI ≥ 25	Biguanide alone or in combination
	BMI < 25	Biguanide or sulfonourea alone or in combination
≥ 9%	--	2 agents from different classes or insulin basal and/or preprandial

Biguanide (Metfomin - Glucophage®)

PROS
- Improve insulin uptake & ↓ hepatic glucose production
- HbA1c ↓ ~1mmol/L
- Data demonstrating benefits on clinical outcomes
- No hypoglycemia
- Minor weight loss
- Inexpensive
- Many years of experience
- ↓ LDL and triglycerides
- ↓ C-reactive protein

CONS
- GI upset (e.g., nausea, cramps & diarrhea)
- Caution in renal or hepatic or cardiac dysfunction
- Lactic acidosis (really rare)

FIRST LINE AGENT!

Sulfonylureas
(Glyburide - Diabeta®, Gliclazide - Diamicron®, Glimepiride -Amaryl®)

PROS
- Promote insulin secretion from pancreas (Insulin secretatogue)
- HbA1c ↓ ~1-1.4 mmol/L
- Rapid reduction in BG
- Years of experience
- Inexpensive
- Once or BID dosing

CONS
- Hypoglycemia risk
- Weight gain

MOST COST EFFECTIVE 2nd LINE AGENT!

Meglitinides
(Repaglinide-Gluconorm®, Nateglinide-Starlix®)

PROS
- Increase insulin release from pancreas
- HbA1c ↓ ~1-1.6 mmol/L
- Short acting ↓ risk of hypoglycemia

CONS
- Hypoglycemia
- Taken with meals
- Short acting (frequent dosing, e.g., tid or qid)
- Costly

Thiazolidinediones or "glitazones"
rosiglitazone-Avandia®, pioglitazone-Actos®

PROS
- ↓ hepatic glucose production & may ↑ insulin sensitivity (↑ muscle uptake)
- ↓ All cause mortality, nonfatal stroke & MI (NNT=49)
- ↑ HDL's, ↓ triglycerides and FFAs
- No adjustment in renal dysfunction
- ↓ C-reactive protein

CONS
- Edema
- Weight gain
- Worsen heart failure (NNH = 23)
- Weeks to be effective
- Fracture risk
- Costly

Benefit and Risk

Pioglitazone vs. placebo for type 2 diabetes and macrovascular events

Outcomes at mean 34.5 months	Pioglitazone	Placebo	RRR (95% CI)	NNT (95% CI)
Primary Composite endpoint*	20%	22%	9.2% (-0.9 to 18)	Not Significant
Main Secondary Composite Endpoint**	12%	14%	15% (1.9 to 26)	49 (27 to 407)
Any serious adverse event	46%	48%	4.6% (-1.1 to 9.9)	Not Significant
			RRI (95% CI)	NNH (95% CI)
Heart Failure	11%	8%	40% (22 to 60)	23 (16 to 38)

* Death from any cause, non-fatal myocardial infarction, stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg.
** Death from any cause, non-fatal myocardial infarction, or stroke.

RRR = relative risk reduction; NNT = number needed to treat; RRI = relative risk increase; NNH = number needed to harm

Dormandy JA, et al. *Lancet.* 2005; 336: 1279-1289.
Isley W. *ACP J Club.* 2006; 142(2): 34.

Glitazone meta-analysis

	Death, MI or stroke (%)	Serious heart failure (%)		MI (%)	Heart failure (%)
Pioglitazone	4.4	2.3	Rosiglitazone	1.5	1.6
Control	5.7	1.8	Control	1.1	0.8
Relative risk	23	28	Relative risk	36	100
Absolute risk	1.3	0.5	Absolute risk	0.4	0.8
NNT/NNH	77	200	NNT/NNH	250	125

JAMA 2007;298:1180-8; JAMA 2007;298:1189-95

Alpha-glucosidase inhibitors
(Acarbose - Glucobay®)

PROS
- Delays absorption of sugars
- Weight loss
- Non-systemic action
- No hypoglycemia

CONS
- Considerable GI upset and flatulence
- Modest HbA1c ↓ ~0.6 mmol/L
- Cost
- TID dosing
- Limited data showing benefits on clinical outcomes
- Used in combination with other agents

DPP-4 Inhibitors (Sitagliptin - Januvia®), Saxagliptin - Onglyza®, vildagliptin - Galvus®*)

PROS

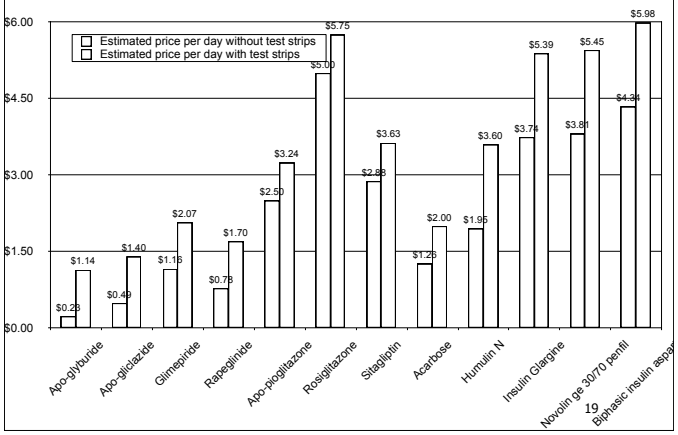
- Enhances incretin effects resulting in ↑ insulin release & ↓ glucagon release
- Modest HbA1c ↓ ~0.7 mmol/L
- No Weight gain
- No hypoglycemia
- Quite costly

CONS

- Unclear if safe in heart failure
- Urticaria, rash
- Avoid in moderate-severe renal failure
- CrCl <50ml/min

*Not currently sold in Canada

Estimated costs/day



Class	Advantages	Disadvantages
Biguanides (metformin)	**Evidence for CVD reduction! No hypoglycemia No weight gain**	**BID administration GI complaints**
Sulfonylureas, (gliburide, glipizide & glimepiride)	**Inexpensive Titratability ?CVD reduction**	**Hypoglycemia Wt. gain**
Metaglitinides (repaglinide & nateglinide)	**Repaglinide has a > reduction on A1C (vs nateglinide)**	**TID dosing Expense May not decrease CVD**
Thiazolidinediones (glitazones)	**?CVD reduction (pioglitazone)**	**Expensive Worsen HF (Edema) Wt. gain; Fractures**
Alpha-glucosidase inhibitors	**No hypoglycemia No wt. gain**	**GI complaints; Expensive TID; May not decrease CVD**
Incretins (GLP1 (exenatide) & DPPIV inhibitors	**Weight loss (exenatide) or weight neutral No hypoglycemia (both)**	**Expensive; limited data Injected (exenatide) May not decrease CVD**
Insulins (human and analogues)	**Titratability Efficacy for A1C reduction ?CVD reduction**	**Wt. gain Hypoglycemia Injected**

What's the best 2nd line choice?

- CADTH Systematic Review

- Evidence from 40 RCTs (n = 17,995)
- All important clinical outcomes assessed
- All drug classes resulted in significant A1C reductions
- Outcomes entered into an economic model for analysis
- Multiple sensitivity analyses and meta-regressions were highly consistent with the reference case analysis

http://www.cadth.ca/index.php/en/compus/second-line-therapies-type-2-diabetes/reports

CADTH Results Summary for 2nd line options

Treatment vs. metformin monotherapy	A1C (%) MD (95% CrI)	Weight (kg) MD (95% CrI)	Overall hypoglycemia Mean OR (95% CrI)
Sulfonylureas	**-0.81 (-1.06, -0.53)**	**2.02 (1.11, 2.95)**	**8.81 (4.52, 16.63)**
Meglitinides	**-0.65 (-1.14, -0.20)**	**1.81 (0.37, 3.30)**	**10.04 (3.47, 25.20)**
TZDs	**-0.86 (-1.13, -0.59)**	**2.59 (1.68, 3.51)**	**1.18 (0.54, 2.27)**
DPP-4 Inhibitors	**-0.77 (-1.00, -0.53)**	**0.57 (-0.44, 1.60)**	**1.13 (0.56, 2.21)**
α-glucosidase inhibitors	**-0.72 (-1.14, -0.32)**	**-0.91 (-2.34, 0.53)**	**1.14 (0.01, 6.67)**
GLP-1 analogues	**-0.85 (-1.22, -0.45)**	**-1.77 (-3.40, -0.15)**	**1.37 (0.33, 3.90)**
Basal insulin	**-0.83 (-1.49, -0.21)**	**1.60 (-0.39, 3.66)**	**6.76 (1.48, 21.46)**
Biphasic insulin	**-0.96 (-1.57, -0.38)**	**3.01 (1.00, 5.07)**	**13.77 (3.48, 40.43)**

CrI – credible interval, DPP – dipeptidyl peptidase, GLP - kg- kilogram, MD – mean difference, OR – odds ratio, TZD – thiazolidinedione

The Bottom Line

- The sulfonylureas (e.g., gliclazide, glyburide) are the most cost-effective 2nd line therapy. Hence, it was RECOMMENDED that a "**sulfonylurea be added to metformin for most patients with type 2 diabetes inadequately controlled on metformin monotherapy"**
  - voting: 12 members agree (unanimous); strong recommendation; low-quality evidence

http://www.cadth.ca/index.php/en/compus/second-line-therapies-type-2-diabetes/reports

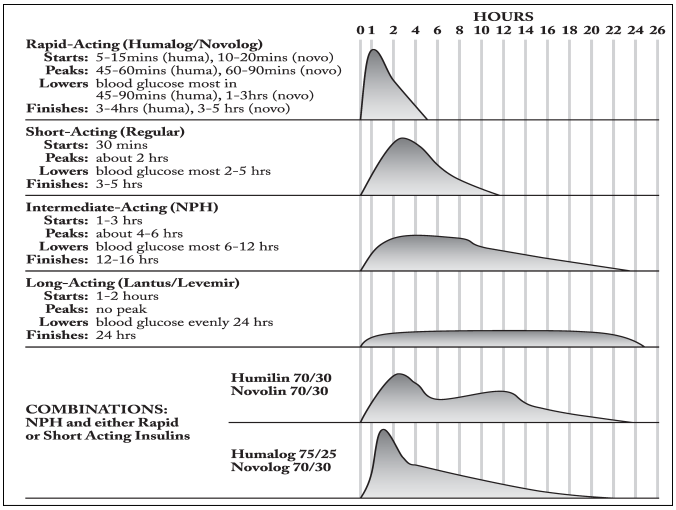
Insulin for Type 2 Diabetes

- If individual treatment goals are not reached by medications, insulin therapy (0.1-0.5 units/kg) can improve glycemic control
- Insulin may be used as initial therapy in type 2 DM if marked hyperglycemia is present (A1C ≥ 9.0%)
- Combining insulin and specific oral antihyperglycemic agents is effective in type 2 diabetes
- Use NPH prior to using long acting insulin analogues for most adults with type 1 or type 2 DM*
- Use human or rapid acting insulin analogues in adults with type 1 or type 2 DM*
- Use Lispro or Aspart preferentially in children and adolescents (less hypoglycemia)*

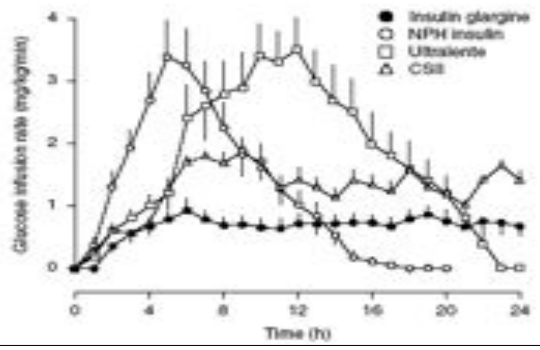
*CADTH. *Optimal Therapy Report - COMPUS* 2008;2(7).

Insulin- tips

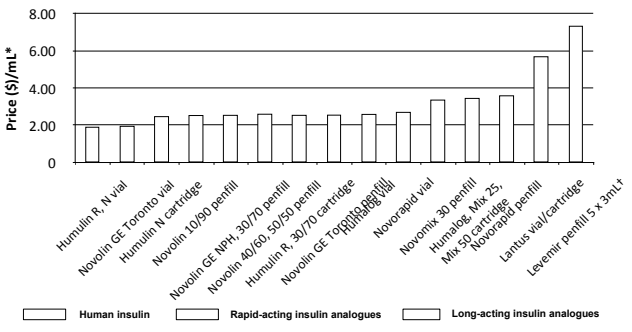
- Most patients started on long acting basal insulin (e.g., NPH then try glargine) ~0.2 units/kg at HS
- Usually adjust by 1-4 units every 2-3 days until target BG
- Reg 30 min pre-meal - ↓ post meal & fasting BG prior to next meal
- NPH at breakfast - ↓ post lunch and fasting supper
- NPH at supper- ↓ fasting bedtime (peak at night)
- NPH at bedtime- ↓ HS glucose and fasting breakfast
- Don't use Reg at HS (hypoglycemia at night)
- Target ONE lab value at a time (i.e. morning fasting)
- Fix the LOWS first then the HIGHs



Long Acting Insulin's Glucose-Lowering Effects



Insulin price comparison



**Ontario Drug Benefits Formulary/Comparative Drug Index* [database on the Internet]; 2008 Dec 3.
† D. Groleau, NovoNordisk Canada, Mississauga, ON: personal communication, 2008 Dec 9.

Targets for Glycemic Control

	A1C (%)	FPG (mmol/L)	2h Postprandial (mmol/L)
Target for most patients (age >12)	≤ 7.0	4.0 – 7.0	5.0 – 10.0
IF SAFE – To reduce nephropathy – Must balance with more hypoglycemia & potential mortality risk	≤ 6.5	4.0 – 6.0	5.0 – 8.0

Aim for target A1C in 6-12 months

* **Treatment goals and strategies must be tailored to the patient, with consideration given to individual risk factors**

Intensive glucose control

Accord - 3.5 years - 6.4% vs 7.5% A1c - 10,251, 62 y/o, diab 10 years, 35% CVD
Advance - 5 years - 6.5% vs 7.3% A1c - 11,140, 66 y/o, diab 8 years, 32%CVD

	Overall mortality (%)		Cardiovascular events (%)		Combined macro and micro* (%)	New or worsening nephropathy**(%) (subset of combined)	Hospitalization (%)	Hypoglycemia requiring medical assistance (%)		Weight gain >10kg (%)	
	ACC	ADV	ACC	ADV	ADVANCE	ADVANCE	ADVANCE	ACC	ADV	ACC	ADV
Intensive	5	8.9	6.9	10	18.1	4.1	45	10.	2.7	29	0.7kg↑
Standard	4	9.6	7.2	10.6	20	5.2	43	3.5	1.5	14	
ARR	1	NSS			1.9	1.1	2	7	1.2	15	NA

* MICROVASCULAR DATA NOT YET REPORTED FOR ACCORD
** DEVELOPMENT OF MACROALBUMINURIA ↓ BY 1.2% - NSS IN DOUBLING OF CREATININE OR DIALYSIS
SERIOUS ADVERSE EVENT DATA NOT REPORTED

N ENGL J MED 2008;358:2560-72 AND 2545-59

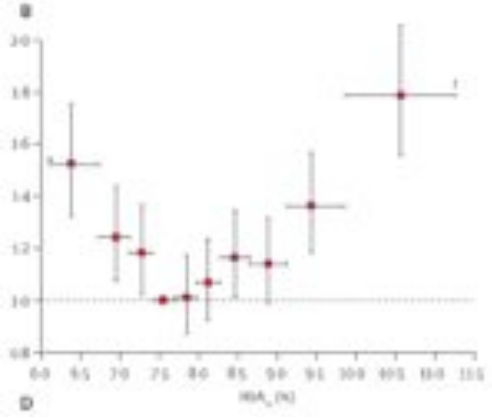
Impact of HbA_1C on absolute risks of cardiovascular events

10 year risk - UKPDS risk engine*

Age	Sex	HbA_1C	CHD (%)	Fatal CHD (%)	Stroke (%)	Fatal Stroke (%)
55	F	6	8.3	4.2	3.3	0.5
		8	10.7	6.2		
		10	13.8	8.8		
	M	6	15.2	7.7	4.6	0.7
		8	19.5	11.1		
		10	24.7	15.7		

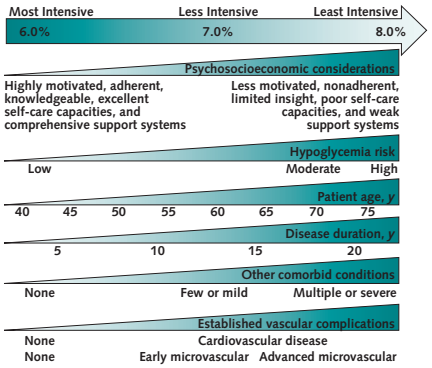
*Non-smoker, TC 5, HDL 1, SBP 140, diabetes 5 years

Mortality by A1C



Lancet 2010; 375: 481–89

Figure. **Framework to assist in determining glycemic treatment targets in patients with type 2 diabetes.**

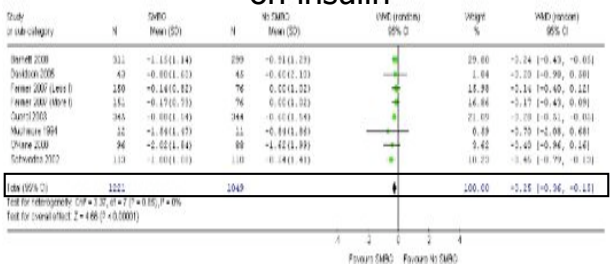


Ismail-Beigi F et al. Ann Int Med, 2012

BG/HbA1c Monitoring

- Hemoglobin A1C q3months
- Self-monitoring of blood glucose
  - Type 1 or type 2 with insulin – 2-3 times daily
  - Type 2 – Only at disease onset and at times of change in medications (or when using insulin secretagogues)
- Ketone testing
  - Type 1 diabetics in periods of acute illness

Systematic Review of SMBG in T2DM not on insulin



SMBG resulted in a slightly lower A1C **{-0.25 (95% CI -0.36 to -0.15)}** vs no monitoring in adults with T2DM not on insulin

SMBG in those not taking insulin is of little clinical value

- Other Systematic Reviews
  - 0.25% decrease in HgA1C[1]
  - O.39% decrease in HgA1C[2]
- RCT: 0.3% decrease in HgA1C[3]
- RCT: no diff in HgA1C[4]
  - More hypoglycemic in self monitoring (NNH=6)
- RCT: no diff in A1C, med use, hypoglycemia,[5]
  - Higher depression scores (by 6%)

1) Diabet Med. 2000;17:755-61; 2) Cochrane. 2005;2:CD005060; 3) Diabetes Metab 2003; 29: 587-94; 4) BMJ 2007;335;132-25; 5) Esmon BMJ 2008; 336:1174-77

CADTH Recommendation for SMBG

- **For most adults with T2 DM not taking insulin, the routine use of blood glucose strips is NOT recommended.**

  Voting: 8 agree, 4 disagree; strong recommendation; moderate quality evidence
- Exceptions:
  - Hypoglycemia concerns (e.g., Those taking secretagogues, history of severe hypoglycemia, inadequate calorie intake, etc)
  - Acute illness
  - Changes in pharmacology or routine
  - Pregnant or planning to be

Hypoglycemia: Symptoms

- Neurogenic (autonomic)
  - Trembling, palpitations, sweating, anxiety, hunger, nausea, tingling
- Neuroglycopenic
  - Difficulty concentrating, confusion, weakness, drowsiness, vision changes, difficulty speaking, headache, dizziness, tiredness

Severity of Hypoglycemia

- Mild
  - Autonomic symptoms present; individual can self-treat
- Moderate
  - Autonomic and neuroglycopenic symptoms; individual can self-treat
- Severe
  - Individual requires assistance of another person; unconsciousness can occur. Plasma glucose typically <2.8 mmol/L

Hypoglycemia - Treatment

Severity	Treatment of hypoglycemia	
Mild to moderate	▪15g of carbohydrate preferably as glucose or sucrose tablets or solution ▪Wait 15 minutes, retest and retreat with 15g if BG<4.0	
Severe	Conscious	▪ 20g of carbohydrate preferably as glucose or sucrose tablets or solution ▪ Wait 15 minutes, retest and retreat with 15g if BG<4.0
	Unconscious	▪ 1mg glucagon SC or IM if ≥ 5 years old ▪ Emergency services should be called

- Once the BG is within target, the person should have the usual snack or meal, or if this is more than 1 hour away, a snack should be taken

Monitoring Complications

Area	Type of screening	Type of diabetes	Recommendation	
Neuropathy	Assess loss of sensation at great toe	Type 1	After 5 years duration in post pubertal, then annually	
		Type 2	At diagnosis, then annually	
Retinopathy	Exam by experienced professional	Type 1	Annually 5 years after onset of diabetes in those ≥ 15 years old	
		Type 2	At time of diagnosis, then every 1-2 years	
Nephropathy	Random urine ACR & random urine dipstick	Type 1	After 5 years duration in post pubertal, then annually	
		Type 2	At diagnosis, then annually	
Dyslipidemia	Fasting lipid profile	Both types	At diagnosis & every 1-3 years. Targets:	
			Moderate risk: LDL-C <3.5 mmol/L TC:HDL-C <5.0	High risk: LDL-C <2.5 mmol/L TC:HDL- C <4.0
Hypertension		Both types	Measured at every visit, target 130/80 mm Hg	

Time to Butt Out

Adil Virani, BSc (Pharm), Pharm D, FCSHP

Objectives

After this presentation, participants should be able to:

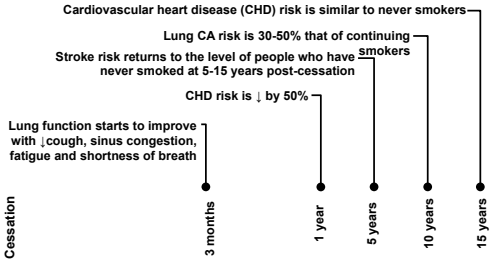
1. Describe the benefits of smoking cessation
2. List the withdrawal symptoms of quitting smoking
3. List the main treatment options to help people quit smoking and their likelihood of producing abstinence at 6-12 months
4. Describe the advantages and drawbacks of various pharmacological smoking cessation treatment options
5. List the appropriate dosages and duration of treatment of smoking cessation medications
6. Describe the monitoring parameters you would use when initiating a specific smoking cessation treatment

Smoking Cessation

"The single most important step that smokers can take to enhance the length and quality of their lives."

US Surgeon General, Guide to quitting smoking. American Cancer Society, 2006

Potential Lifetime Health Benefits of Quitting Smoking[1-2]



1. CDC. Surgeon General Report 2004: American Cancer Society. Guide to Quitting Smoking.
2. US Department of Health & Human Services. The Health Benefits of Smoking Cessation: A Report of the Surgeon General. 1990.

Smoking Cessation

"Stopping smoking…may have a greater effect on reducing the risk of mortality among patients with CHD who smoke than the effect of any other intervention or treatment."

Critchley JA, Capewell S *JAMA*;2003;290:86-97

Smoking cessation is considerably more "cost effective" per life year saved than most pharmacological therapies (e.g., drugs for hypertension, hyperlipidemia).

Benowitz NL *Prog Cardiovasc Dis* 2003;46:91-111

Did you know?

- ~40% of smokers attempt quitting each year
- Most attempts are unaided
- 6 mo abstinence rates (unaided) = 3-5%
  - Most relapse in the first week
  - Most smokers have several triggers
- Nicotine's half life is <2 hrs
- Withdrawal symptoms peak at 1 week and can last months

Nides, M. Am J Med 2008:121;S20-31

If you had a patient (with your age and medical history) who smoked 1ppd x 4 yrs – what method would you use to quit?

Going "smoke free"

- Ask, Assess and Assist
- Nonpharmacological approaches
- Nicotine Replacement Therapy (NRT)
  - The 'patch'
  - Chewing gum, lozenges
  - Nasal spray
  - Nicotine Inhaler
- Delayed onset options
  - Bupropion (antidepressant)
  - Varenicline
  - Nortriptyline (antidepressant) 2nd line [OR = 2.14 (1.49-3.06)]
  - Clonidine (antihypertensive) 2nd line [OR = 1.89 (1.30-2.74)]

Choosing a stop smoking medication?

	Description	Instructions	Cost	Possible Side Effects
Nicotine Patch	• Nicotine from the patch is absorbed through the skin into the blood • Nicotine patches come in 3 strengths - 7, 14 & 21 mg • Takes up to four hours to reach peak levels of nicotine in the blood • Provides a steady dose of nicotine	• Apply patch on to clean, dry skin • Change patch every 24 hours • If you have difficulty sleeping, remove before bedtime • Regularly change location on the skin	$25-30/wk	• Skin rash • Sleep disturbance • Headache • Dizziness • Nausea • Stomach upset
Nicotine Inhaler	• Nicotine from the inhaler is absorbed through the mouth into the blood • The nicotine inhaler is a thin plastic tube containing a nicotine cartridge • Takes 20 minutes to reach peak nicotine levels in the blood	• Do not puff on inhaler like a cigarette • Nicotine vapour is held in the mouth and not drawn into the lungs • Puff is needed to release nicotine • Take slow puffs to avoid throat burn • Avoid eating and drinking 15 minutes before and after use • Mouth piece can be cleaned and reused	$40/wk	• Irritation mouth/throat • Headache • Nausea
Nicotine Gum	• Nicotine from the gum is absorbed through the mouth into the blood • Nicotine gum comes in 2 strengths—2mg & 4mg • Takes 30 minutes to reach peak nicotine levels in the blood	• Nicotine gum is not chewed like regular gum • Chew until there is a peppery taste and then park between the teeth and inside of cheek	$40-55/wk	• Cough to decrease • Nausea • Hiccups • Jaw pain • Irritate mouth
Nicotine Lozenge	• Nicotine from the lozenge is absorbed through the mouth into the blood • Nicotine lozenge comes in 3 strengths—1mg, 2mg & 4mg • Takes 30 minutes to reach peak nicotine levels in the blood	• Allow the lozenge to dissolve in the mouth	$40-55/wk	• Nausea • Headache • Heartburn • Coughing • Hiccups
Stop Smoking Prescription Medications	Bupropion SR (Zyban) • Comes as a pill • Also used as an anti-depressant • Reduces nicotine withdrawal symptoms	• To be taken one week before stopping smoking • Not recommended for people with a history of seizures, eating disorders or using certain medications	$15-36/wk	• Sleep disturbance • Dry mouth
	Varenicline (Champix) • Comes as a pill • Reduces nicotine withdrawal symptoms and smoking satisfaction	• To be taken one week before stopping smoking		• Nausea • Sleep disturbance • Severe mood change (rare)

Ask, Assess and Assist

Ask: *"Are you willing to try quitting?"*

YES:

- ***S*** ...Set a quit date
- ***T*** ...Tell family & friends
- ***A*** ...Anticipate challenges
- ***R*** ...Remove tobacco items
- ***T*** ...Tobacco replacements?

Assess Conviction: 1 to 10

Assess Confidence: 1 to 10

NO:

Here to help if you change your mind.

Need a Comprehensive Strategy

- Smoking addiction has two main components:
  - Psychological *(behavioural factors)*
  - Physiological *(pharmacological treatment)*
- Advice and behavioural support increase the chances of successfully quitting!
- The biggest predictor of success is the number of quit attempts.

Jarvis MJ. *BMJ* 2004;328:277-279.
Hughes JR. *CA Cancer J Clin* 2000;50:143-151.

Nicotine Replacement Therapy (NRT)

- Delivers nicotine that binds to the nicotinic acetylcholine receptor (nAChR) receptors[1]
- Does not counter the additional satisfaction from smoking[1]
- NRTs does not deliver nicotine to the circulation as fast as smoking[2]

1. American Heart Association website.
2. Sweeney CT *et al. CNS Drugs* 2001;15:453-467.

Nicotine Plasma Levels by Cigarettes vs. NRT Products

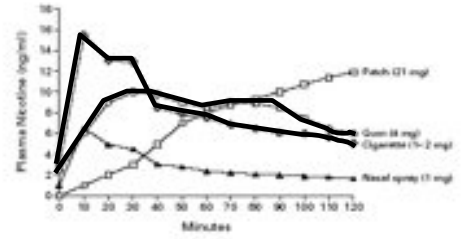


Figure 2. Plasma Nicotine Levels after a Smoker Has Smoked a Cigarette, Received Nicotine Nasal Spray, Begun Chewing Nicotine Gum, or Applied a Nicotine Patch.
The amount of nicotine in each product is given in parentheses. The pattern produced by the use of the nicotine inhaler (not shown) is similar to that for nicotine gum. Modified from Garrett et al.[3]

Sweeney CT *et al. CNS Drugs* 2001;15:453-467.

NRT: Nicotine Gum

- Nicotine polacrilex
  - (*e.g.*, Nicorette®, Thrive gum ®)
- Method of delivery:
  - Nicotine released from gum upon chewing
  - Bite the gum then, chew, chew until tingle, then park for 30-60 sec, repeat for 30 min
  - Start with about 10-12 pieces/day
  - Chew regularly for 4 - 12 wks, then PRN cravings for up to 6 months
- Avoid acidic beverages *(coffee, alcohol, pop, citrus fruit juice)* within 15 min (absorption)

NRT: Nicotine Lozenge

- Dehydrated Nicotine bitartrate
  - *e.g.*,Thrive Lozenge®
  - Nicotine released by sucking on lozenge..then park lozenge (when taste is strong); repeat x 30 min
- Dosage:
  - ≥ 20 cigarettes / day = 2mg
  - < 20 cigarettes / day = 1 mg
  - 5-15 lozenges/ day for 1-3 months, then PRN cravings

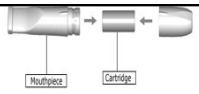
Nicotine Gum or Lozenge: Common Adverse Events

Local
- □ Jaw pain, tooth disorders
- □ Gum sticking to dentures
- □ Throat irritation (5%)
- □ Stomatitis (4%)
- □ Gingivitis (1%)
- □ Taste perversion

GI
- □ Hiccups (10%)
- □ Dyspepsia (9%)
- □ Nausea (9%)

CNS symptoms
- □ Headache (11%)
- □ Dizziness (4%)
- □ Insomnia (2%)

Nicotine Inhaler



- Nicotine is absorbed through oral mucosa
- Dose:
  - 1 cartridge (4mg)
  - 4-12 cartridges/d X 3 mo, then taper
  - 20 min/cartridge
  - Expires within 24 hours if not used
- Side effects
  - Cough
  - Mouth and throat irritation
    - Changing the technique might help in these cases (small puffs less irritating than long puffs)
  - Rhinitis, pharyngitis

NRT: Nicotine Patches

- E.g., Habitrol®, Nicoderm®
- New patch (7, 14, 21 mg) applied every 24 hrs, taper dose q 3-4 wks
- 3 months therapy
- Advantages:
  - Eliminate variability of GI absorption
  - Reduce nicotine first-pass metabolism
  - Enhance patient compliance
- Disadvantages:
  - Local skin irritation
  - Insomnia
  - Wears off in 20-24 hrs

Efficacy of NRT vs. Placebo
(@ 6 or longer)

Comparison	Trials (n)	Participants (n)	Pooled OR (95% CI)
Gum	52	17,783	1.66 (1.52–1.81)
Patch	37	16,691	1.81 (1.63–2.02)
Nasal spray	4	887	2.35 (1.63–3.38)
Inhaler	4	976	2.14 (1.44–3.18)
Tablets/lozenges	4	2739	2.05 (1.62–2.59)
Combination vs. single type	7	3202	1.42 (1.14–1.76)
Any NRT vs. control	103	39,503	1.77 (1.66–1.88)

1. Silagy C *et al. Cochrane Database Syst Rev* 2004;(3):CD000146.
2. Stead L, Lancaster T. *Int J Epidemiol* 2005;34:1001–1003.

Is it withdrawal or too much NRT?

Symptoms	Withdrawal	Overdose
Anxiety, irritability	√	
Insomnia	√	
Headache, dizziness	√	√
Nausea, vomiting, abdominal pain, diarrhea		√
Salivation		√
Sweating, flushing		√
Palpitations		√

NRT Contraindications

- Unstable cardiac condition
  - 2 weeks following heart attack
  - Unstable angina
  - Any unstable cardiac condition
- Pregnancy and breastfeeding ???
- Patients under 18 years old ???

Safety of NRT

- NRT delivers nicotine without the toxins associated with smoking[1]
  - Toxins, not nicotine, cause most tobacco-related health concerns[1]
  - Tobacco smoke contains >4000 chemicals; at least 50 are carcinogenic[2]
- In more than 100 clinical trials, including long-term (>5-yr) data,[3] NRT has not been associated with increased risk of cancer[1]

1. Benowitz NL. In: Benowitz NL (ed.). *Nicotine safety and toxicity*. Oxford University Press, 1998; pp.185-95.
2. Health Canada. *The facts about tobacco*.http://www.hc-sc.gc.ca/hecs-sesc/tobacco/facts/index.html.
3. Murray RP, *et al: Chest* 1996; 109(2):438-45.

NRT: Key Messages

- Safe and effective for smoking cessation (esp. in conjunction with a behavioural program).
- Delivers nicotine (more slowly and at lower levels vs. smoking) to nAChR receptors
- NNT vs placebo ~11-19
- Acidic beverages affect absorption
- NO Carbon monoxide, oxidants or >4000 other chemicals and mutagens!
- The use of NRT is not associated with any increase in risk of MI, stroke, cancer or death.

Hubbard R et al. *Tobacco Control* 2005;14:416-21
Benowitz NL. *Nicotine safety and toxicity.* Oxford University Press, 1998; pp.185-95.

Which of the following statements regarding bupropion is/are TRUE?

A. Bupropion's efficacy at 6 months is equivalent or slightly better than NRT
B. Bupropion's efficacy at 6 months is less effective than NRT
C. Bupropion's efficacy at 6 months is superior to nortriptyline
D. Bupropion's efficacy at 6 months is equivalent to varenicline

Bupropion SR (Zyban®, Wellbutrhin®)

- Non-nicotine SR tablet
  - Blocks reuptake of dopamine and noradrenaline[1,2]
  - Non-competitive inhibition of brain nicotine receptors
- Started 1-2 wks before quit date
  - 150mg once daily x 3 days, then bid for 7 - 12 wks
- Contraindications
  - History of head injury, CNS tumour, seizures
  - Anorexia, bulimia, heavy alcohol use

1. Henningfield JE *et al. CA Cancer J Clin* 2005;55:281–299.
2. Foulds J *et al. Expert Opin Emerg Drugs* 2004;9:39–53.

Most Frequent Adverse Events With Bupropion

Insomnia	20-40%
Dry mouth	10%
Disturbed concentration	9%
Dizziness	9%
Nausea	9%
Constipation	8%
Discontinuations	8%

Nortriptyline

- Tricyclic antidepressant
  - Blocks the reuptake of NA and 5HT
- Start 1-3 wks before quit date
- 25mg daily and titrate up to 100 mg
- Treat for 12 wks
- As effective as buproprion
- Side effects:
  - Dry mouth, blurred vision, constipation, sedation, confusion, urinary retention

Bupropion & Nortriptyline: Key Messages

- >30 RCTs for Bupropion (n>7,000)
- Abstinence rates at 12 months:
  - BUP 19% vs 9% Placebo
  - Pooled OR ~ 2
- Nortriptyline (75-100mg) as effective as BUP
- NNT (for both agents) ~ 10-12

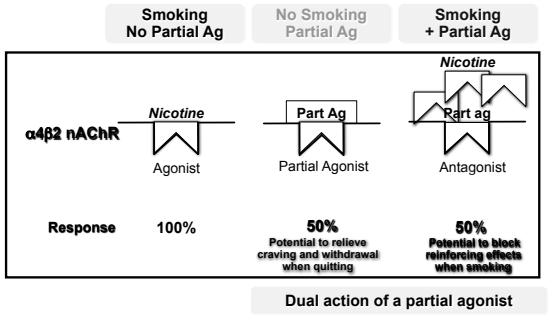
Hughes JR et al. The Cochrane Library, 2004, Issue 3, Art. NO CD 000031.
NICE Guidance on the use of NRT and bupropion for smoking cessation. No. 39. March 2002.
Eisenberg MJ et al. CMAJ. July 2008;179(2):135-144

Varenicline (Champix®)

- Partial agonist and antagonist at ($\alpha4\beta2$) nAchR
  - Health Canada NoC: January 24, 2007
- Start before quit date
- 0.5mg – 1mg bid x 12 weeks
- Though not studied, given the mode of action, there may be limited additional benefit of combo with NRT
- May be more effective than NRT or bupropion?

Cahill et al, Cochrane Database of Systematic Reviews, 2007
Gonzales D *et al. JAMA* 2006;296:47-55.
Jorenby DE *et al. JAMA* 2006;296:56-63.

$\alpha4\beta2$ nAChR Partial Agonists



Dual action of a partial agonist

CMAJ JAMC RESEARCH

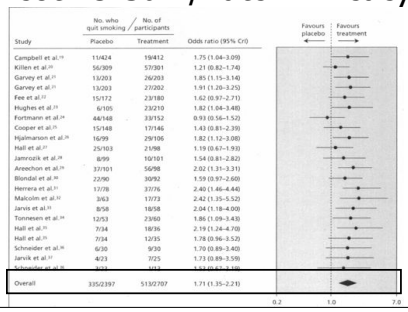
Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials

Eisenberg MJ et al. CMAJ. July 2008;179(2):135-144

Mark J. Eisenberg MD MPH, Kristian B. Filion MSc, Daniel Yavin BSc, Patrick Bélisle MSc, Salvatore Mottillo BSc, Lawrence Joseph PhD, André Gervais MD, Jennifer O'Loughlin PhD, Gilles Paradis MD MSc, Stephane Rinfret MD MSc, Louise Pilote MD PhD

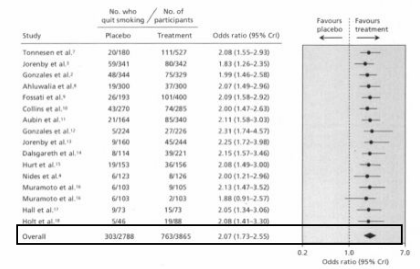
- Extensive Meta-analysis of RCTs
- 69 trials; n=32,908 pts
- Included studies reporting 6-12 mo abstinence rates for 7 pharmacolgical therapies
- Objectives:
  - Summarize the efficacy of approved therapies
  - Compare varenicline vs. bupropion
  - Indirect comparison of all 7 approved therapies

Nicotine Gum/Patch Efficacy



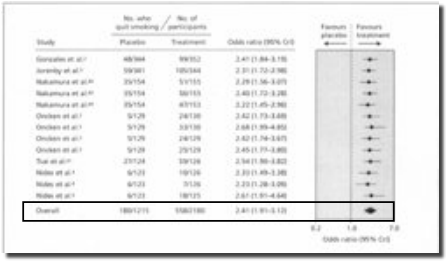
With Nicotine Gum or Patch, the odds of abstinence at 6 months or longer is 1.71 or 1.95

Bupropion Efficacy



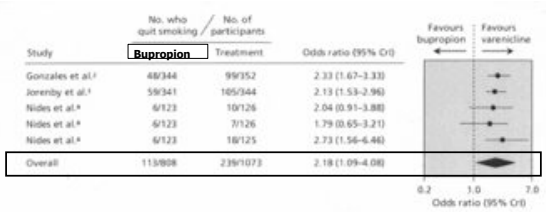
Bupropion doubles your odds of abstinence at 6 months or longer

Varenicline Efficacy



Varenicline more than doubles your odds of abstinence at 6 months or longer

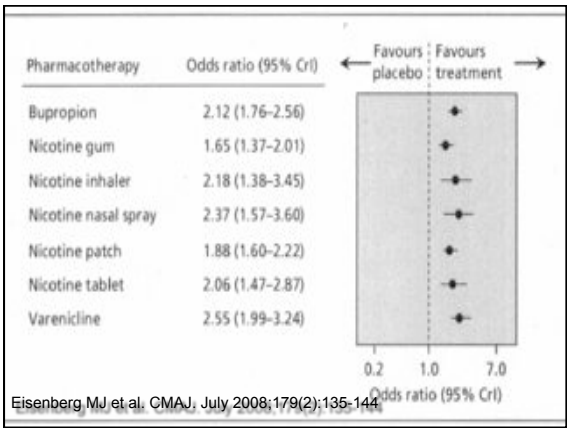
Varenicline vs. Bupropion at 26 wks +



Though quite rates are small, Varenicline increases the odds of abstinence at 6 months over bupropion

Efficacy of treatments

	Nicotine gum	Nicotine patch	Nicotine inhaler	Bupropion	Varenicline
Treatment Duration (months)	1-3	2-3	3-6 **(longer)**	2-3	3
Dosage	2, 4 mg	7, 14, 21mg	6-12 cartridges / day (higher)	150-300 mg/day	**0.5** - 1 mg bid
Efficacy at 6-12 month vs Placebo (OR [CI])	**1.66 [1.65]** (1.52-1.81)	**1.81 [1.88]** (1.63-2.02)	**2.14 [2.18]** (1.44-3.18)	**2.06 [2.12]** (1.77-2.40)	**[2.55]** (1.99-3.24)
Abstinence rates at 6 mo (or longer) +/-3%; Placebo =8%	**13%**	**14.5%**	**17%**	**16.5%**	**26%**
NNTs (vs. Placebo) for abstinence at 6 mo or longer).	**19**	**16**	**11**	**12**	**6-8**



Eisenberg MJ et al. CMAJ. July 2008;179(2):135-144

Adverse Effects

	Nicotine gum/ Lozange	Nicotine patch	Nicotine inhaler	Bupropion	Varenicline
Common side effects	• Dyspepsia (9%) • Nausea (9%) • Hiccups (10%) • Headache (11%) • Jaw pain • Denture issues • Throat irritation (5%)	• Headache • Disturbed sleep • Site rash	• Throat irritation • Sneezing • Coughing • Rhinitis • Pharyngitis	• Insomnia (20%) • Dry mouth • Disturbed concentration • Nausea	• Nausea (30%) • Headaches • Abnormal dreams • Constipation
Serious side effects				• Seizures • Angioedema	**Suicidal ideation** **Severe allergic reactions**
Cost/ 3month	• $250 - 400	•$280 - 345	• 500 (6x/d)	•$180 •(Nortriptyline = $75)	•$330

http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2010/champix_2_hpc-cps-eng.php

Limitations of Current data

- Many patients lost to follow up (high drop out rates (30-45%) at 52 wks
- No head-to-head trials of varenicline vs. NRT
- Limited data for some treatment options
- Need to look at a similar time frame
- Abstinence data >12 months is sparse
- Patient characteristics differ
- Publication bias?
  - No negative studies published
  - 2 studies dominate varenicline data (published multiple times?)

Questions?

Prescribing Principles

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Outline

1. Obtaining a thorough medication history
2. Starting and stopping medications
3. Dosing
4. Drug interactions
5. Off label prescribing
6. Documentation
7. Examples of how to write (and not write) prescriptions

Obtaining a Thorough Medication History (BPMH)

+ How do you currently take medication histories?

- What questions do you ask?
- What sources of information do you use?

Components of the Best Possible Medication History (BPMH)

1. All current and relevant past medications (Rx and non-Rx), & complimentary/alternative medications (CAMs)
2. List, for each item, the dose, dosage form, frequency, route, indication, level of patient adherence & info source
3. Information sources: the patient, patient's family, Rx vials/packages, pharmacist/pharmacy, PharmaNet (in BC) primary care provider, & specialists.
4. Assess appropriateness of therapies
5. Identify and reconcile DISCREPANCIES (what the patient is doing vs. what the care provider believes)

http://www.saferhealthcarenow.ca/
www.canadapharma.org (Knowledge is best Medicine)

Medication History: TIPS

+ Use both open-ended questions (what, how, why, when) and yes/no questions
+ Use a systematic approach to best get complete information (e.g., meds over last 24 hrs or head to toe)
+ Non-judgmental approach
+ Keep it simple: e.g., avoid medical jargon
+ Avoid leading questions
+ Explore vague responses (non-compliance)
+ Prompt for specific types of medications (e.g., pain, sleep, GI, eye/ear drops, patches, creams/ointments, inhalers)

Medication History Sample Questions

MEDICATION HISTORY SCRIPT

Allergies
- Do you have an allergy to or avoid any medications due to side effects?
- What type of reaction do you have?

Prescription Medications
- What prescription medications do you take on a regular basis?
- When do you take them?

Non-prescription Medications
- What non-prescription over-the-counter medications do you take on a regular basis?
- When do you take them?

Herbals, Supplements, Vitamins
- What herbal, natural or homeopathic remedies do you take?
- What vitamins or minerals do you take?
- When do you take them?

ADDITIONAL QUESTIONS

Do you use any:
- Eye drops
- Nose sprays
- Puffers (inhalers)
- Medicated lotions or creams
- Medicated patches

Do you receive any:
- Needles (injections)
- Samples from the doctor's office
- Study medications

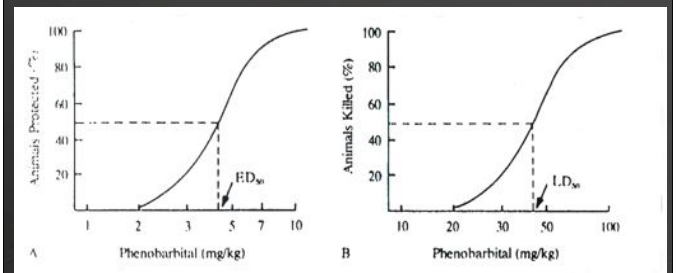
Do you take any medication on a regular basis for:
- Sleep
- Your stomach
- Your bowels
- Pain

Did you or your doctor recently change or stop any of your medication?

Dosing principles

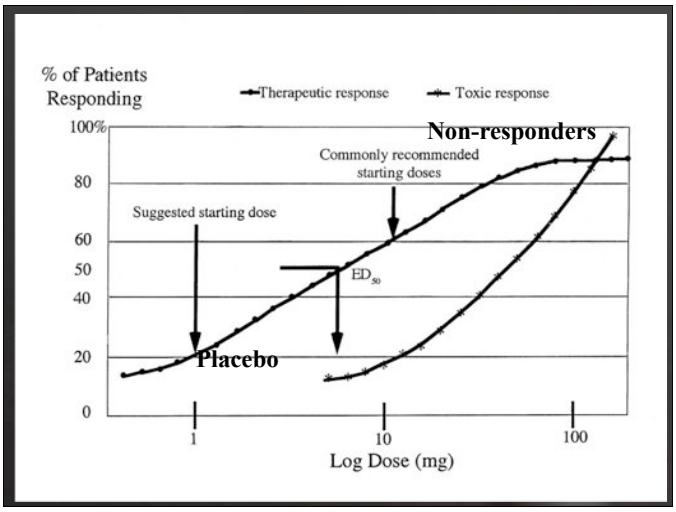
1. For the majority of conditions there is rarely a need to get an immediate result
2. For many marketed drugs, the recommended starting doses are too high
3. The placebo group response (not the placebo effect) for numerous conditions is approximately 20-40%
4. There is no reliable way to predict how a patient will respond to a drug (pharmacodynamics) or how they will eliminate a drug (pharmacokinetics)
5. Approximately ¾ of side effects of drugs are dose related

Seizure prevention Lethal overdose



Rat Data

Fig. 2-2. Quantal dose-response curves based on all-or-none responses. A. Relationship between the dose of phenobarbital and the protection of groups of rats against convulsions. B. Relationship between the dose of phenobarbital and the drug's lethal effects in groups of rats. (Data adapted from C. R. Craig and F. E. Shideman, J. Pharmacol. Exp. Ther. 176:35, 1971.)



Discussion with Patient

1. There is no urgency to getting a response - find the lowest effective dose for you over the next few months
2. No way to know ahead of time what dose is the "best" one for you
3. The typical recommend starting doses for many medications are too high
4. Starting with a 1/4 to an 1/8 of the dose - decrease the chance of side effects
5. Many conditions get better over time
6. "You" will determine the correct dose
7. You may get better because of the drug, or tincture of time effect

6.25 mg of hydrochlorothiazide	effective at lowering blood pressure –first marketed at 50 to 200 mg daily
6.25 mg of captopril	effective at lowering blood pressure as a single dose and when dosed chronically BID - captopril 25 mg PO TID is still a commonly recommended initial starting dose for hypertension
25 mg of sildenafil (Viagra)	effective dose for erectile dysfunction
25 mg of sumatriptan (Imitrex)	works almost as well as100 mg - most drugs in this class a flat dose-response curve is seen at the doses studied
5 mg daily of fluoxetine (Prozac)	effect similar to 20 mg 40 mg daily
0.25 mg of ezetimibe (Ezetrol)	1/40th of the recommended initial starting dose of 10 mg provides 50% of the LDL lowering effect seen with 10 mg
15 mg of elemental iron daily	as effective for anemia in the elderly as 50 mg and 150 mg with a lower incidence of side effects
150 mg daily of bupropion (Zyban)	produces the same rate of smoking cessation at one year as 300 mg daily
10 mg of atorvastatin	produces 2/3 of the effect on cholesterol as that seen with an 80 mg (8-fold increase) dose
200 mg of ibuprofen (Motrin)	as effective as 400 mg for migraine headache
25 mg of ranitidine (Zantac)	as effective as 125 mg for heartburn relief

Practical Suggestions

1. Not all drugs come in dosage forms that allow small doses to be used
2. The majority of tablets can be split - use a pill cutter
3. Some capsules can be opened
4. Increase the interval
5. Liquid form - pediatric dosage forms may be useful to start

Dosing

If Dying - Give lots
If No hurry - start with at most a 1/2, and maybe even 1/4 to 1/8

"Drugectomies"

in the beginning - until proven otherwise
Assume the drug is wrong
Assume the dose is wrong

Come up with a monitoring plan in conjunction with the patient
Cut dose in 1/2 for a week or two
Cut dose in 1/2 again for a week or two
Then stop

Drug Interactions

either pharmacodynamic or pharmacokinetic

1.Pharmacodynamic - result in additive or antagonistic pharmacological effects

2.Pharmacokinetic - involve induction or inhibition of metabolizing enzymes in the liver or elsewhere, displacement of drug from plasma protein binding sites, alterations in gastrointestinal absorption, or competition for active renal secretion

from http://www.nephrologypharmacy.com/downloads/druginteraction2e.pdf

http://www.drugs.com/drug_interactions.php

http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-herbal-di.pdf

iPhone app - medscape, Epocrates, Lexicomp, Micromedex

most important DDIs

Warfarin	Thyroid, NSAIDs, cimetidine, fibric acid, barbiturates, sulfinpyrazone
Benzodiazepines	Azoles
Carbamazepine	Propoxyphene, macrolides
Cyclosporine	Rifampin
Dextromethorphan	MAOIs
Digoxin	Clarithromycin
Ergots	Macrolides
Ganciclovir	Zidovudine
MAOIs	Sympathomimetics
Meperidine	MAOIs
Methotrexate	Trimethoprim
Nitrates	Sildenafil
Pimozide	Macrolides, azoles
SSRIs	MAOIs
Theophylline	Quinolones, fluvoxamine

Duplicate action drugs
Sedation
blood pressure
Potassium

J Am Pharm Assoc 2004;44:142–151

PPIs

Off Label Prescribing

- Use of a prescription medication to treat a condition Health Canada has not granted an "indication"
- A medication that is "not indicated" for a particular use, is NOT necessarily contraindicated for that condition?
- How does a drug get an indication for a medical condition?
- What patient populations often do not have indications?
- Must consider each patient's circumstances when off label prescribing. Document your rationale and monitoring plan

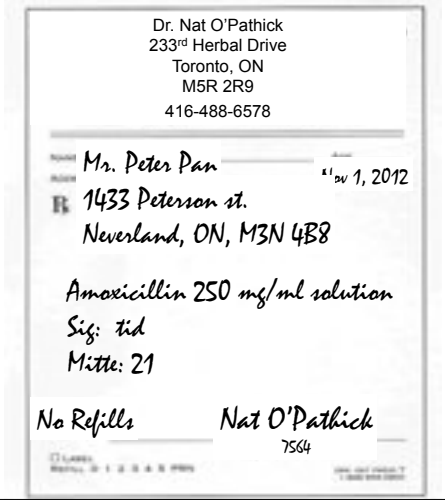
Writing Prescriptions

Prescription Requirements

Ontario College of Pharmacists

1. Date
2. Name and address of patient
3. Name, strength, quantity and form of drug or ingredient(s)
4. Directions for use (include frequency or interval or maximum daily use)
5. Refill authorization (# and interval between refills) - 0 if left blank
6. Name and College ID of practitioner
7. Signature

Can this prescription be improved?



Prescriber Information

1. Name
2. Address
3. Telephone number
4. College of Naturopathic Physicians Identity Number
5. Imprinted on blank prescription or personalized self-inking stamp
6. SIGNATURE

Ontario College of Pharmacists Legislation

- Prescriptions need to be either:
  - Written & signed
  - Dictated to a pharmacist by telephone (except straight narcotics)
  - Sent electronically (Faxed)
- Prescriptions for medications are active for 1 year from the date on the prescription (except oral contraceptives, which are 2 years)
- Pharmacists keep prescriptions for at least 2 years

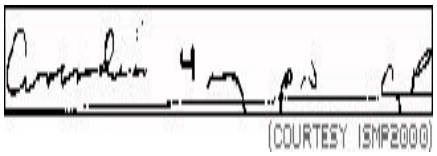
Common Issues that <u>may</u> result in Medication Errors

+Illegible handwriting
+Use of abbreviations
+Incomplete directions
+Lack of patient information (allergies)
+Lack of appropriate dosing information (decimals & trailing zeros)

Prescription Checklist

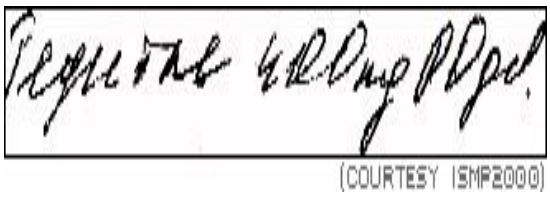
1. Patient Name*
2. Address*
3. Age/weight
4. Purpose
5. Date*
6. Drug Name*
7. Manufacturer
8. Strength*
9. Mitte(Send)/Quantity*
10. Dosage form
11. Sig(Take)/Directions* (Include frequency & daily maximum if PRN)
12. Prescriber Signature*
13. ND ID Number*
14. Prescriber address and phone #*
15. Refills

Which medication is this?



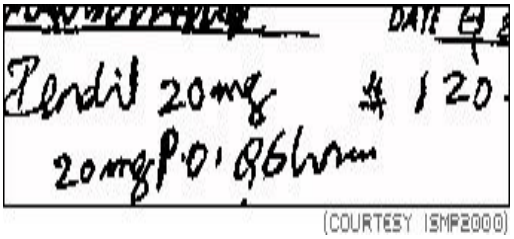
⇨ **Avandia** – rosiglitazone 4 mg
-antidiabetic

Coumadin – warfarin 4 mg
-anticoagulant



Tegretol (carbamazepine) 400 mg orally daily
-anticonvulsant

⇨ **Tequin** (gatifloxacin) 400 mg orally daily
-quinolone antibiotic



Plendil (felodipine) 20 mg orally every 6 hours
-Calcium channel blocker

⇨ **Isordil** (isosorbide dinitrate) 20 mg orally every 6 hours

Look Alike/Sound Alike Drugs

Bupropion vs. Buspirone
Plavix vs. Paxil
Adderall vs. Inderal
Metoprolol vs. misprostol
Tegretol vs. toradol
Lasix vs. Losec
Flomax vs. Fosamax
Atarax vs. Ativan

National association of Chain Drug Stores has a list www.nacds.org

Additional Prescribing Tips

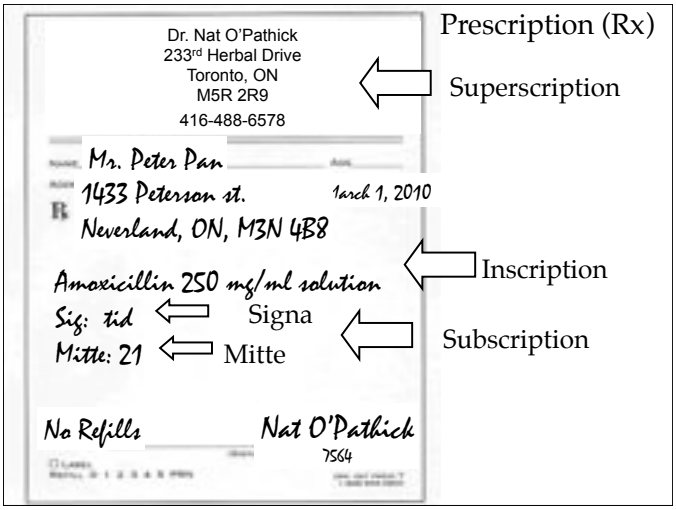
1. Consider including diagnosis or purpose (if appropriate)
+ helps confirm medication and provide context for consitent education

2. For children or those < 40 kg
+ Include age or weight
+ List mg/kg dose you used (pharmacist to double check and confirm dose)
+ List dosage form (e.g., liquid preferred)

3. Use generic drug name

4. If you don't want substitution of your prescription, write the manufacturer's name OR "Do Not Substitute"

5. Specify: # of Refills and time interval between refills e.g. Repeat 3 x q 30 days



Types of Signa (Directions)

- Usually uses a standard Latin abbreviation
- Useful shorthand for physicians
- Aids pharmacists detect forged prescriptions
- Common Signa: qd, bid, tid, qid, q8h,hs,PRN, pc
- Note: PRN (alone) is not acceptable when used alone...must include specific frequency, interval or MAX DAILY DOSE and preferentially indication for use
- e.g. qHS PRN sleep

Common Latin Rx Terms

Latin	Abbrev.	Meaning
Bis in die	bid	Twice a day
Ter in die	tid	3 times
Quarter in	qid	4 times
Ante cibum	ac	Before
Post cibum	pc	After meals
Hora somni	hs **	At bedtime
Pro re nata	prn	As needed
Quaque die	q 3 h	Every 3
Per os	po	By mouth

Abbreviations to avoid (ISMP)

Abbreviation /Dose Expression	Intended Meaning	Misinterpretation	Correction
Apothecary symbols	dram minim	Misunderstood or misread (symbol for dram misread for "3" and minim misread as "mL").	Use the metric system.
AU	aurio uterque (each ear)	Mistaken for OU (oculo uterque—each eye).	Don't use this abbreviation.
D/C	discharge OR dis-continue	Premature discontinuation of medications when D/C (intended to mean "discharge") has been misinterpreted as "discontinued" when followed by a list of drugs.	Use "discharge" and "discontinue."
Drug names		Don't abbreviate the drug name	Use the complete spelling for drug names.
No zero before decimal	0.5 mg vs .5 mg	Could be mistaken for 5 mg (if the decimal point is faint or not seen.	Use zero before a decimal
AZT	zidovudine (RETROVIR)	azathioprine	

ISMP Dangerous Abbreviations

CPZ	COMPAZINE (prochlorperazine)	chlorpromazine	
DPT	DEMEROL-PHENERGAN-THORAZINE	diphtheria-pertussis-tetanus (vaccine)	
HCl	hydrochloric acid	potassium chloride (The "H" is misinterpreted as "K.")	
HCT	hydrocortisone	hydrochlorothiazide	
HCTZ	hydrochlorothiazide	hydrocortisone (seen as HCT250 mg)	
MgSO4	magnesium sulfate	morphine sulfate	
MSO4	morphine sulfate	magnesium sulfate	
MTX	methotrexate	mitoxantrone	
TAC	triamcinolone	tetracaine, ADRENALIN,cocaine	

ISMP Dangerous Abbreviations

ZnSO4	zinc sulfate	morphine sulfate	
Zero after decimal	1.0 vs 1 mg	Misread as 10 mg if the decimal point is not seen	Do not use terminal zeros for doses
"Nitro" drip	nitroglycerin infusion	sodium nitroprusside infusion	
"Norflox"	norfloxacin	NORFLEX	
ug	microgram	Mistaken for "mg" when handwritten.	Use "mcg."
o.d. or OD	once daily	Misinterpreted as "right eye" (OD—oculus dexter)and administration of oral medications in the eye.	Use "daily."
TIW or tiw	three times a week.	Mistaken as "three times a day."	Don't use this abbreviation.
per os	orally	The "os" can be mistaken for "left eye."	Use "PO," "by mouth," or "orally."
q.d. or QD	every day	Mistaken as q.i.d., especially if the period after the "q" or the tail of the "q" is misunderstood as an "i."	Use "daily" or "every day."

qn	nightly	Misinterpreted as "qh" (every hour).	Use "nightly."
qhs	nightly	Misread as every hour.	Use "nightly."
q6PM, etc.	every evening at 6 PM	Misread as every six hours.	Use 6 PM "nightly."
q.o.d. or QOD	every other day	Misinterpreted as "q.d." (daily) or "q.i.d. (four times daily) if the "o" is poorly written.	Use "every other day."
sub q	subcutaneous	The "q" has been mistaken for "every" (e.g., one heparin dose ordered "sub q 2 hours before surgery" misunderstood as every 2 hours before surgery).	Use "subcut." or write "subcutaneous."
SC	subcutaneous	Mistaken for SL (sublingual).	Use "subcut." or write "subcutaneous."
U or u	unit	Read as a zero (0) or a four (4), causing a 10–fold overdose or greater (4U seen as "40" or 4u seen as 44").	"Unit" has no acceptable abbreviation. Use "unit."

IU	international unit	Misread as IV (intravenous).	Use "units."
cc	cubic centimeters	Misread as "U" (units).	Use "mL."
x3d	for three days	Mistaken for "three doses."	Use "for three days."
BT	bedtime	Mistaken as "BID" (twice daily).	Use "hs."
ss	sliding scale (insulin) or ½ (apothecary)	Mistaken for "55."	Spell out "sliding scale." Use "one-half" or use "½."
> and <	greater than and less than	Mistakenly used opposite of intended.	Use "greater than" or "less than."
/ (slash mark)	separates two doses or indicates "per"	Misunderstood as the number 1 ("25 unit/10 units" read as "110" units.	Do not use a slash mark to separate doses. Use "per."
Name letters and dose numbers run together (e.g., Inderal40 mg)	Inderal 40 mg	Misread as Inderal 140 mg.	Always use space between drug name, dose and unit of measure.

Protecting Prescription Guidelines

+ Minimize number of pads in use
+ Do not leave visible in office
+ Store in secure place (to avoid theft)
+ Consider writing amounts of desired medications numerically + alphabetically
+ Never sign Rx blanks in advance
+ Write Rx in ink
+ Do not use Rx blanks for notes or memos which can be erased and used for forgery

Documenting Your Prescription

When recommending a treatment for a patient, what information do you document?

Suggestions for Documentation when Writing a Prescription

1. Date
2. Subjective and observed symptoms
3. Assessment of the patient's problem (if known)
4. Purpose and/or Goal(s) of Medication(s)/ Treatment
5. Name, dose, dosage form and quantity of medication prescribed
6. Monitoring plan (efficacy and safety)
7. Discussion you had with patient about treatment and monitoring plan
8. Did you have 'informed consent'?
9. Signature

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Proton pump inhibitors (antacids): possible risk of *Clostridium difficile*-associated diarrhea

Information Update
2012-23
February 16, 2012
For immediate release

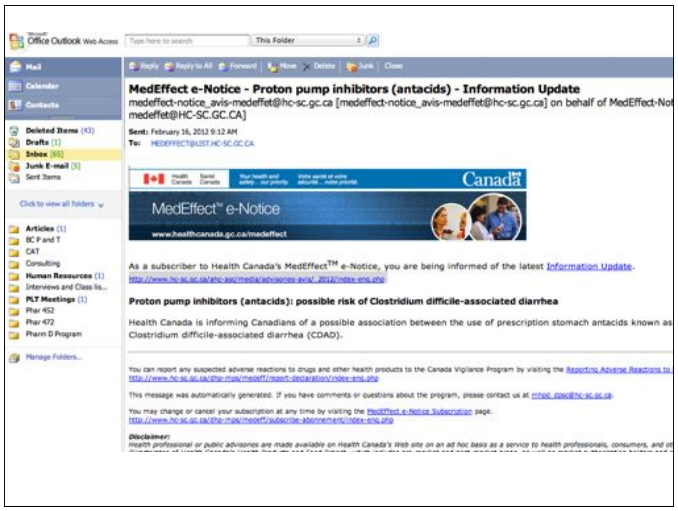
OTTAWA - Health Canada is informing Canadians of a possible association between the use of prescription stomach antacids known as proton pump inhibitors (PPIs) and an increased risk of *Clostridium difficile*-associated diarrhea (CDAD).

Clostridium difficile, commonly called *C. difficile*, is a bacterium that can cause diarrhea and may lead to more serious intestinal conditions. Healthy people are not usually vulnerable to *C. difficile*. Factors known to increase the risk of infection include advanced age, severe underlying illness, hospitalization, or antibiotic use.

PPIs reduce stomach acid and are widely used to treat conditions such as acid reflux, and stomach and small intestine ulcers. See below for a list of Proton Pump Inhibitors.

There have been a number of studies suggesting a possible link between PPIs and an increased risk of *CDAD*, particularly in vulnerable patients. Health Canada has been assessing this data on an ongoing basis.

The studies acknowledge important limitations with regards to http://www.hc-sc.gc.ca/ahc-asc/media/advisories- impossibility of establishing a definite cause-and-effect relationship between PPIs and an increased risk of CDAD, as there are a number of other factors that may play a role.



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Mail
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Contacts

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Drafts [1]
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Junk E-mail (5)
Sent Items

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BC P and T
CAT
Consulting
Human Resources (1)
Interviews and Class lis...
PLT Meetings (1)
Phar 452
Phar 472
Pharm D Program

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MedEffect e-Notice - Proton pump inhibitors (antacids) - Information Update
medeffect-notice_avis-medeffet@hc-sc.gc.ca [medeffect-notice_avis-medeffet@hc-sc.gc.ca] on behalf of MedEffect-Not
medeffet@HC-SC.GC.CA]

Sent: February 16, 2012 9:12 AM
To: MEDEFFECT@LIST.HC-SC.GC.CA

Canada

MedEffect™ e-Notice
www.healthcanada.gc.ca/medeffect

As a subscriber to Health Canada's MedEffect™ e-Notice, you are being informed of the latest Information Update.
http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2012/index-eng.php

Proton pump inhibitors (antacids): possible risk of Clostridium difficile-associated diarrhea

Health Canada is informing Canadians of a possible association between the use of prescription stomach antacids known as
Clostridium difficile-associated diarrhea (CDAD).

You can report any suspected adverse reactions to drugs and other health products to the Canada Vigilance Program by visiting the Reporting Adverse Reactions to
http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php

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Infectious Disease
Otitis media, Bronchitis, Strep throat, Sinusitis, CAP, Influenza, SSTI, UTI's,

James McCormack, B.Sc. (Pharm), Pharm.D.
Professor
Faculty of Pharmaceutical Sciences
University of British Columbia

Pharmacology 101

Inhibit synthesis of or activate enzymes to disrupt the bacterial cell wall
- penicillins, cephalosporins, vancomycin, imidazole antifungals

Act directly on cell wall
- polymyxin, amphotericin,

Affect function of bacterial ribosomes and create a reversible inhibition of protein synthesis
- chloramphenicol, tetracyclines, macrolides, and clindamycin

Bind to 30 S ribosomal subunits and alter protein synthesis
- aminoglycosides

Antimetabolites that block essential metabolic steps
- sulfonamides, trimethoprim

Prevent supercoiling of DNA
- quinolones

ORAL Antibiotic Susceptibility Chart

	Streptococcus pneumoniae/S. viridans/S. faecalis (Enterococcus faecalis)	*Staphylococcus aureus or S. epidermidis* (Non-Penicillinase Producing/ Penicillinase Producing/ Methicillin Resistant)	*Escherichia coli or Proteus mirabilis*	*Klebsiella pneumoniae*	*Haemophilus influenzae* (Ampicillin Sensitive/ Ampicillin Resistant)	*Neisseria gonorrhoeae* (Non-Penicillinase Producing/ Penicillinase Producing)/*Neisseria meningitidis*	*Chlamydia spp/ Mycoplasma/ Legionella*	*Pseudomonas aeruginosa* or *Acinetobacter calcoaceticus*	Anaerobes Above the Diaphragm (Anaerobic Cocci)	Anaerobes Below the Diaphragm (*Bacteroides fragilis*)
penicillin V or G	yes/yes/var	yes/no/no	no	no	no/no	yes/no/yes	no	no	yes	no
amoxicillin, ampicillin	yes/yes/var	yes/no/no	yes	no	yes/no	yes/no/yes	yes/no/no	no	yes	no
amoxicillin-clavulanate	yes/yes/yes	yes/yes/no	yes	yes	yes/yes	yes/yes/yes	yes/no/no	no	yes	yes
cloxacillin	yes/yes/no	yes/yes/no	no	no	no/no	no/no/no	no	no	yes	no
cephalexin	yes/yes/no	yes/yes/no	yes	yes	no/no	no/no/no	no	no	yes	no
cefuroxime, cefuroxime axetil, cefaclor	yes/yes/no	yes/yes/no	yes	yes	yes/yes	yes/yes/yes	no	no	yes	no
cefixime	yes/yes/no	no/no/no	yes	yes	yes/yes	yes/yes/yes	no	no	yes	no
chloramphenicol	yes/yes/no	yes/yes/var	yes	yes	yes/yes	yes/no/yes	yes/yes/yes	no	yes	yes
ciprofloxacin, norfloxacin(bladder)	no/no/yes	yes/yes/no	yes	yes	yes/yes	yes/yes/yes	yes/yes/yes	yes	no	no
levofloxacin, moxifloxacin -resp	yes/no/yes	yes/yes/no	yes	yes	yes/yes	yes/yes/yes	yes/yes/yes	yes	no	no
clindamycin	yes/yes/no	yes/yes/no	no	no	no/no	no/no/no	yes/no/no	no	yes	yes
trimethoprim-sulfamethoxazole	yes/yes/yes	yes/yes/var	yes	yes	yes/yes	no/no/yes	var/var/var	no	var	no
erythromycin	yes/yes/no	yes/yes/no	no	no	yes/var	yes/no/no	yes/yes/yes	no	yes	no
clarithromycin, azithromycin	yes/yes/no	yes/yes/no	no	no	yes/var	yes/no/no	yes/yes/yes	no	yes	no
metronidazole	no/no/no	no/no/no	no	no	no/no	no/no/no	yes/no/no	no	yes	yes
tetracycline, doxycycline	yes/yes/no	no/no/no	var	no	yes/yes	var/var/yes	yes/yes/yes	no	yes	yes (doxycycline) var (tetracycline)

yes = clinically useful: no = not clinically useful: var = variable depends on local sensitivities

The only oral antibiotics you really need to use

Penicillin V
Amoxicillin
Cloxacillin
Cephalexin
Macrolide - erythromycin/clarithromycin
Cotrimoxazole (trimethoprim/sulfamethoxazole)
Doxycycline
Ciprofloxacin/levofloxacin - maybe
Clindamycin
Metronidazole
Nitrofurantoin

Evidence

OTITIS MEDIA	ABX (%)	PLACEBO (%)
Pain at 24 hours	NSS	
Pain at 2-7 days	16	22
Vomiting, diarrhea, skin rash	16	10
Contralateral otitis	NSS	
Recurrences	NSS	
Tympanometry	NSS	
Deafness	NSS	
Perforation	NSS	
Mastoiditis	NSS	

Cochrane

ACUTE BRONCHITIS	ABX (%)	PLACEBO (%)
Limitation in work, productive cough at follow up, adverse effects	NSS	
Cough at follow-up	33	51
Night cough at follow-up	30	45
Days of cough, feeling ill	0.6 less	
Not improved at follow-up MD's global assessment	8	18

productive cough and sometimes LRTI ruled out by x-ray Cochrane

STREP THROAT	ABX (%)	PLACEBO (%)
Otitis media at 14 days	0.5	1.9
Quinsy	0.1	2.3
Rheumatic fever	0.7	1.7
Symptoms of sore throat at 3 days	49	66
Mean reduction in Sx	16 hours	
Fever day 3	12	18
Headache day 3	22	41
Sinusitis	NSS	
Glomerulonephritis	NSS	

Cochrane

most studies in 50s

Steroids for pain relief in patients with a sore throat

Complete pain relief at 24 hours
39% (steroid)
12% (placebo)

BMJ 2009;339:b2976

ACUTE SINUSITIS	ABX (%)	PLACEBO (%)
Cure or improvement at 7-15 days	90	83
Improvement at 16-60 days	NSS	

Cochrane

Empiric recommendations for CAP

British Guidelines

1st - Amoxicillin - if pen allergic erytho/clarith
Amoxicillin plus macrolide if hospitalised
Cefuroxime plus macrolide if severe

Canadian Guidelines

1st -Erythromycin, azithromycin, clarithromycin or doxycycline
COLD – newer macrolide or doxycycline
COLD + recent abx – respiratory flouroquinolone or amox-clav or 2nd gen ceph plus macrolide

American Guidelines

1st - Erythromycin, azithromycin, clarithromycin or doxycycline
Recent abx - A respiratory fluoroquinolone alone, an advanced macrolide plus high-dose amoxicillin, or an advanced macrolide plus high-dose amoxicillin-clavulanate

ß-lactam versus antibiotics with activity against atypical organisms

(Mycoplasma, Chlamydia, Legionella)

18 studies - 6,749 subjects
4 unpublished

meta-analysis to compare the efficacy of beta lactam antibiotics with antibiotics active against atypical pathogens in adults with community acquired pneumonia

BMJ (published 31 January 2005)

ß-lactam versus antibiotics with activity against atypical organisms (2% overall mortality)

	% failing to achieve clinical cure or improvement
Macrolide	17
ß-lactam	20
Quinolone	18
ß-lactam	18
Total	18
ß-lactam	18

All results NSS

BMJ (published 31 January 2005)

ß-lactam versus antibiotics with activity against atypical organisms (found in 7-8% of patients)

	# failing to achieve clinical cure or improvement		
	Mycoplasma	Chlamydia	Legionella
Macrolide/ Quinolone	11/152	8/63	4/38
ß-lactam	20/159	2/52	15/38
	NSS	NSS	SS

BMJ (published 31 January 2005)

"No benefit of survival or clinical efficacy was shown to empirical atypical coverage in hospitalized patients with CAP. This conclusion relates mostly to the comparison of quinolone monotherapy to beta-lactams (BL) or cephalosporins. Further trials, comparing BL or cephalosporins therapy to BL or cephalosporins combined with a macrolide in this population, using mortality as its primary outcome, should be performed."

Atypicals better with Legionella
No difference in overall adverse effects - more GI (1% higher) in beta-lactam group

Cochrane Library CD004418

Ambulatory community-acquired pneumonia Choice of Drug

"Currently available evidence from RCTs is insufficient to make evidence-based recommendations for the choice of antibiotic to be used for the treatment of CAP in ambulatory patients"

Cochrane CD002109

Duration of treatment

There is lots of evidence that treatment for longer than 5 days for AECB, otitis media, and GABHS tonsillopharyngitis is unnecessary and increases the chance of adverse effects.

Drugs 2003;63:2169-84

"Three to six days of oral antibiotics had comparable efficacy compared to the standard duration 10 day oral penicillin in treating children with acute GABHS pharyngitis. In countries with low rates of rheumatic fever, it appears safe and efficacious to treat children with acute GABHS pharyngitis with short duration antibiotics"

Cochrane Library CD004872

"There are no controlled trials that have specifically assessed the optimum duration of antimicrobial treatment in CAP"

"Until further data are available, it seems reasonable to treat bacterial infections such as those caused by S. pneumoniae until a patient is afebrile for 72 h"

Lancet 2003;362:1991–2001

very good review - suggests 5 days and afebrile for 2-3 days"

Curr Opin Infect Dis 2007; 20:177–81

Three versus eight days of antibiotics for pneumonia

Patients

119 adults with pneumonia (mild to moderate-severe) who had substantially improved after 3 days of IV therapy - median age 57, approx 60% male,

Treatment

3 days IV amoxicillin followed by placebo or oral amoxicillin for 5 days

Duration

8 days

Results

Cure rates - 3 day (90%), 8 days (88%)

Mild adverse events 3 day (11%), 8 days (21%)

BMJ 2006;332:1355-61

Non-severe community-acquired pneumonia - duration

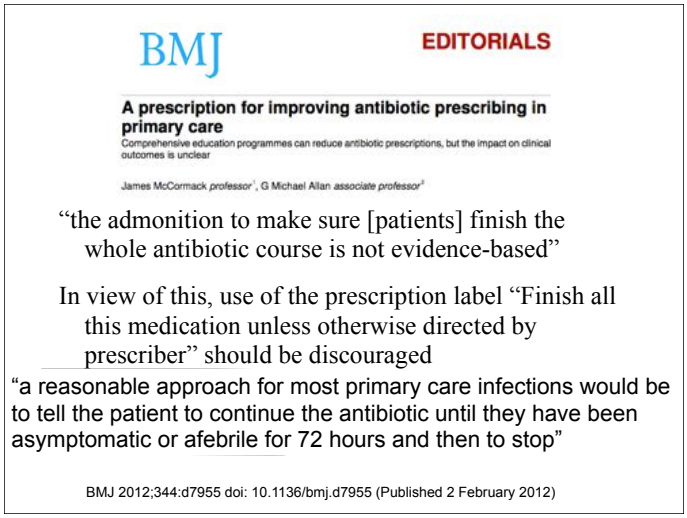
"The evidence of this review suggests that a short course (three days) of antibiotic therapy is as effective as a longer treatment (five days) for non-severe CAP in children under five years of age. However, there is a need for more well-designed RCTs to support our review findings"

Cochrane CD 005976

Three days of i.v. benzylpenicillin for the treatment of adults with meningococcal disease is effective

Internal Medicine Journal 2004;34:383–387

BUT - short duration not for all infections - osteomyelitis, endocarditis, prostatitis etc


BMJ EDITORIALS

A prescription for improving antibiotic prescribing in primary care

Comprehensive education programmes can reduce antibiotic prescriptions, but the impact on clinical outcomes is unclear

James McCormack professor[I], G Michael Allan associate professor[II]

"the admonition to make sure [patients] finish the whole antibiotic course is not evidence-based"

In view of this, use of the prescription label "Finish all this medication unless otherwise directed by prescriber" should be discouraged

"a reasonable approach for most primary care infections would be to tell the patient to continue the antibiotic until they have been asymptomatic or afebrile for 72 hours and then to stop"

BMJ 2012;344:d7955 doi: 10.1136/bmj.d7955 (Published 2 February 2012)


BMJ EDITORIALS

A prescription for improving antibiotic prescribing in primary care

Comprehensive education programmes can reduce antibiotic prescriptions, but the impact on clinical outcomes is unclear

James McCormack professor[I], G Michael Allan associate professor[II]

"Delayed prescriptions can reduce the proportion of people who receive antibiotics for upper respiratory tract infections from 93% to 32%"

"Patients who are not given a prescription initially will still ultimately get an antibiotic 14% of the time"

"Most community acquired infections still respond to the same antibiotics that have been used for decades and many guidelines still support their use"

Neuroaminidase inhibitors (oseltamivir, zanamivir)

25 studies - primarily adults during influenza season

Time to first alleviation of symptoms - 160 hours (placebo) - 139 hours (oseltamivir) - no effect on hospitalization

Nausea - 10% (drug) vs 6% (placebo)

Vomiting - 9% vs 4%

Diarrhea 6% vs 7% Cochrane CD008965

6 studies children - oseltamivir and zanamivir reduced illness by ~ 36 hours and otitis media from 19% to 9% in those with confirmed influenza - vomiting increased from 12% to 19% with oseltamivir

Influenza vaccine

28 children over the age of 6 need to be vaccinated to prevent one case of laboratory confirmed influenza and 8 children to prevent one symptomatic case

under age of 2 no benefit CD 004879

in adults vaccine reduced the number of people with influenza symptoms from 4% down to 1% CD001269

elderly - poor quality dataCD004876

COPD - reduced exacerbations/patient but no difference in number of patients CD002733

The flu vaccine
How well does it work?

Vancouver Sun from Oct 15 - New report questions science behind flu vaccine efficacy and use policy

Report from the university of Minnesota entitled " The compelling need for game-changing vaccines"

It's all about the numbers

Previous evaluations - 70-90% effective

Every year 1-10% per year adults – roughly 5% - chance reduced to 1% - less if unmatched

5-20% in children – roughly 10% - therefore reduced to 2%

New report - no new studies - but looked at different diagnostic endpoints – earlier evaluations used studies that used antibodies as the diagnosis – this one used culture

Instead of the effect being 70-90% - they found 60% for the flu shot – nasal spray was 85% effective in children 6 months to 6 years old

5% down to 2% in adults

10% goes down to 4% in children

Other flu evidence

In patients with asthma

- No effect seen in reducing exacerbations caused by influenza

In patients with COPD

- Does reduce the number of exacerbations

In the elderly – some effect but

- The available evidence is of poor quality BUT SUGGESTS BENEFIT and provides no guidance regarding the safety, efficacy or effectiveness of influenza vaccines for people aged 65 years or older.

Safety

- Guillain-Barre syndrome relatively rare neurologic disorder a condition in which the body damages its own nerve cells (outside of the brain and spinal cord), resulting in muscle weakness and, in some cases, paralysis.
- Febrile seizures

Skin and soft tissue infections

In an otherwise healthy individual

Cloxacillin/cephalexin - erythromycin or clindamycin if penicillin allergic

5 days has been shown to be as good as 10 days

In areas where CA-MRSA has become clinically important (10-15% resistance) - risk factors include children, competitive atheletes, Native Ameicans, IVDU

Trimethoprim/sulphamethoxazole or clindamycin? or doxycycline have been shown to work BUT clinical trials are lacking

UTIs

Duration - 3 days is long enough - single dose?

Prevention - half a regular DS tablet daily or just treat when symptoms occur

Sulfamethoxazole/trimethoprim - rash issues – use trimethoprim

Ciprofloxacin

- For UTI's - break a 500 mg tablet in 4
- ¼ tablet BID x 3 days – two tablets

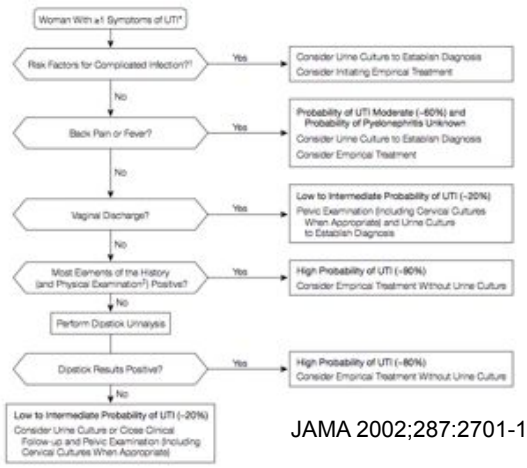
Nitrofurantoin

- 100 mg BID

Do you need a dipstick urinalysis?

In women with dysuria, frequency, and no vaginal discharge the probability of UTI is 96%

JAMA 2002;287:2701-10



JAMA 2002;287:2701-10

Abx Choice

21 studies (6016 participants)

Trimethoprim-sulfamethoxazole (TMP-SMX) was as effective as fluoroquinolones in achieving short-term (RR 1.00, 95% CI 0.97 to 1.03) and long-term (RR 0.99, 95% CI 0.94 to 1.05) symptomatic cure.

Beta-lactam drugs were as effective as TMP-SMX for short-term (RR 0.95, 95% CI 0.81 to 1.12) and long-term (RR 1.06, 95% CI 0.93 to 1.21) symptomatic cure.

Short-term cure for nitrofurantoin was similar to that of TMP-SMX (RR 0.99, 95% CI 0.95 to 1.04) as was long-term symptomatic cure (RR 1.01, 95% CI 0.94 to 1.09)

No differences were observed between the classes of antimicrobials included in this review for the symptomatic cure of acute uncomplicated UTI

Fluoroquinolones proved more effective than beta-lactams for the short-term bacteriological outcome, probably with little clinical significance.

Individualised treatment should take into consideration the predictable susceptibility of urinary pathogens in local areas, possible adverse events and resistance development, and patient preference.

Cochrane Library CD007182

Nitrofurantoin vs placebo for UTIs

78 patients randomised to nitro 100 mg QID or placebo for three days

Improved and cure	3 days (%)	7 days (%)
Nitrofurantoin	77	88
Placebo	54	52

Another study suggested a 24% spontaneous cure rate for bladder infections
Scand J Infect Dis 2004;36:296-301

Br J Gen Pract 2002;52:708-10

UTI Prevention

50% recurrence per year on placebo

"clinical recurrences (CRPY) the RR was 0.15 (95% CI 0.08 to 0.28)"

"One RCT compared postcoital versus continuous daily ciprofloxacin and found no significant difference in rates of UTIs, suggesting that postcoital treatment could be offered to woman who have UTI associated with sexual intercourse."

Cochrane Library

Ciprofloxacin for 7 days vs14 days
pyelonephritis

Women with acute pyelonephritis - fever and at least one other symptom - 44 years old – 90% E. coli

7 days or 14 days of cipro 500 mg BID

Clinical and bacteriological outcome 10-14 days after completion of active treatment

248 patients - only 156 assessed – because randomnly assigned before a definitive diagnosis was established

Short term/cumulative efficacy – roughly 95% success rate both groups

Side effects – 0 patients in 7 day had mucosal candida infection – 5 in the 14 day group

Lancet August 4, 2012

	No history of allergy to sulfonamide antibiotic	History of allergy to sulfonamide antibiotic	History of allergy to penicillin
Reaction within 30 days of a sulfonamide non-antibiotic	1.6%	9.1%	14.6%

N Engl J Med 2003;349:1628-35

Things to think about

- Ask patients if they have used erythromycin previously
- Consider doxycycline
- Consider high-dose amoxicillin
- Consider cutting ciprofloxacin tablets
- Is resistance futile?
- Patients are not more adherent to once a day vs twice a day therapy
- If you are an allergic person you are an allergic person
- The dose and duration of treatment with antibiotics is often not well-defined

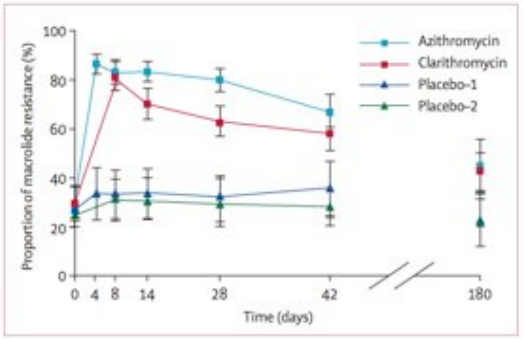
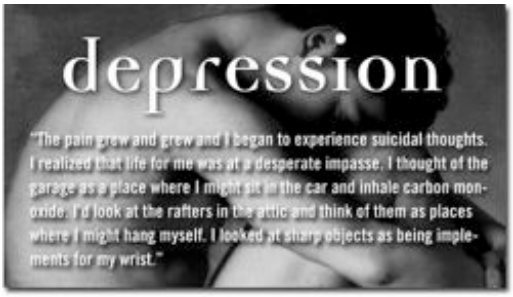


Figure 2: Temporal changes in the proportion of macrolide-resistant streptococci after azithromycin and clarithromycin use
Data shown are for all 204 volunteers followed through to day 42, and for 99 volunteers followed through to day 180. Error bars are 95% CI.

Withdrawal from market

- Grepafloxacin/sparfloxacin - withdrawn because of concerns about cardiac toxicity associated with prolongation of the Q-T interval
- Temafloxacin - withdrawn because of serious hemolysis
- Trovafloxacin - has been reported to be associated with life-threatening toxicity



Adil Virani, BSc (Pharm), Pharm D, FCSHP

Outline

- Learning Objectives
- Emily's case
- Goals of therapy
- Overview of pharmacology of antidepressants
- Treatment overview & guidelines
- Factors to consider
- Comparing antidepressants

Suggested Reading: Belmaker RH, Agam Galila. Major Depressive Disorder. N Engl J Med 2008; 358:55-68.

Epidemiology:

- Average age of onset is mid 20s
- Lifetime Risk
  - ~1 in 5 Women
  - ~1 in 10 Men
- ~1 in 50 children < 12
- ~1 in 15 adolescents

Overall:

At any given time, ~1 in 20 Canadians suffer from clinical depression!

* WHO Report 2001. Mental Health; New Understanding, New Hope.

Emily

- 25 yo woman, wt = 60kg, with low mood x 4 mo
- Dropped out of BCIT because she couldn't concentrate and didn't want to be a student any more
- Sleeps 12 hrs/night & says she "can't get out of bed"
- Chief complaint: Low mood, confused and constantly irritated. Says she "can't win" and is never hungry
- Failed 2 courses in school
- Broke up with her partner 3 months ago
- NKAs and no other medical conditions

How would you rate Emily's symptoms?

What do you think Emily should do?

- Write down what you think the Goals of Therapy are for Emily
- What treatment options would you consider?
- Please write a prescription for Emily…

Goals of Therapy

- SHORT TERM (e.g., 2-3 months)
  - Stabilize depressive symptoms
  - Prevent complications (e.g., suicide)
  - Minimize side effects
  - Induce remission (not only response)
  - Improve quality of life
  - Education

- LONG TERM (e.g.,>3 months)
  - Prevent relapse and recurrence
  - Maintain a stable mood
  - Manage side effects
  - Education

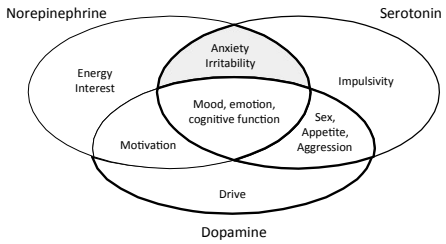
Depression Treatment Options

1. Antidepressant medication(s)
2. Psychotherapy
   - Cognitive behavioural therapy (CBT)
   - Intrapersonal therapy (IPT)
3. Electroconvulsive therapy (ECT)
4. Light therapy
5. Alternative therapies
   - St. John's wort, SAM-e, transcranial magnetic stimulation therapy, etc.

Overview of Antidepressant Pharmacology

- Acute:
  Block reuptake or degradation of monoamines (NE, 5HT, DA)
  - post-synaptic alpha-1 receptor
  - presynaptic autoreceptors
- Chronic:
  - Down regulation of the post-synaptic receptors
  - Alteration of second messenger systems
  - Alteration of protein synthesis

Neurotransmitters Involved in Regulating Mood



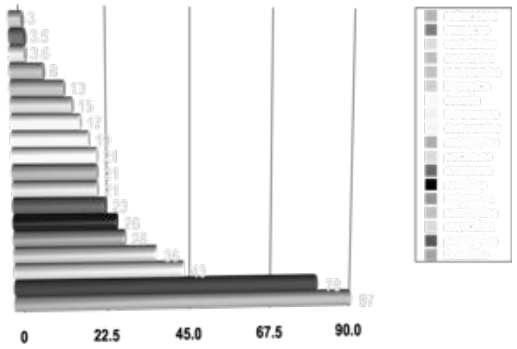
Adapted from Stahl SM. Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 2nd ed. Cambridge, UK: Cambridge University Press; 2000:152.

Overview of Antidepressant Pharmacokinetics

In general:

- Absorption is rapid
- Metabolism: extensive 1st pass
- Oxidation, hydroxylation, demethylation
- 5% = "slow acetylators"
- Many have drug-drug interactions to be aware of
- Protein bound: 90 – 95%

Antidepressant half-lives (hrs)



Antidepressant MoAs

1. Inhibit the reuptake of serotonin and noradrenaline:
   - Tricyclic antidepressant (TCA) & serotonin-noradrenaline reuptake inhibitor (SNRI)
2. Decrease the metabolism of serotonin, noradrenaline, and dopamine by inhibiting monoamine oxidase:
   - Monoamine oxidase inhibitors (MAOI)
   - Riversible inhibitors of Monoamine oxidase (RIMA)
3. Inhibit the reuptake of serotonin:
   - Selective serotonin re-uptake inhibitor (SSRI)

Stahl, 1999

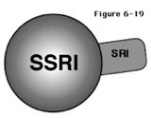
Antidepressant MoAs

4. Antagonize serotonin 5HT2 action at post-synaptic receptors and inhibit the reuptake of serotonin:
   - Serotonin antagonist/reuptake inhibitor (SARI)
5. Inhibit the reuptake of noradrenaline and dopamine:
   - Noradrenaline-dopamine reuptake inhibitor (NDRI)
6. Modulates the serotonin system to increase release of noradrenaline and serotonin
   - Noradrenergic & specific serotonergic antidepressant (NaSSA)

Overview of Antidepressant Classes

OPTIONS FOR 1ST OR 2ND CHOICE		
TCAs:	Tricyclic antidepressants	8 agents
SSRIs:	Selective serotonin reuptake inhibitors	6 agents
NaSSA:	Noradrenergic and serotonergic specific antidepressant	1 agent
RIMA	Reversible Inhibitor of Monoamine Oxidase	1 agent
NDRIs:	Noradrenaline dopamine reuptake inhibitors	1 agent
SNRIs:	Serotonin noradrenaline reuptake inhibitors	3 agent
RESERVED		
SARIs:	Serotonin antagonists/reuptake inhibitors	1 agent
MAOIs:	Monoamine oxidase inhibitors	2 agents
Heterocyclics: Maprotiline		1 agent

SSRI Similarities



- Similar MoA
- Equally effective for depressive & anxiety disorders
  - ~ 70% in adults; 50-60% in C&A
- Relatively similar rate of GI, CNS and sexual side effects
- Comparable cost
- Similar profiles on brain imaging
- Brand names have 2 syllables and an “X” or a “Z”

SSRI Differences

SSRI	Additional Receptor Activity	Potential Clinical Implication	Drug Interactions	Withdrawal Effects
Fluoxetine	5HT2c antagonist Noradrenaline RI	Bulimia; increase arousal	+++	-
Fluvoxamine	Sigma 1 receptor blockade	Psychotic depression; OCD	+++	++
Sertraline	Dopamine RI	Panic Disorder; OCD; no prolactin incr.	+	++
Paroxetine	Noradrenaline RI Muscarinic RI	Panic Disorder; OCD; anticholinergic	++	+++
Citalopram	More selective for serotonin receptors	Less drug interactions	-/+	+
Escitalopram	Most selective for serotonin receptors	Less drug interactions	+	+

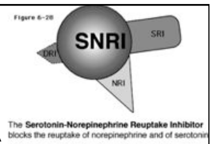
RI = Reuptake Inhibitor

SSRI Dosing

- Relatively flat dose-response curve in depression
- Higher doses used in anxiety disorders (e.g., OCD)

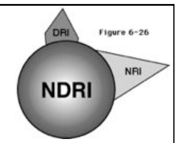
SSRI	Starting Dose (mg)	Target Dose (mg)	Maximum Dose (mg)	Canadian Approval
Fluoxetine	10-20	20-40	80	Nov. 1988
Fluvoxamine	50-100	100-200	300	July 1990
Sertraline	25-50	50-150	200	Jan. 1992
Paroxetine	10-20	20-40	60	May 1993
Citalopram	10-20	20-40	60	Feb. 1999
Escitalopram	10	20	20-30	Dec. 2004

Venlafaxine & Duloxetine



- Venlafaxine - Dual reuptake blockade of 5HT & NA at intermediate doses. At high doses DA blockade
- Drug interactions: <SSRIs; CYP2D6 inhibition; potentiates 5-HT effects
- Similar side effects to SSRIs
  - Intermediate sexual side effects
- NA side effects may be observed at higher doses
  - Insomnia, restlessness, tremor, sweating, BP increase
- Withdrawal reactions with abrupt cessations

Bupropion (NDRI):



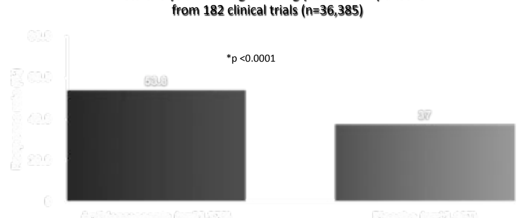
- Demonstrated equivalent to SSRIs for depression
- Blocks reuptake of NE & DA
- Drug interactions:<SSRIs; CYP2D6 inhibition
- Effective for ADHD and smoking cessation
- No documented withdrawal reactions
- Minimal sexual side effects
- Side effects/precautions:
  - Agitation, dry mouth, constipation, headache, tremor, seizure risk, hypertension
- Ask patients if they are taking "Zyban"

Mirtazapine (NaSSA):

- Enhances NA and 5HT1A effects by mediating serotonergic neurotransmission
- H1 receptor blockade
  - Sedation (especially at low doses: 15-30 mg/day)
- 5HT2C receptor blockade
  - (appetite stimulation/weight gain)
- Minimal drug interactions
- Less sexual dysfunction than SSRIs

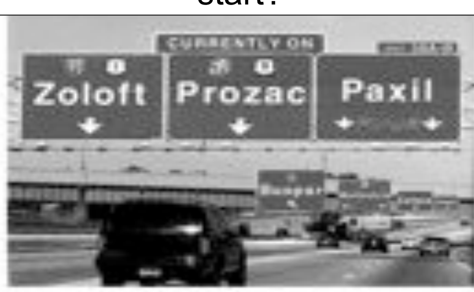
Overall Response Rates: Antidepressants

Meta-analysis including 262 drug-placebo comparisons from 182 clinical trials (n=36,385)



Papakostas, Fava. Eur Neuropsychopharmacol 2009:19:34-40

How do you pick which treatment to start?



REVIEW | Annals of Internal Medicine

Dec 2011; 155:772-85

Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive Disorder

An Updated Meta-analysis

Gerald Gartlehner, MD, MPH; Richard A. Hansen, PhD, RPh; Laura C. Morgan, MA; Kylie Thaler, MD, MPH; Linda Lux, MPA; Megan Van Noord, MSIS; Ursula Mager, PhD, MPH; Patricia Thieda, MA; Bradley N. Gaynes, MD, MPH; Tania Wilkins, MSc; Michaela Strobelberger, MA; Stacey Lloyd, MPH; Ursula Reichenpfader, MD, MPH; and Kathleen N. Lohr, PhD

Background: Second-generation antidepressants dominate the management of major depressive disorder (MDD), but evidence on the comparative benefits and harms of these agents is contradictory.

Purpose: To compare the benefits and harms of second-generation antidepressants for treating MDD in adults.

Data Sources: English-language studies from PubMed, Embase, the Cochrane Library, PsycINFO, and International Pharmaceutical Abstracts from 1980 to August 2011 and reference lists of pertinent review articles and gray literature.

Study Selection: 2 independent reviewers identified randomized trials of at least 6 weeks' duration to evaluate efficacy and observational studies with at least 1000 participants to assess harm.

Data Extraction: Reviewers abstracted data about study design and conduct, participants, and interventions and outcomes and rated study quality. A senior reviewer checked and confirmed extracted data and quality ratings.

Data Synthesis: Meta-analyses and mixed-treatment comparisons of response to treatment and weighted mean differences were conducted on specific scales to rate depression. On the basis of 234 studies, no clinically relevant differences in efficacy or effectiveness were detected for the treatment of acute, continuation, and maintenance phases of MDD. No differences in efficacy were seen in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbid conditions. Individual drugs differed in onset of action, adverse events, and some measures of health-related quality of life.

Limitations: Most trials were conducted in highly selected populations. Publication bias might affect the estimates of some comparisons. Mixed-treatment comparisons cannot conclusively exclude differences in efficacy. Evidence within subgroups was limited.

Conclusion: Current evidence does not warrant recommending a particular second-generation antidepressant on the basis of differences in efficacy. Differences in onset of action and adverse events may be considered when choosing a medication.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2011;155:772-785. www.annals.org

For author affiliations, see end of text.

Major depressive disorder (MDD) affects more than 16% of adults at some point during their lifetime (1). The estimated U.S. economic burden of depressive disorders is approximately $83 billion annually (2), and projected workforce productivity losses related to depression are $24 billion annually (3).

Pharmacotherapy is the primary choice for medical management of MDD. As of 2005, approximately 27 million persons in the United States had received antidepressant therapy (4). Second-generation antidepressants now comprise most antidepressant prescriptions. These drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors, and other drugs with related mechanisms of action that selectively target neurotransmitters (Table 1). In 2009, these drugs accounted for $9.9 billion in U.S. sales and were the fourth top-selling therapeutic class of prescription drugs (5).

Several systematic reviews have assessed the comparative efficacy and safety of second-generation antidepressants (6–14). Two recent comparative effectiveness reviews provide the most comprehensive, albeit contradictory, assessments to date (15, 16). One review, conducted by some of the authors of this article, concluded that efficacy does not differ substantially among second-generation antidepressants (16); conversely, the MANGA (Multiple Meta-Analyses of New Generation Antidepressants) study group reported that escitalopram and sertraline have the best efficacy–acceptability ratio compared with other second-generation antidepressants (15).

This article updates a previous systematic review funded by the Agency for Healthcare Research and Quality (AHRQ) (16) and uses the same statistical approach as the MANGA study group did. We assessed evidence on comparative benefits and harms of second-generation antidepressants for acute, continuation, and maintenance phases of MDD, including variations of effects in patients with accompanying symptoms and among patient subgroups.

See also:

Print
Editors' Notes 773

Web-Only
Appendix Tables
Appendix Figures
CME quiz (preview on page I-27)
Conversion of graphics into slides

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conducted on specific scales to rate depression. On the basis of 234 studies, no clinically relevant differences in efficacy or effectiveness were detected for the treatment of acute, continuation, and maintenance phases of MDD. No differences in efficacy were seen in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbid conditions. Individual drugs differed in onset of action, adverse events, and some measures of health-related quality of life.

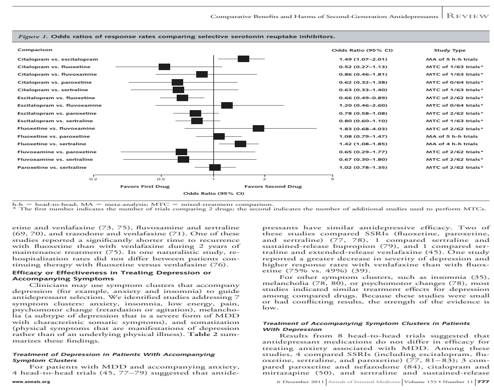


Figure 1. Odds ratios of response rates comparing selective serotonin reuptake inhibitors.

Comparison	Odds Ratio (95% CI)	Study Type
Citalopram vs. escitalopram	1.49 (1.07–2.01)	MA of 5 h-h trials
Citalopram vs. fluoxetine	0.52 (0.27–1.13)	MTC of 1/63 trials*
Citalopram vs. fluvoxamine	0.86 (0.46–1.81)	MTC of 1/63 trials*
Citalopram vs. paroxetine	0.62 (0.32–1.38)	MTC of 0/64 trials*
Citalopram vs. sertraline	0.63 (0.33–1.40)	MTC of 1/63 trials*
Escitalopram vs. fluoxetine	0.66 (0.49–0.89)	MTC of 2/62 trials*
Escitalopram vs. fluvoxamine	1.20 (0.46–2.60)	MTC of 0/64 trials*
Escitalopram vs. paroxetine	0.78 (0.58–1.08)	MTC of 2/62 trials*
Escitalopram vs. sertraline	0.80 (0.60–1.10)	MTC of 1/63 trials*
Fluoxetine vs. fluvoxamine	1.83 (0.68–4.03)	MTC of 2/62 trials*
Fluoxetine vs. paroxetine	1.08 (0.79–1.47)	MA of 5 h-h trials
Fluoxetine vs. sertraline	1.42 (1.08–1.85)	MA of 4 h-h trials
Fluvoxamine vs. paroxetine	0.65 (0.29–1.77)	MTC of 2/62 trials*
Fluvoxamine vs. sertraline	0.67 (0.30–1.80)	MTC of 2/62 trials*
Paroxetine vs. sertraline	1.02 (0.78–1.35)	MTC of 2/62 trials*

h-h = head-to-head; MA = meta-analysis; MTC = mixed-treatment comparison.
* The first number indicates the number of trials comparing 2 drugs; the second indicates the number of additional studies used to perform MTCs.

etine and venlafaxine (73, 75), fluvoxamine and sertraline (69, 70), and trazodone and venlafaxine (71). One of these studies reported a significantly shorter time to recurrence with fluoxetine than with venlafaxine during 2 years of maintenance treatment (75). In one naturalistic study, rehospitalization rates did not differ between patients continuing therapy with fluoxetine versus venlafaxine (76).

Efficacy or Effectiveness in Treating Depression or Accompanying Symptoms

Clinicians may use symptom clusters that accompany depression (for example, anxiety and insomnia) to guide antidepressant selection. We identified studies addressing 7 symptom clusters: anxiety, insomnia, low energy, pain, psychomotor change (retardation or agitation), melancholia (a subtype of depression that is a severe form of MDD with characteristic somatic symptoms), and somatization (physical symptoms that are manifestations of depression rather than of an underlying physical illness). **Table 2** summarizes these findings.

Treatment of Depression in Patients With Accompanying Symptom Clusters

For patients with MDD and accompanying anxiety, 4 head-to-head trials (45, 77–79) suggested that antidepressants have similar antidepressive efficacy. Two of these studies compared SSRIs (fluoxetine, paroxetine, and sertraline) (77, 78), 1 compared sertraline and sustained-release bupropion (79), and 1 compared sertraline and extended-release venlafaxine (45). One study reported a greater decrease in severity of depression and higher response rates with venlafaxine than with fluoxetine (75% vs. 49%) (39).

For other symptom clusters, such as insomnia (35), melancholia (78, 80), or psychomotor changes (78), most studies indicated similar treatment effects for depression among compared drugs. Because these studies were small or had conflicting results, the strength of the evidence is low.

Treatment of Accompanying Symptom Clusters in Patients With Depression

Results from 8 head-to-head trials suggested that antidepressant medications do not differ in efficacy for treating anxiety associated with MDD. Among these studies, 4 compared SSRIs (including escitalopram, fluoxetine, sertraline, and paroxetine) (77, 81–83); 3 compared paroxetine and nefazodone (84), citalopram and mirtazapine (50), and sertraline and sustained-release

Factors to Consider When Starting Therapy

- Severity of episode
- Age
- Long term adherence
  - Risk of relapse increases if discontinued early (35%-60% vs. 10%-25%)
- Previous treatment response
- Comorbid psychiatric or medical disorders
- Drug interactions
- Accessibility
- Pharmacokinetics
- Potential side effects
- Suicide risk/impulsivity
- Patient preferences
- Clinician experience
- Effectiveness of treatment

Things to Review when Starting an Antidepressant

1. Address patient's concerns
2. Purpose of medication(s)
3. Expected minimum treatment duration
4. Time to benefit & relapse prevention
5. Likelihood of benefiting
6. Dosing do's and don'ts
7. Side effects
8. Reassurance (not addictive)
9. Don't stop just because you feel better
10. When its time to stop, taper slowly (where appropriate)

Prognosis: Relapse rates

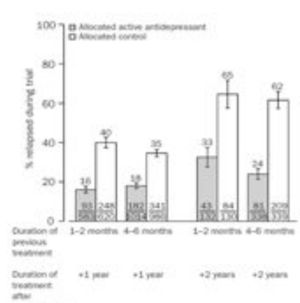
# of previous episodes	Risk (in 5 yrs) of having an additional episode if not taking meds
1	35-60 %
2	70 %
3	90 %

- 5-10% of individuals with a single depressive episode have a manic episode

Keller MB. J Clin Psych. 1999; 60(suppl 17):41-45

Antidepressant Relapse Prevention

Relapse rates after 1 or 2 years of antidepressant treatment in patients already treated for 1–2 or 4–6 months after an acute episode of depression



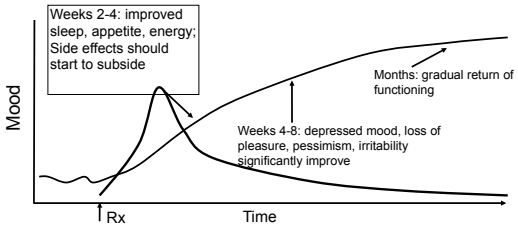
Odds of relapse:
↓50-70% with continued Rx

Average relapse rates:
Antidepressant: 18%
Placebo: 41%

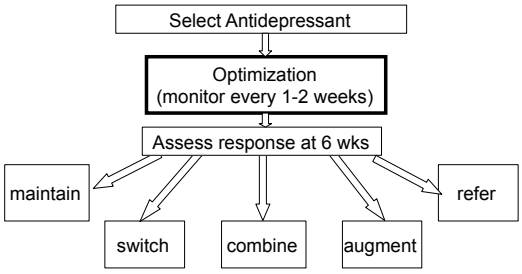
Geddes et al. Lancet 2003

Antidepressants: Onset of Effect

- Symptoms begin to improve slowly over several weeks
- 6/10 see a noticeable improvement at 4 wks
- If no improvement at 3-4 wks, 20% probability of benefiting



Strategies for Reaching Remission



Kennedy et al, 2001

Clinical Issues with Antidepressants

- Intolerability
- Persistent side effect burden
- Withdrawal syndromes
- Need for multiple medications
- Suicide/self harm controversy
- Non-adherence
- Safety during pregnancy
- Safety in overdose
- Public/self perceptions

General Antidepressant Side Effects

1. Anticholinergic
2. CNS effects
   - Activation/agitation
   - Sedation
   - Paresthesias
   - Seizures
   - Increased suicidality
3. Cognitive
4. Dermatitis
5. GI
6. Cardiovascular
7. Sexual
8. Weight Gain

Serotonin Syndrome

- Idiosyncratic drug reaction that is usually caused by a drug interaction when combining 2 or more serotonergic agents (e.g., SSRIs and MAOIs,, meperidine, amphetamines, linezolid, DM, 2nd generation antipsychotics, triptans)
- Symptoms
  - Variable reaction: mild to death (Libby Zion Death/Law)
  - Delirium, agitation, hyperpyrexia, diaphoresis, myoclonus, hyperreflexia, tremor, hypertension, diarrhea, incoordination
- Treatment
  - Stop suspected drug(s)
  - Supportive care

SSRI/SNRI Discontinuation Syndrome

- Seen with abrupt cessation of SSRI or SNRI (usually the ones with short half lives)
- Modest but clinically significant increase in favor of SSRIs vs. TCAs
- 1-2 weeks of feeling “off” or “fluish”
  - Common: dizziness, anxiety, nausea, sweating, coryza, headache, insomnia,
  - Occasionally: electric shock-like sensations, parasthesias, visual disturbances, myalgias, chills, confusion
- Can be VERY DISTRESSING and DISABLING

Michelson et al. Br J Psychiatry 2000

SSRI/SNRI Discontinuation Syndrome

- Management:
  - Prevent by advising patient not to stop SSRI/SNRI cold turkey (exception fluoxetine)
  - Taper SSRI/SNRI over 1-4 weeks
  - If mild symptoms: encourage them to try to let it pass over 1-2 weeks
  - If moderate to severe or symptoms > 2 weeks REINTRODUCE SSRI and taper more slowly or switch to fluoxetine (long $t_{1/2}$) then taper

Michelson et al. Br J Psychiatry 2000

Monitoring Parameter	Timeline
1. Target Symptoms for Depression, severity of symptoms and functioning (efficacy of antidepressant – aim for remission)	q7-14 days for 4-6 wks then q 1-3 months (to watch for relapse
2. Antidepressant adverse effects (depends on the medication selected – you should be able to identify which ones you'd be concerned with)	q7-14 days for 4 wks then q 3 months
3. Increase in obsessive, obtrusive suicidal thoughts/behaviours (especially in children, adolescents and young adults)	q7-14 days for 4-8 wks
4. Serotonin syndrome	First 2 wks of AD or new medication
5. Discontinuation syndrome	At discontinuation of therapy

Key Messages

1. All antidepressants are equally efficacious at reducing symptoms of depression.
2. Antidepressants help reduce symptoms of (moderate to severe) depression in 50-60% of adults and decrease the risk of relapse by approximately 50% (at 1 yr).
3. Benefits over placebo are greater as severity of depression increases (mostly because placebo effects decrease).

Key Messages

4. Use low doses initially
5. Despite the publication bias in adult MDD trials, antidepressants are, on average, more EFFECTIVE (than placebo) at reducing the symptoms of depression.
6. Reduce reliance on antidepressants (reserve them for moderate to severe depression)
7. Ensure adequate patient contact and monitoring

Questions?

Treating Anxiety Disorders

Adil Virani, BSc (Pharm), Pharm D, FCSHP

Outline

- Michelle's Case
- Types of anxiety disorders
- Goals of therapy
- Treatment options and guidelines
- Pharmacological options
- Benzodiazepines and Buspirone
- Discussion

Learning Objectives

After completion of this session, participants will be able to:

1. List the treatment options for 6 types of anxiety disorders
2. Compare and contrast the efficacy and safety of antidepressants, buspirone and benzodiazepines for anxiety disorders
3. List monitoring parameters for assessing efficacy and toxicity of antidepressants, buspirone and benzodiazepines for anxiety disorders

Matthew's case

- 28 yo male, 64kg, lawyer who complains of feeling "anxious"
- *When you ask what his concerns are, he says* "I'm a worrier…my mind is always thinking about something that might happen and I can't relax"
- "Before, it would come and go…but now it is worse. I worry about money, my friends, my diet, my health, you get the picture. I can't seem to quiet my mind"
- Also complains of restless sleep, fatigue and has missed 10 work days in the last month, which makes him feel worse...

Matthew's Case Cont'd

- PMHx:
  - GAD x 1 year
  - Type 1 DM
- Current Meds:
  - buspirone 10 mg po bid for 6 weeks with not a big effect on symptoms
  - Insulin Lispro (Humalog) and Glargine (Lispro)

Occasional EtOH, caffeine, smoking

- Checks BG 7 times daily, HgA1C = 8%

Individual/Group Activity (~10 min)

1. Discuss the case and briefly list the goals of treatment
2. What are the treatment options for Matthew?
   - What are the pros and cons of the different treatment options? (e.g., what is the role of buspirone for treating anxiety disorders)
3. Write a prescription for Matthew
4. What will you be monitoring and how often?
5. Fill in the types of anxiety disorders

Types of Anxiety Disorders

1. Panic Disorder (+/- agoraphobia)
2. Social Anxiety Disorder (Social Phobia)
3. Obsessive-Compulsive Disorder (OCD)
4. Generalized Anxiety Disorder (GAD)
5. Post-Traumatic Stress Disorder (PTSD)
6. Phobic Disorders - specific phobias
7. Separation Anxiety Disorder (SAD)
8. Anxiety Disorder due to a Medical Condition
9. Anxiety Disorder due to a Substance
10. Anxiety Disorder Not Otherwise Specified

Goals of Therapy

- Short term (over 6-12 weeks)
  - Reduce or resolve symptoms
  - Improve functioning
  - Minimize side effects
  - Discuss realistic goals: Note: difficult to achieve total remission in OCD and PTSD
  - Education about treatment options and side effects

Goals of Therapy

- Long term (>12 weeks)
  - Aim for return to normal functioning (remission) where possible
  - Adherence to treatment
  - Manage side effects
  - Education (e.g. techniques on how to prevent or minimize future episodes)

Matthew's Goals of Therapy

- Reduce or resolve his persistent worrying
- Decrease fatigue, improve sleep
- Improve functioning
- Education about GAD and various treatment options
- Minimize side effects
- Improve HgA1C?
- Reduce amount of monitoring of BG?

Initial Recommendations for Matthew

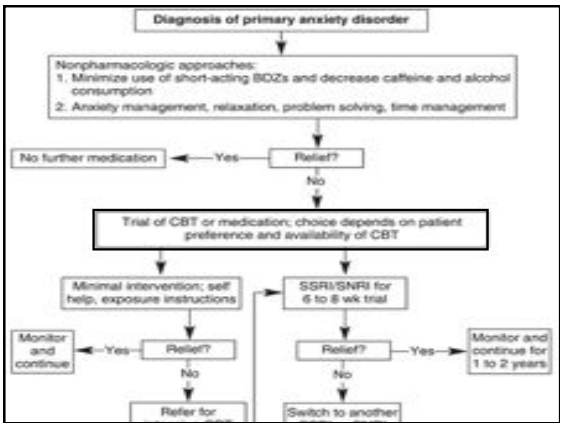
- Decrease caffeine, EtOH intake
- Regular aerobic exercise
- Quite smoking (if he's ready)
- Diet modification (regularly spaced meals)/ Improved glucose control
- Relaxation and breathing retraining techniques
- Good sleep hygiene – minimize use of sedatives or hypnotics where possible
- CBT
- SSRI

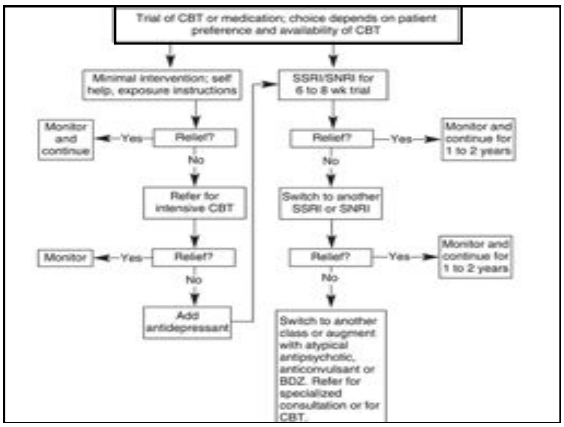
Treatment Options

❖Pharmacotherapy

❖Psychotherapy

❖Self Management





Factors to Consider:

1. Patients in trials may not be like the patient you are treating
   - Exclusions e.g. comorbid depression, substance use
   - Outpatient psychiatric clinics or academic centres
2. Endpoints are typically a decrease in symptoms (e.g. by 50%) and not total remission
3. Initial treatment may require both a BZD & antidepressant depending on patient factors

Non-Pharm: Psychotherapy

- Cognitive Behaviour Therapy (CBT)
  - Cognitive: change thinking patterns that keep people from overcoming fears
  - e.g. panic symptoms do not mean a heart attack
  - Behaviour: change peoples reactions to anxiety provoking situations
  - Slower onset of response vs. pharmacotherapy but may be longer-lasting
  - Improved outcomes if used with pharmacotherapy

Factors that Favour CBT over Pharmacotherapy

- Avoidance behaviours
- Clear ability to concentrate
- Capacity to understand and address psychological factors
- Willingness to try self-help assignments
- Previous failure of pharmacotherapy
- Preference for CBT/Non pharm approach
- Access to CBT
- Previous success with CBT

Non-Pharm: Psychotherapy

- Exposure & response prevention
  - E.g. OCD patient with fear of dirt and germs may be encouraged to wait before hand washing
  - Therapists provide strategies to cope with anxiety
- Desensitization, breathing retraining, relaxation techniques, biofeedback
- Supportive counseling
  - To assist patient with dealing with stress/anxiety
- Psychoeducation

Non-Pharm: Self Management

- Relaxation techniques
  - Massage, meditation, yoga
- Non prescription meds & herbs
- Exercise
- Mental health support groups
- Self-help books
- Internet
- Personal journals

Factors to Consider When Selecting a Medication

- Patient characteristics and preferences
- Past history of treatment/response
- Presence of comorbid psychiatric or medical condition
- Family history
  - previous response of a family member
- Financial status/coverage of meds
- Sensitivity to side effects
- Clinician experience

Reasons for a Muted Response

- Early age of onset
- Inadequate duration of therapy
- Comorbidity – personality disorders
- Biological markers
  - high systolic BP and heart rate
- Substance abuse
  - Alcohol or stimulant abuse

Drugs used for Managing Anxiety Disorders:

Anxiety disorder	First choice	Second choice
•OCD	•SSRIs	•NaSSA , Clomipramine, SGA[X]
•Panic disorder	•SSRIs, BDZ[X] (clonazepam, lorazepam, alprazolam)	•Clomipramine, SNRI
•Social phobia (aka Social anxiety disorder)	•SSRIs, SNRIs	•RIMA, Gabapentin[X], Propranlol
•Generalized anxiety	•SSRIs, SNRI, Buspirone, +/- BDZ[x]	•TCAs
•PTSD	•SSRIs, Clonidine	•NaSSA, SGA[X]
•Specific phobia	•Benzodiazepines[x]	•Propranolol

Antidepressant Dosing for Most Anxiety Disorders

DRUG	STARTING DOSE	DOSE RANGE
Citalopram	10-15 mg daily	20-30 mg
Fluoxetine	5-10 mg daily	20-80 mg
Fluvoxamine	25 mg daily	50-300 mg
Paroxetine	10 mg daily	40-60 mg
Sertraline	25-50 mg daily	50-200 mg
Venlafaxine XR	37.5 mg daily	75-**150** mg
Clomipramine	50-75 mg daily	75-200 mg
Desipramine	10-25 mg daily	150-300 mg
Imipramine	10-25 mg daily	150-300 mg

Phobia Treatment

- Simple phobias: Exposure therapy (90%) CBT
- Performance phobia:
  - Alprazolam 0.25 mg prn
  - Lorazepam 0.5 mg prn
  - Propranolol 10-20 mg prn

Benzodiazepines (BDZ)

- Relatively quick acting (1-5 days)
- Generally used for short term treatment of insomnia or anxiety
- Quick response may help to build relationship
- Usually well tolerated in the short term
- Evidence for efficacy, but first line use is not recommended except as an adjunct during onset of treatment
- May be useful for those who don't respond to antidepressants alone
- Use lowest effective dose for shortest period of time where possible

BDZs Cont'd

- BDZs considered 'targeted substances' in Canada
- Can interfere with CBT treatment or driving if patient is too sedated
- Some patients are concerned about long term use while others are concerned about withdrawing a medication that has helped them in the past
- Tolerance to sedation may be seen by 2-3 weeks, however tolerance to anxiety/ "anti-seizure" effect is highly variable
- Use should be avoided (where possible) in patients with a previous history of alcohol or drug abuse

Benzodiazepine Adverse Effects

1. Drowsiness/tiredness
2. Incoordination
3. Headaches
4. Cognitive impairment
5. Anterograde amnesia
6. Dizziness
7. Respiratory depression
8. Paradoxical effects
9. Muscle weakness

Pharmacokinetic Comparison

Generic Name	Elimination half-life (hr)	Active Metabolite	Pathway of metabolism	Rate of Onset of Action	Indication/Uses
Alprazolam	12 - 15	N	Oxidation	Intermediate	A, PA
Chlordiazepoxide	> 100	Y	Oxidation	Intermediate	A,AW,SE, PS
Clonazepam	20 - 80	N	Oxidation	Fast	A,E
Clorazepate	> 100	Y	Oxidation	Fast	A, AW, E
Diazepam	> 100	Y	Oxidation	Very fast	A,AW,MS,PS,SE
Flurazepam	> 100	Y	Oxidation	Fast	S/H
Lorazepam	10 - 20	N	Conjugation	Intermediate	A, AW, S/H, SE
Oxazepam	5 - 14	N	Conjugation	Slow	A, AW, S/H
Temazepam	10 - 20	N	Conjugation	Intermediate	S/H
Triazolam	1.5 - 5	N	Oxidation	Intermediate	S/H

A = Anxiety, AW = Alcohol withdrawl, E = Epilepsy, MS = Muscle spasms, PA = Panic attacks, PS = Perioperative sedation, SE = Status Epilepticus, S/H = Sedative/Hypnotic

Buspirone

- Anxiolytic & weak antidepressant properties
- Useful for GAD
- Less drowsiness and psychomotor impairment than BZD
- Mode of action is dose dependent
  - Low doses (5-30 mg):
    - presynaptic partial agonist at 5-HT_{1A} receptors
  - High doses (30-60 mg):
    - postsynaptic partial agonist at 5- HT_{1A} receptors

Comparison of Anxiolytics

BZD	BUSPIRONE
Potentiate GABA	Modulates serotonin
Variable onset; Effective PRN	Slow onset (3-5 weeks); Not effective PRN
Anxiolytic, sedative, muscle relaxant, anticonvulsant	Chronic anxiety disorders, depression, irritability, aggression
S.E.: sedation, ataxia fatigue, depression memory impairment	S.E.: dizziness, nausea, nervousness, headache, paresthesias
Tolerance, withdrawal	No abuse potential
Interacts with alcohol	No alcohol interaction

Efficacy of Anxiolytics

Many of these listed are adjunctive and imply that they are not often used first line for these indications and have little evidence to support their use. Hence, data on this table may differ from the other tables.

Disorder	BZD	Buspirone
GAD	+	+ (first line)
Panic Disorder	alprazolam,lorazepam, clonazepam (adjunctive)	-
Social Phobia	alprazolam, clonazepam (adjunctive)	adjunctive
OCD	If SSRIs not helpful	adjunctive
PTSD	adjunctive	adjunctive

Choice of Antidepressant

1. Evidence: First line consideration for anxiety disorders given overall long-term effectiveness (except specific phobias)
2. Patient characteristics & preferences
   -E.g. Past response, drug interactions, current symptoms, age
3. Receptor and neurotransmitter activity define selectivity, potency and side effects
4. Aim to treat for year
5. Comorbid illnesses
6. Toxicity in overdose
7. Cost

Antidepressants Used in Anxiety Disorders

DRUG	GAD	PANIC DIS.	SOC. PHOBIA
SSRIs	+	+	+
Venlafaxine	+	2nd	+
Bupropion	-	-	-
Tricyclics	clomipramine imipramine	clomipramine	-
MAOI or RIMA	-	moclobemide phenelzine	moclobemide phenelzine
Mirtazapine	Prelim. Data	-	-

Antidepressants Used in Anxiety Disorders

DRUG	OCD	PTSD
SSRIs	+	+
Venlafaxine	-	-
Bupropion	-	-
Tricyclics	Clomipramine 2nd	amitriptyline imipramine
MAOIs	-	phenelzine
Mirtazapine	2nd	2nd

Monitoring Parameters

- Target symptoms
  - Have they been reduced? To what extent? What symptoms are still present and to what degree?
  - Symptom diary or checklist
  - Check q 3 months
- Overall functioning
- Adverse effects associated with treatment selected
- Possible drug interactions

Factors to consider…

<u>Antidepressants prescribed? Consider:</u>

- The time required to see a benefit (4-6 weeks); take as prescribed; treatment for a year or longer
- May initially worsen agitation (dose-related)
- Barriers to compliance
- Not addictive
- Don't discontinue suddenly
- Counsel on side effects (and some management strategies) & special precautions
- Drug interactions (if applicable)

Factors to consider...

Using Benzodiazepines? Consider:

- Not increasing dose without discussing with prescriber
- The intended length of treatment (initial treatment is usually 2-6 wks)
- Issues regarding the potential for physical dependence/abuse (their concerns, past history in family)
- Initial identification of patients at risk of bdz dependence/withdrawal
- Not discontinuing them suddenly
- Side effects (not driving initially, avoid alcohol)

Internet Websites on Anxiety Disorders

1. National Institute of Mental Health http://www.nimh.nih.gov/anxiety/anxiety.cfm
2. Anxiety Disorders Association of America http://www.adaa.org/
3. National Depressive and Manic Depressive Association http://www.ndmda.org/
4. Obsessive Compulsive (OC) Foundation http://www.ocfoundation.org
5. Social Phobia/Social Anxiety Association http://www.socialphobia.org/
6. National Center for PTSD http://www.ncptsd.org/

Guidelines for Assessing and Treating Anxiety Disorders

- Evidence-based guidelines for the pharmacological treatment of **anxiety disorders**: *J Psychopharmacol* 2005;19(6):567-96. http://www.bap.org.uk/consensus/Anxiety_Disorder_Guidelines.pdf
- Canadian Psychiatric Association. Can J Psychiatry 2006; 51 (8) Suppl 2; 9S-91S
- American Psychiatric Association Practice Guidelines (panic disorder)
  - http://www.psych.org/psych_pract/treatg/pg/pg_panic.cfm
- New Zealand Guideline Group
  - http://www.nzgg.org.nz/library/gl_complete/anxiety/index.cfm
- The Assessment and Treatment of Children and Adolescents With Anxiety Disorder
  - http://www.aacap.org/clinical/Anxtysum.htm

Insomnia: Help me make it though the night…

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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?

What is Insomnia?

- Difficulty falling asleep, maintaining sleep, or not feeling rested in spite of sufficient opportunity to sleep
- Most common sleep complaint
- Common reason to seek advise from a health care professional
- Can be transient or persistent

DSM IV Diagnostic Criteria for Primary Insomnia

- Difficulty initiating or maintaining sleep, or having nonrestorative sleep for at least a month
- Causes distress or impairment in social, occupational or other important areas of functioning
- Not related to medical disorder or other sleep disorder
- Not the result of substances

Classification of Insomnia

Primary:
Psychophysiological

Secondary:
Psychiatric, Medical, Substance Use

Categories

Transient	⇒	2-3 days
Short-term	⇒	< 3 weeks
Long-term	⇒	> 3 weeks

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

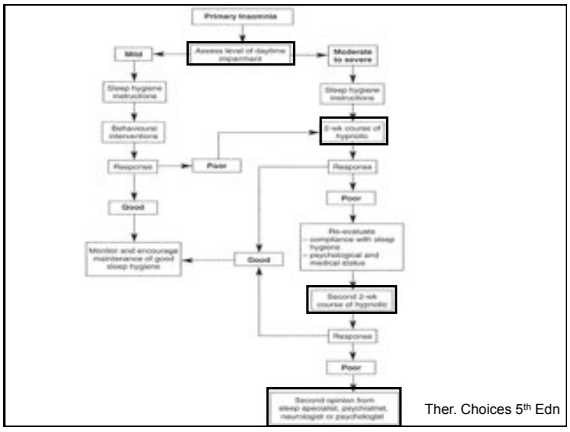
- Time data
  - Napping, bed time, lights, how long to fall asleep, how many times awoken, longest awake period, time out of bed, hours of sleep
- Questions about the sleep period
  - Physical symptoms preventing sleep (pain), mental or emotional symptoms (worry, anxiety), what awakens during the night (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


Sleep History Questionnaire

http://www.sjo.org/documents/1/sleephistoryquestionnaire.pdf

Medications that can Cause or Worsen Insomnia

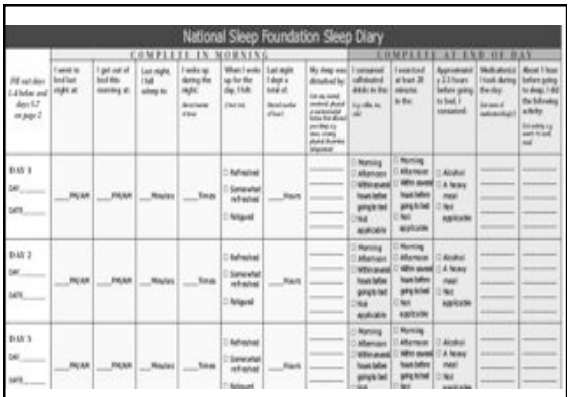
- Antidepressants
  - bupropion, fluoxetine, SNRIs, MAOIs, TCAs
- Antihypertensives
  - beta blockers, methyldopa
- Nicotine
- Sympathomimetic Amines
  - amphetamines, methylphenidate, caffeine, cocaine, decongestants, appetite suppressants, bronchodilators (e.g., salbutamol),
- Miscellaneous
  - corticosteroids,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



Ther. Choices 5th Edn

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)


National Sleep Foundation Sleep Diary

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.

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


Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults

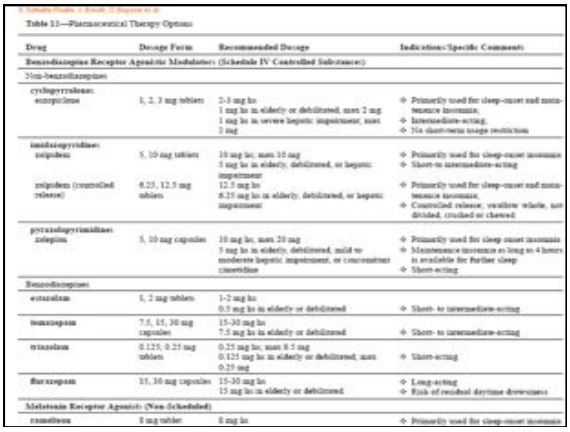
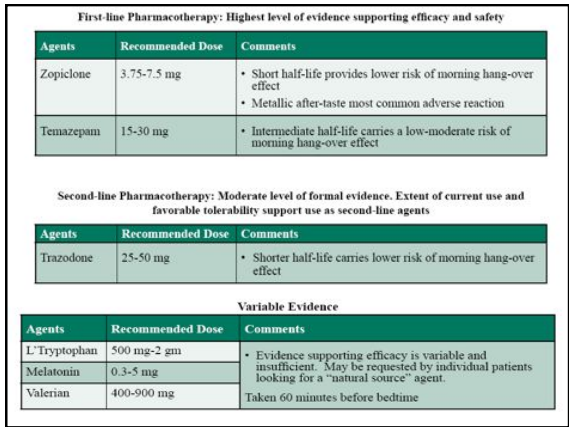


Table 11—Pharmaceutical Therapy Options

Drug	Dosage Form	Recommended Dosage	Indications/Specific Comments
Benzodiazepine Receptor Agonistic Modulators (Schedule IV Controlled Substances)			
Non-benzodiazepines			
cyclopyrrolones: eszopiclone	1, 2, 3 mg tablets	2-3 mg hs 1 mg hs in elderly or debilitated, max 2 mg 1 mg hs in severe hepatic impairment, max 2 mg	✧ Primarily used for sleep-onset and maintenance insomnia ✧ Intermediate-acting ✧ No short-term usage restriction
imidazopyridines: zolpidem	5, 10 mg tablets	10 mg hs, max 10 mg 5 mg hs in elderly, debilitated, or hepatic impairment	✧ Primarily used for sleep-onset insomnia ✧ Short- to intermediate-acting
zolpidem (controlled release)	6.25, 12.5 mg tablets	12.5 mg hs 6.25 mg hs in elderly, debilitated, or hepatic impairment	✧ Primarily used for sleep-onset and maintenance insomnia ✧ Controlled release; swallow whole, not divided, crushed or chewed
pyrazolopyrimidines: zaleplon	5, 10 mg capsules	10 mg hs, max 20 mg 5 mg hs in elderly, debilitated, mild to moderate hepatic impairment, or concomitant cimetidine	✧ Primarily used for sleep-onset insomnia ✧ Maintenance insomnia as long as 4 hours is available for further sleep ✧ Short-acting
Benzodiazepines			
estazolam	1, 2 mg tablets	1-2 mg hs 0.5 mg hs in elderly or debilitated	✧ Short- to intermediate-acting
temazepam	7.5, 15, 30 mg capsules	15-30 mg hs 7.5 mg hs in elderly or debilitated	✧ Short- to intermediate-acting
triazolam	0.125, 0.25 mg tablets	0.25 mg hs, max 0.5 mg 0.125 mg hs in elderly or debilitated, max 0.25 mg	✧ Short-acting
flurazepam	15, 30 mg capsules	15-30 mg hs 15 mg hs in elderly or debilitated	✧ Long-acting ✧ Risk of residual daytime drowsiness
Melatonin Receptor Agonists (Non-Scheduled)			
ramelteon	8 mg tablet	8 mg hs	✧ Primarily used for sleep-onset insomnia


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. Taken 60 minutes before bedtime
Melatonin	0.3-5 mg	
Valerian	400-900 mg	

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

Not Recommended

The following agents are not recommended for the management of conditioned insomnia except in cases where the agent is being used specifically to mange a co-morbidity such as depression.

Agents	Comments
Antidepressants - mirtazapine, fluvoxamine, tricyclics	Relative lack of evidence
Amitriptyline	Relative lack of evidence and significant adverse effects (such as weight gain)
Antihistamines - chlorpheniramine	Relative lack of evidence or excessive risk of daytime sedation, psychomotor impairment and anticholinergic toxicity
Antipsychotics (Conventional or 1st-Generation) - chlorpromazine, methotrimeprazine, loxapine	Relative lack of evidence and unacceptable risk of anticholinergic and neurological toxicity
Antipsychotics (Atypical or 2nd-Generation) - risperidone, olanzapine, quetiapine	Relative lack of evidence and unacceptable cost and risk of metabolic toxicity
Benzodiazepines (Intermediate and Long-Acting) - diazepam, clonazepam, flurazepam, lorazepam, nitrazepam, alprazolam, oxazepam Benzodiazepines (Short-Acting) - triazolam	Excessive risk of daytime sedation and psychomotor impairment No longer recommended due to unacceptable risk of memory disturbances, abnormal thinking and psychotic behaviors

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

Selected References

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2. Neubauer DN. Current and new thinking in the management of comorbid insomnia. Am J Manag Care. 2009 Feb;15 Suppl:S24-32. Available from: http://www.ajmc.com/media/pdf/A228_09feb_Neubauer_S24to32.pdf\
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
4. Bhat A, Shafi F, El Solh AA. Pharmacotherapy of insomnia. Expert Opin Pharmacother. 2008 Feb;9(3):351-62.
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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7. Sullivan SS, Guilleminault C. Emerging drugs for insomnia: new frontiers for old and novel targets. Expert Opin Emerg Drugs. 2009 Sep;14(3):411-22.
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
10. Krystal AD. A compendium of placebo-controlled trials of the risks/benefits of pharmacological treatments for insomnia: the empirical basis for U.S. clinical practice. Sleep Med Rev. 2009 Aug;13(4):265-74.

QUESTIONS???

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Overview

- Case
- Treatment Options
- Treatment Guidelines
- 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.

Please write down what first comes to mind as your best treatment option. How well does that option work and what are 2 pros and cons?

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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 4

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® ®)
  - 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

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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

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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

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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.

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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 1.2 mg/kg/day	Maintain Dose for a min. of 7-14 days before adjusting to 1.2 mg/kg/day	Lesser of 1.4 mg/kg/day or 80 mg/day	Lesser of 1.4 mg/kg/day or 80 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

2011 CADDRA GUIDELINES

SECOND LINE/ADJUNCTIVE AGENTS – short-acting and intermediate-acting preparations

Dexedrine® (dextroamphetamine sulphate)	5 mg tab	2.5-5 mg b.i.d.	▼ 2.5-5 mg	▼ 2.5-5 mg	40 mg
Dexedrine® Spansule® (dextroamphetamine sulphate)	10, 15 mg cap	10 mg q.d. a.m.	▼ 5 mg	▼ 5 mg	40 mg
Ritalin® (methylphenidate)	10, 20 mg tab	5 mg b.i.d. to t.i.d.	▼ 5-10	▼ 5-10	60 mg
Ritalin® SR® (methylphenidate HCl)	20 mg tab	20 mg q.d. a.m.	▼ 20 mg	▼ 20 mg	60 mg

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2011 CADDRA GUIDELINES

SECOND LINE/ADJUNCTIVE AGENTS – short-acting and intermediate-acting preparations

Dexedrine® (dextroamphetamine sulphate)	5 mg tab	2.5-5 mg b.i.d.	▼ 2.5-5 mg	▼ 2.5-5 mg	40 mg
Dexedrine® Spansule® (dextroamphetamine sulphate)	10, 15 mg cap	10 mg q.d. a.m.	▼ 5 mg	▼ 5 mg	40 mg
Ritalin® (methylphenidate)	10, 20 mg tab	5 mg b.i.d. to t.i.d.	▼ 5-10	▼ 5-10	60 mg
Ritalin® SR® (methylphenidate HCl)	20 mg tab	20 mg q.d. a.m.	▼ 20 mg	▼ 20 mg	60 mg

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CADDRA 2011 2nd and 3rd line options?

Table 1. MEDICAL TREATMENT FOR ADHD UNCOMPLICATED – CHILDREN (continued)
Alphabetically Listed – Refer to product monographs for complete prescribing information.

Brand Name (active chemical)	Dosage Form	Starting Dose	Titration Schedule Every 7 days		Maximum (up to)
			Per product Monograph	Per CADDRA Board	Per Product Monograph
GENERIC MEDICATIONS					
PMS® or Ratio®-methylphenidate	5, 10, 20, mg tab	5 mg q.d. a.m. and noon	▼ 5 mg (add 4pm dose)	▼ 5 mg	60 mg
Nano-MPH CR-C® (methylphenidate)	18, 27, 36, 54 mg tab	18 mg q.d. a.m.	▼ 18 mg	▼ 18 mg	54 mg
THIRD LINE AGENTS					
These medications (imipramine, bupropion, modafinil, etc.) should only be initially or first prescribed by a spe					

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

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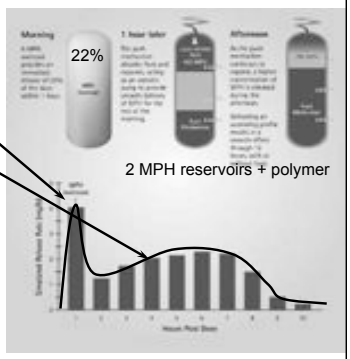
OROS-Methylphenidate (Concerta®)

- 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'



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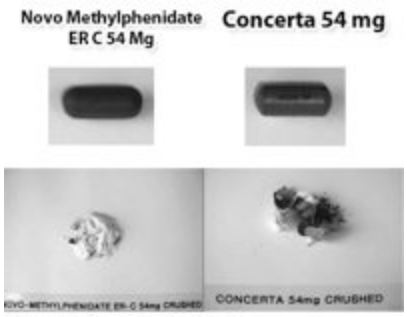
Generic Concerta – but is it really?



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Methylphenidate (Biphentin®)

- Canadian 40% IR / 60% CR release formulation
- Multilayer beads inside gelatin capsule (can sprinkle)
- First peak: ~2 hrs
- Second peak: ~6-7 hrs
- Duration: Up to 12 hrs
- Available: 10, 15, 20, 30, 40, 50, 60, 80 mg capsules

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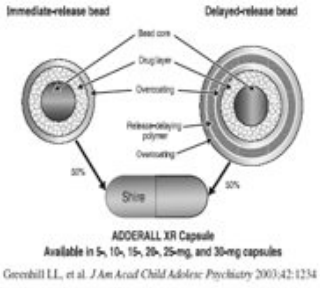
Mixed Amphetamine Salts (Adderall XR®)

- 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

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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

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

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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

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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 25

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.

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Thanks for your 'Attention'!

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Pain therapeutics

Acetaminophen/NSAIDs
Acute pain
Osteoarthritis
Migraine
Acute Gout
Neuropathic pain

James McCormack, Pharm.D.
Professor
Faculty of Pharmaceutical Sciences, UBC

Common types of pain killers

1. Acetaminophen (Tylenol)
2. Anti-inflammatories
   NSAIDs (aspirin, ibuprofen (Motrin, Advil), naproxen, 15 others)
   NSAIDs COX –2's - celecoxib (Celebrex)
3. Narcotics - codeine, morphine
4. Combinations of the above
5. Steroids - prednisone

Acetaminophen for post-operative pain

"About half of participants treated with paracetamol at standard doses achieved at least 50% pain relief over four to six hours, compared with about 20% treated with placebo" CD004602

Acetaminophen for acute migraine headaches

"For all efficacy outcomes paracetamol was superior to placebo, with NNTs of 12, 5.2 and 5.0 for 2-hour pain-free and 1- and 2-hour headache relief, respectively, when medication was taken for moderate to severe pain. Nausea, photophobia and phonophobia were reduced more with paracetamol than with placebo at 2 hours (NNTs of 7 to 11); more individuals were free of any functional disability at 2 hours with paracetamol (NNT 10); and fewer participants needed rescue medication over 6 hours (NNT 6)." CD008040

NSAIDs vs acetaminophen for acute pain in children

336 children; ibuprofen, acetaminophen or codeine
Ibuprofen better than either (for pain score and attaining "adequate" pain relief.

68 children; ibuprofen or aceta+codiene
No difference in pain scores

336 children; ibuprofen vs acetaminophen+codeine

No difference in mean pain scores – Ibuprofen less functional limitation & adverse events

Pediatrics 2007;119:460-7
Acad Emerg Med 2009;16:711-6
Ann Emerg Med 2009;54:553-60

NSAIDs vs acetaminophen for osteoarthritis

"NSAIDs are superior to acetaminophen for improving knee and hip pain in people with OA"CD004257

Patient global assessment (dichotomous)
40% acetaminophen, NSAID 50%
pain scores about 25% better on average

No difference in tolerability but studies typically 6 weeks

Topical NSAIDS for chronic musculoskeletal pain

"Topical NSAIDs can provide good levels of pain relief; topical diclofenac solution is equivalent to that of oral NSAIDs in knee and hand osteoarthritis, but there is no evidence for other chronic painful conditions. Formulation can influence efficacy. The incidence of local adverse events is increased with topical NSAIDs, but gastrointestinal adverse events are reduced compared with oral NSAIDs" CD007400

Topical NSAIDs for acute pain

"Topical NSAIDs can provide good levels of pain relief, without the systemic adverse events associated with oral NSAIDs, when used to treat acute musculoskeletal conditions" CD007402

Systematic review - ibuprofen, piroxicam, salicylates, diclofenac, eltenac

Topical NSAIDs vs placebo

Chronic pain (2 weeks) - OA, tendinitis -13 trials -1983 patients

> 50% pain relief (week 1) - 74 vs 44% (placebo)

> 50% pain relief (week 2) - 92 vs 58% (placebo)

> 50% pain relief (week 4) - 55 vs 57% (placebo)

Topical NSAIDs were not statistically significantly different compared to oral NSAIDs except during the first week

BMJ 2004;329:324-6

Capsaicin (0.075%)

Musculoskeletal pain - 4 weeks

3 placebo controlled trials - 368 patients

> 50% pain relief - 38 vs 25% (placebo)

Local adverse effects - 49% vs 10%

BMJ 2004;328:991-4

Topical NSAID RX

Topical NSAID's—generic, available at your favorite compounding Pharmacy (Pennsaid is more $ and smells like garlic)

RX-

Diclofenac or ketoprofen,10% in Difusimax

Disp.-100gm

Rub on joint am and pm. No need to protect hands

Slide stolen with permission from Mike Allan

GI Risks of Using NSAIDs

1. 10-20% of patients develop abdominal pain, dyspepsia, nausea
2. Symptomatic upper GI ulcers occur in 1% of patients over 6 months (3-4% over 1 year?)

Risk of GI haemorrhage with long term use of aspirin: meta-analysis

24 trials

66,000 patients

No difference between low dose/high dose or modified release formulations

Other studies support this finding – Heart 2001;85:265-71, Am J Gastroenterol 2000;95:2218-24

	GI bleed (%)
Aspirin	2.5
Placebo	1.4
Relative risk inc	79
Absolute risk	1.1
Number needed to harm	263

BMJ 2000;321:1183-7

COX-2 versus other NSAIDs

1. Appear to be equally effective
2. No difference in overall adverse effects
3. No difference in kidney effects
4. No effects of COX-2 on platelets
5. Upset stomach symptoms
   1. 3 studies – no difference
   2. 1 showed a 2% absolute difference
   3. 1 showed a 10% absolute difference
6. Approximately a 10-25% absolute difference in endoscopically-proven ulcers

COX-2 versus other NSAIDs

Serious GI events differences

1. One publication showed a 0.5% difference over 12 months in serious gastrointestinal complications (1.8% on old NSAIDs, 1.3% on COX-2)
2. To prevent one symptomatic ulcer you need to treat 300 people with one of the new NSAIDs for 1 year
3. To prevent 1 upper GI bleed = 600 people
4. No difference in death from GI complications
5. Cardiovascular issues

Of 50 Patients With a GI Bleed on an NSAID

16% of patients reported being informed of adverse effects

4% of patients informed about what to do if adverse symptoms occur

36% (18) of the patients had stomach pain before the bleed and all but 2 of these patients continued taking the drug

Br J Clin Pharmacol 1996;42:253-6

NSAID Concerns

1. NSAIDs are a common cause of stomach and bowel disorders (stomach upset, ulcers to perforation and fatal gastrointestinal bleeding)
2. NSAIDs, along with alcohol, are likely the most common drugs to produce drug-induced high blood pressure
3. NSAIDs will, in some people, reverse some of the beneficial effects of drugs used in patients with heart failure and they can damage kidney function in susceptible individuals
4. Some NSAIDs can cause mental confusion, especially in the elderly
5. NSAIDs do not retard or prevent the progression of either rheumatoid or osteoarthritis

Acetaminophen Benefits

1. Acetaminophen as a pain killer has a number of advantages over the NSAIDs
2. Acetaminophen produces almost no adverse effects on the heart, blood vessels, stomach, or the kidney and therefore is safer in people with stomach ulcers, heart failure, and high blood pressure
3. While acetaminophen is effective for some/many people, some people will require an NSAID to obtain partial or complete pain control

Acetaminophen and Dosing

1. While acetaminophen can cause liver damage, it rarely occurs except in overdose
2. Single doses can range from 325mg to 1-1.5 grams (2-3 of the extra strength or 500 mg tablets) – can be repeated every 6-8 hours
3. Many people will find much lower doses (325 mg or one regular strength tablet) may work for either their acute or chronic pain
4. Maximum daily dose in people with normal liver function is 4 grams (8 pills of the extra strength or 500 mg tablets) per day (2 grams per day if one has liver disease or consumes moderate to large amounts of alcohol on a regular (daily) basis)

The "BEST" dose

1. People respond very differently to different pain killers and/or doses therefore, it is important that the dose be adjusted to the least amount, least often, which will control the pain
2. Virtually none of the NSAIDs, when dosed daily, have to be given more frequently than twice daily
3. People with osteoarthritis do not necessarily have constant or consistent pain, and therefore dosing of an NSAID on a regular basis may not be needed
4. Many people may do well by dosing the acetaminophen or an NSAID 1 hour prior to a known aggravating factor (e.g., prior to walking to the store, or at bedtime if pain disturbs sleep)
5. Consider treating osteoarthritis with regular doses of acetaminophen and use NSAIDs on an as needed basis

NSAIDs versus placebo in sports injuries

19 trials in total
- 11 trials: NSAID better
- 7 trials: no difference
- 1 trial: placebo better

Quality of trials in general was fairly low

NSAID versus acetaminophen+/- a narcotic in sports injuries

8 trials in total
- 5 trials: no difference (regularly dosed narcotics produced more side effects)
- 1 trial: naproxen less pain - no difference in tenderness, swelling or limitation of movement
- 1 trial: ibuprofen returned patients to sport faster (not designed to evaluate this parameter)
- 1 trial: diclofenac better on day 6 and 7

Quality of trials in general was fairly low

"There is growing support for using paracetamol, also known as acetaminophen, in some countries including the United States of America, as first-line treatment for musculoskeletal sprains and strains, because paracetamol may be just as effective an analgesic as NSAIDs, yet will not increase bleeding into the injury site or potentially impair healing"

Physiotherapy Theory and Practice 2011;27:482–91


BMJ

BMJ 2012;345:e4737 doi: 10.1136/bmj.e4737 (Published 18 July 2012)

SPORTS DRINKS

The truth about sports drinks

Sports drinks are increasingly regarded as an essential adjunct for anyone doing exercise, but the evidence for this view is lacking. **Deborah Cohen** investigates the links between the sports drinks industry and academia that have helped market the science of hydration

Deborah Cohen *investigations editor*

BMJ July 2012

The Evidence

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

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

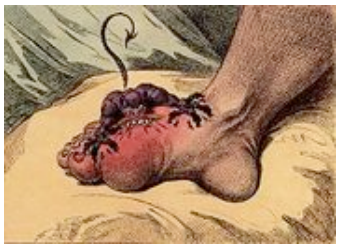
"A meta-analysis of data from cyclists in time trials concluded that relying on thirst to gauge the need for fluid replacement was the best strategy."

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

Too much water?

"There have been 16 recorded deaths and 1600 people taken critically ill during competitive marathon running due to a drop in their serum sodium"

Drugs for gout



Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in acute gout

Indomethacin 50 mg TID

Prednisolone 30 mg

Both could use PRN paracetamol

Equally effective with fewer adverse effects

Adverse Effects	Indomethacin (N=46)	Prednisolone (N=44)	*P* Value
Any adverse event, No. (%)	29 (63)	12 (27)	.0007
Epigastric pain, of No. (%)	14 (30)	0 (0)	<.0001
Other abdominal pain, No. (%)	3 (7)	0 (0)	.09
Rash, No. (%)	1 (2)	3 (7)	.25
Dizziness, No. (%)	9 (19)	2 (5)	.03
Drowsiness, No. (%)	9 (19)	7 (16)	.79
Dry mouth, No. (%)	11 (24)	9 (20)	.83
Indigestion, No. (%)	14 (30)	4 (9)	.02
Nausea, No. (%)	12 (26)	3 (9)	.02
Vomiting, No. (%)	4 (9)	0	.05
Diarrhea, No. (%)	3 (7)	0	.09
Serious adverse effects requiring admission, No. (%)	7 (15)	0	.007
Gastrointestinal hemorrhage, No. (%)	5 (11)	0	<.05
Shortness of breath, No. (%)	1 (2)	0	.98
Chest pain, No. (%)	1 (2)	0	.98

*Percentages may not sum to 100, because of rounding.

Ann Emerg Med 2007;49:670-7

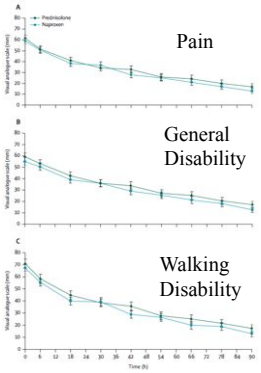
Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomized equivalence trial

120 patients with acute gout

35 mg prednisolone daily or

500 mg naproxen BID for 5 days

No difference in adverse effects



Lancet 2008;371:1854–60

Colchicine for acute gout

"Colchicine is an effective treatment for the reduction of pain and clinical symptoms in patients experiencing acute attacks of gout, although in the regimen studied its low benefit to toxicity ratio limits its usefulness. It should be used as a second line therapy when NSAIDs or corticosteroids are contraindicated or ineffective. More evidence is needed to compare the efficacy of colchicine to that of NSAIDs or corticosteroids, the current first line therapy for acute gout." CD006190

Colchicine dosing

THE WRONG WAY

"Colchicine should be taken at an initial dose of 1.2mg followed by 1 tablet every 2 hours until the gouty pain is relieved, gastrointestinal symptoms develop, or the maximum dose (6mg) is reached.

THE RIGHT WAY

"Colchicine should be taken at an initial dose of 1.2mg followed by 1 tablet (0.6mg) 1 hour later"

Colchicine for gout

184 patients with an acute gout flare

placebo vs low dose (1.8 mg total over 1 hour) vs high dose (4.8 mg over 6 hours)

	50% ↓ in pain at 24h	Diarrhea (%)	Severe diarrhea (%)	Nausea
Placebo	9	14	0	5
Low dose	38	23	0	4
High dose	33	77	19	17

Arth Rheum 2010;62:1060-8

Febuxostat/allopurinol

52 weeks - 760 patients - age 52, BMI 33, male 96%

	Gout flares (%)	Serum urate <6mg/dL (%)
Febuxostat 80 mg	22	74
Febuxostat 160 mg	36	80
Allopurinol 300 mg	21	36

NEJM 2005;353:2450-61

J Rheumatol 2009;36;1273-1282 - similar results

Gout tips

Asymptomatic hyperuricemia should not be treated

A diagnosis of gout should be made with joint aspiration not an elevated serum uric acid

Aim for a serum uric acid of less than 360

To reduce the chance of mobilization gout add in low dose NSAIDs or colchicine or prednisone for the first few months of allopurinol therapy

Drugs for headaches

Drugs that cause headaches

Amitriptyline, imipramine
ASA, acetaminophen (frequent use)
Benzodiazepines
Nitroglycerine
MAOIs
Metoclopramide
Estrogen
Sulphonamides
Theophylline
NSAIDS
Fluoxetine

Withdrawal of:
Benzodiazepines
Caffeine Ergotamine
Methysergide
ASA, APAP (±codeine)
some antihypertensives

Aspirin for migraine

Migraine headache pain will be reduced from moderate or severe to no pain by 2 hours in approximately 25% of people taking a single dose of 1000 mg of aspirin, compared with about 10% taking placebo. CD008041

Migraine headache pain will be reduced from moderate or severe to no worse than mild pain by 2 hours in roughly 50% of people taking a single dose of 1000 mg of aspirin compared with approximately 33% taking placebo. CD008041

ASA vs sumatriptan vs ibuprofen vs placebo for acute migraine

Patients

312 patients - cross-over DB RCT - mean age 38, 81% women, severe headaches (45%)

Treatment

effervescent ASA (1000 mg), sumatriptan (50 mg), ibuprofen (400 mg), or placebo

Cephalalgia 2004;24: 947–54

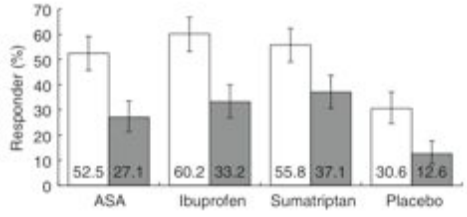


Figure 1 Pecentage of ITT patients (responders, mean and 95% confidence intervals) with reduction in headache severity from severe or moderate to mild or no pain at 2h (□) and percentage of patients (responders) pain-free at 2h (■). All active drugs are superior to placebo.

Cephalalgia 2004;24: 947–54

Adverse events

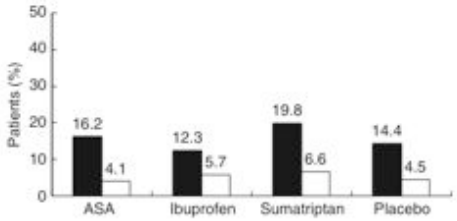


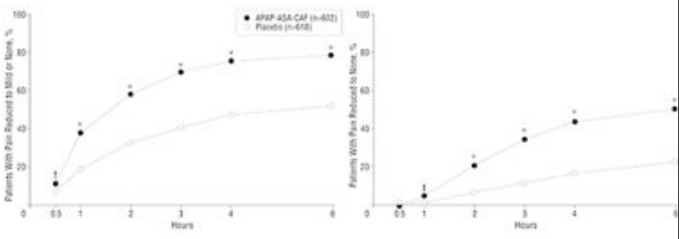
Figure 5 Adverse events (safety population, $n = 313$). Total adverse events (■); drug-related averse events (□) were investigstor attributed.

Stats and type of AE not reported

Cephalalgia 2004;24: 947–54

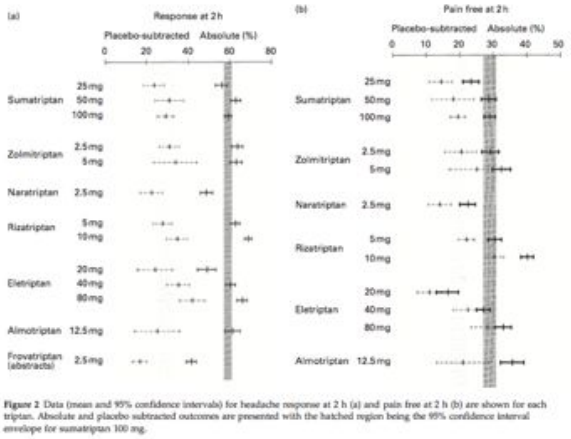
500 mg aspirin/500 mg acetaminophen/130mg caffeine or placebo

1220 patients with moderate "migraine"

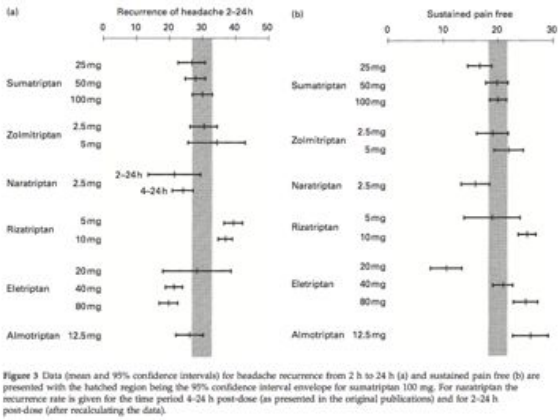


Percentage of patients with pain intensity reduced to mild or none (left) or to none (right)

Arch Neur 1998;55:210-7



Cephalalgia 2002;22:633–58



Cephalalgia 2002;22:633–58

Triptan AEs

"tingling, paraesthesias, and warm sensations in the head, neck, chest, and limbs; less frequent are dizziness, flushing, and neck pain or stiffness"

Much rarer 'central nervous system (CNS) AEs "asthenia, abnormal dreams, agitation, aphasia, ataxia, confusion, dizziness, somnolence, speech disorder, thinking abnormal, tremor, vertigo, and other focal neurological symptoms) and notably the 'chest- related AEs' (chest pressure, chest pain, radiating pain in arm, other chest feelings, heavy arms, shortness of breath, palpitations, and anxiety)"

Cephalalgia 2002;22:633–58

Triptan dosage forms

Oral
sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, frovatriptan
Nasal spray
sumatriptan, zolmitriptan
Subcutaneous inj
sumatriptan

Dihydroergotamine

Can be used SC, IM, IV

more nausea but less chest pain than the triptans

An approach for migraines

Mild - NSAID/acetaminophen/caffeine +/- metoclopramide

If no effect in an hour - triptan

If no effect in a couple of hours - narcotic

Who is a candidate for prophylaxis?

Recurring migraines which significantly interfere with daily routines, despite acute treatment

Frequent headaches

Contraindication to, failure of, or overuse of acute treatments

Adverse effects with acute treatments

Patient preference

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Effects of starting prophylactic therapy

During 6-12 mos following initiation of prophylaxis:

- Office visits ↓ 51%
- ED visits ↓ 82%
- CT scans ↓ 75%, MRIs ↓ 88%
- 21% ↓ triptan utilization
- Triptan cost/month ↓ $48 - $132

Headache 2003;43:171-8

Slide stolen with permission from Peter Loewen

Principles of Prevention

Loneliness, Pain, Tears. Denise Auger

Avoid trigger factors

- Oral contraceptives

Use lowest effective doses

May take 2-4 months for effect

Educate (mechanism, goals, likely adverse effects)

Discuss expectations

- frequency vs. severity

Design formal management plan (including rescue plan)

Headache diaries (frequency, severity, duration, disability, treatment response, adverse effects)

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All agents below have demonstrated efficacy superior to placebo in randomized trials of appropriate duration:

Propranolol 80-240mg/d, Nadolol 80-240mg/d, Atenolol 100mg/d, Timolol 20-30mg/d, Metoprolol 200mg/d, Bisoprolol 5mg/d

Flunarizine 10mg/d, Verapamil 240mg/d

Methysergide 6mg/d, Pizotifen 1.5-6 mg/d

Naproxen 500 mg/d, Flurbiprofen 200 mg/d, Fenoprofen 1800 mg/d, Mefenamic acid 1500 mg/d, Ketoprofen 150 mg/d, ASA 500-650mg/d

Amitriptyline 30-150mg/d, Fluoxetine 20 qOd – 40mg/d

Valproic Acid / Divalproex 500-1500 mg/d, Topiramate 25-325 mg/d, Gabapentin 900-2400 mg/d

Riboflavin (B2) 400 mg/d,Magnesium 400-600 mg (16-24mmol)/d,Feverfew 50-82 mg/d, Histamine 1ng SC 2x weekly

Lisinopril 20mg daily, Bromocriptine 2.5 mg tid (menstrual), Naratriptan 1 mg bid (menstrual), Estradiol 1.5 mg/d via gel x 7 days (menstrual), Botulinum toxin A?

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The Bottom Line on Prevention

RESPONSE = ≥50% reduction in headache severity, frequency, or duration (usually assessed at 3 mos)

Across all high-quality trials, **24%** will have response to placebo, **45%** respond to drug

each patient's chance of response with drug:

- either **"50/50"** or
- **"1 in 5"** depending on whether you are comparing to doing "nothing" or giving placebo.

Van der Kuy & Lohman. Cephalalgia 2002;22:265-70

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ASTHMA

Symptomatic vs Preventative

	Symptomatic 	Preventative 
Asthma	Acute asthma attack/ symptoms	Exercise-induced Asthma exacerbations
COPD	Acute exacerbation/ symptoms	Smoking cessation COPD exacerbations Pneumonia

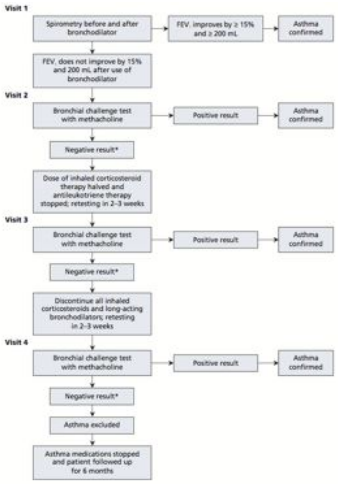
CMAJ RESEARCH

Overdiagnosis of asthma in obese and nonobese adults

Shawn D. Aaron MD, Katherine L. Vandemheen BScN, Louis-Philippe Boulet MD, R. Andrew McIvor MD, J. Mark FitzGerald MD, Paul Hernandez MD, Catherine Lemiere MD, Sat Sharma MD, Stephen K. Field MD, Gonzalo G. Alvarez MD, Robert E. Dales MD, Steve Doucette MSc, Dean Fergusson PhD, for the Canadian Respiratory Clinical Research Consortium

Interpretation: "About one-third of obese and non-obese individuals with physician-diagnosed asthma did not have asthma when objectively assessed. This finding suggests that, in developed countries such as Canada, asthma is overdiagnosed."

CMAJ 2008;179(11):1121-31



"Thus, almost all patients with asthma include wheezing as one of their symptoms compared with about three out of four patients with chronic obstructive pulmonary disease and about three out of ten patients with heart disease."

"The idea that cough can be the sole symptom of patients with asthma is closely linked to the demonstration of nonspecific bronchial hyperresponsiveness in these individuals."

"Sixty percent of patients showed no significant correlation between subjective asthma scores and peak expiratory flow rate measurements."

Clinical vs Surrogate vs Symptomatic outcomes

Symptoms
1. Description
   wheeze, breathlessness, cough, chest tightness, etc.
2. Onset
3. Progression

Severity
A. Severity of symptoms
1. Frequency, number of episodes per day or week
2. Duration
3. Description of typical exacerbation
4. Response to treatment
B. Limitations of daily activity
Walking, distance, pace
Stairs, number of flights
Exercise, sports
Sleep disturbance, early morning symptoms
Daily activity
C. Hospitalizations
Number, frequency, length of stay
Intubation
Intensive care

D.Emergency visits
1. Number, frequency
2. Other unscheduled visits
E.Days lost from work or school
1. School or work performance
F.Medication requirements
1. Systemic corticosteroid use
2. Beta-adrenergic agonist use
   number of puffs per day
   number of canisters per month
3. Inhaled corticosteroids, LABAs, anticholinergics, leukotriene antagonists, cromolyn, theophylline use
4. Changes in medication requirements

Adapted from Ann Allergy Asthma Immunol 1996;76:1–14

G. Tests
1. Previous or home peak flow measurements
2. Previous spirometry
3. Blood gases
4. Pulse oximetry (O2 sat')

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1. Description
wheeze, breathlessness, cough, chest tightness, etc.
2. Onset
3. Progression
Severity
A. Severity of symptoms
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1. Previous or home peak flow measurements
2. Previous spirometry

Clinical trial evidence vs Experience

No treatment vs Treatment

Relative vs Absolute benefit

THESE ARE ALSO THE MONITORING PARAMETERS!!!!

Benefit vs Harm vs Cost vs inconvenience

Non-drug

Provoking or triggering factors
1. Exercise
timing, duration, severity
effect on work, school, recreation
2. Infection
frequency, severity
response to treatment
3. Allergens
seasonal
animals, pets
occupational/home
risk factors for dust mite exposure
related to hobbies, recreation
associated rhinoconjunctivitis
previous allergy testing
4. Irritant
fumes, dust, pollution, smoking, environmental smoke
5. Cold air
exercise in cold air
6. Medications
beta-adrenergic blocking agents, aspirin and non-steroidal anti-inflammatory drugs medications for co-morbid medical condition
7. Emotional stress
hyperventilation
panic attacks
8. Foods
sulfites

Alleviating factors
1. Rest, avoidance of physical activity
2. Avoidance of allergens, irritants

"Chemical and physical methods aimed at reducing exposure to house dust mite allergens cannot be recommended. It is doubtful whether further studies, similar to the ones in our review, are worthwhile."

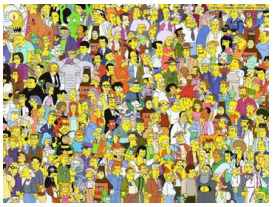
"Whilst recent epidemiological studies suggest that feather bedding is associated with less frequent wheeze than man-made fibre fillings, the evidence currently available is insufficient to assess the clinical benefits of feather bedding in the management of asthma"

Cochrane Library

Most Numbers on the slides are RELATIVE RISK/ODDS RATIO and almost all from the Cochrane Library

VERY ROUGHLY

Baseline = 50%
RR = 0.8
Treatment = 40%
Absolute difference = 10%



Baseline = 10%
RR = 2.5
Treatment = 25%
Absolute difference = 15%

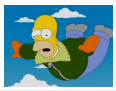
Baseline = 20%
RR = 0.25
Treatment = 5%
Absolute difference = 15%

Benefit vs Harm vs Cost vs inconvenience

ACUTE ASTHMA - baseline 30-50% hospitalization

	BENEFIT	HARM	Costs (choose least expensive)	Inconvenience
O_2	Titrate to achieve O2 sat of at least 93%	100% O_2 - damages lungs over 7-10 days	N/A	Nasal prongs Mask
Short-acting Beta-agonists	Immediate relief	Hypotension, tachycardia, tremor, hypokalemia	Salbutamol Fenoterol Terbutaline	MDI, Spacer, Nebulized, IV
Short-acting Anticholinergics	Hospitalizations 0.75 RR	Dry mouth	Ipratropium	MDI, Spacer Nebulized
Corticosteroids	3-6 hours izations 0.50 RR	Short term - CNS, glucose	Prednisone Hydrocortisone Methylprednisolone	Oral, IM, IV
	s 0.81 RR :24:823–830	Epigastric or facial warmth, flushing, pain, numbness at the infusion site, dry mouth, malaise, hypotension	N/A	IV, Nebulized
	work	Seizures, arrhythmias, GI upset		

ACUTE ASTHMA



	Dose
O_2	not 100% as this may increase PC02 use 40-60% (4-10L/min) Chest 2003;124:1312-17, Thorax doi:10.1136/thx.2010.155259
Short-acting Beta-agonists (SABA	MDI - four puffs over 2 minutes followed by one puff each minute until side effects or until breathing improves - titrate to response
	Nebulized - salbutamol 5 mg repeated every 20 minutes x 3 doses then every 1-2 hours until stable Use 2.5 mg if patient experiences tremor or tachycardia Maintain with 2.5 mg every 4 hours Dilute dose in 4 ml of saline, place in nebulizer with an air flow rate of 6-8 L/min
Short-acting Anticholinergics (SAAC)	Nebulized - 0.5 mg every 20 minutes for three doses followed by 0.5 mg every 2 to 4 hours
Corticosteroids	50mg prednisone PO NOT 40mg 125 mg - 250 mg hydrocortisone IV Q8H 100 mg methylprednisolone IV Q8H

Chronic Asthma
Levels of Asthma Control

TABLE 3 Levels of asthma control

Characteristic	Controlled (all of the following)	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less per week)	More than twice a week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None (twice or less per week)	Any	Three or more features of partly controlled asthma present in any week
Nocturnal symptoms/ awakening	None	Any	Three or more features of partly controlled asthma present in any week
Need for reliever/rescue treatment	None (twice or less per week)	More than twice a week	Three or more features of partly controlled asthma present in any week
Lung function (PEF or FEV1)#	Normal	<80% pred or personal best (if known)	Three or more features of partly controlled asthma present in any week
Exacerbations	None	One or more per year*	One in any week*

PEF: peak expiratory flow; FEV1: forced expiratory volume in one second; % pred: % predicted. #: lung function is not a reliable test for children aged <5 yrs; *: any exacerbation should prompt review of maintenance treatment to ensure that it is adequate; ": by definition, an exacerbation in any week makes that an uncontrolled asthma week.

ALSO SEE www.ginasthma.com

Eur Respir J 2008;31:143-78

Regular terbutaline vs regular budesonide for new-onset asthma

Patients

RDBCT - 103 patients with asthma - mean age 38 – new-onset asthma in last 12 months

Treatment

600 micg budesonide BID or terbutaline 375 micg BID

Duration

2 years

NEJM 1991;325:388-92

	Asthma score (1-10)	Terbutaline (PRN puffs per day)	Withdrew due to lack of effect (%)
Budesonide	2.5 ➞ 1.5	1.25 ➞ 0.5	2
Terbutaline	2.5 ➞ 2.5	1.25 ➞ 1.5	19

Changes seen in first 1-2 weeks

NEJM 1991;325:388-92

Benefit vs Harm vs Cost vs inconvenience

CHRONIC ASTHMA

	BENEFIT	HARM
SABA	Regular vs intermittent salbutamol Exacerbations - no difference in major exacerbations Regular - less rescue medication -0.8 puffs/24 hours – also 7% fewer days with asthma symptoms	Hypotension Tachycardia Tremor
Inhaled corticosteroids (ICS) low doses (400 mcg of beclomethasone dipropionate or equivalent)	Beclomethasone, budesonide Baseline exacerbations - 50% of patients per year? Baseline withdrawal due to exacerbations - approx 10% over 2-3 months Beclomethasone 0.29 RR Budesonide 0.26 RR PRN puffs salbutamol/day Beclomethasone minus 2.32 Budesonide minus 1.6 "there is currently no evidence to support differences in efficacy [of inhaled corticosteroids] when they are administered at equipotent dosages" Ann Allergy Asthma Immunol 2003;91:326-34, Cochrane Library, issue 2, 2005	LOW DOSES Candidiasis 1-5% Dysphonia 1-5%

Benefit vs Harm vs Cost vs inconvenience

CHRONIC ASTHMA

	BENEFIT	HARM
Long-acting beta agonists (LABA)	Adding to inhaled corticosteroids Baseline risk of exacerbations requiring oral steroids - 15% LABA 0.77 RR Baseline hospitalizations - 1% LABA ND Baseline withdrawals due to poor asthma control or exacerbation - 5% LABA 0.5 RR Change in 24 hour symptom score; PRN puffs salbutamol/day 0.58 less puffs per day	Hypotension Tachycardia Tremor
Leukotriene antagonists (LTRA)	Adding to inhaled corticosteroids - no difference in exacerbations, addition of anti-leukotrienes is associated with superior asthma control after glucocorticoid tapering - fewer withdrawals due to poor asthma control 0.64 RR	Increased LFTs diarrhea, rash abdominal pain Drug Int
SAAC	"this review provides no justification for routinely introducing anticholinergics as part of add-on treatment for patients whose asthma is not well controlled on standard therapies"	Dry mouth
Vaccinations	"very limited evidence to support the routine use of pneumococcal vaccine in people with asthma" "Uncertainty remains about the degree of protection vaccination affords against asthma exacerbations that are related to influenza infection"	

Benefit vs Harm vs Cost vs inconvenience

CHRONIC ASTHMA

	Benefit	Harm
LABA vs LTRA	In adults with asthma that is inadequately controlled on low doses ICS Baseline exacerbations 10% - 0.83/year Steroid treated exacerbations LABA vs LTRA 0.83 RR in favour of LABA AQLQ -0.11 in favour of LABA - 0.5 is the minimally important difference	1.3% increase in serious adverse events with LABA
LABA vs increasing ICS dose	In adolescents and adults with sub-optimal control on low dose ICS Baseline exacerbations 10% Steroid treated exacerbations 0.88 RR in favour of LABA Hospitalization - no difference in hospitalization Baseline withdrawals due to poor asthma control - 3% 0.71 RR in favour of LABA Change in daytime symptom score -0.26 (Score 0-4) , 9% greater symptom free days	LABA increased tremor 1-2% reduced thrush by 1-2%
LTRA vs ICS	In patients with mild to moderate asthma Baseline exacerbations - 5% on ICS Steroid treated exacerbation LTRA 1.65 RR Other significant benefits of ICS were seen for symptoms, nocturnal awakenings, rescue medication use, symptom-free days, and quality of life. Baseline withdrawal due to poor asthma control exacerbations – 2% LTRA 2.58 RR	No difference in side effects

Benefit vs Harm vs Cost vs inconvenience

CHRONIC ASTHMA

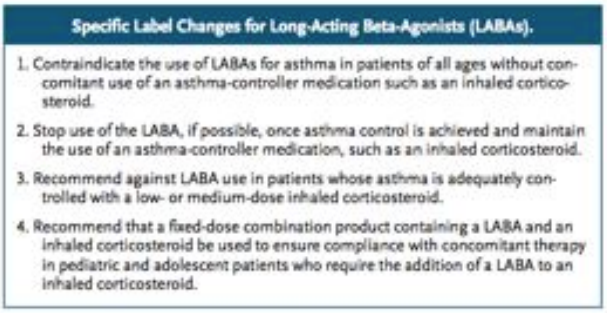
	Costs (choose least expensive)	Inconvenience
SABA	Salbutamol, Fenoterol, Terbutaliine	MDI, Spacer
ICS	Beclomethasone, Budesonide, Fluticasone, Ciclesonide	MDI, Spacer, Dry powder
LABA	Salmeterol, Formoterol (also for acute symptoms)	Dry powder
LTRA	Montelukast, Zafirlukast	Oral
ICS/LABA	Fluticasone/salmeterol Budesonide, formoterol	"The seven identified studies in adults did not show any significant difference in safety between formoterol and budesonide in comparison with salmeterol and fluticasone." "The current evidence does not support use of combination therapy with LABA and ICS as first line treatment in adults and children with asthma, without a prior trial of inhaled corticosteroids."

Equipotent daily doses adults

children - about 2/3 of these doses - inconsistent recom'

	Low daily dose (microg)	Med daily dose	High daily dose
Beclomethasone	200-500	"published data provide little support for dose titration above 400 mcg/d in patients with mild to moderate asthma" Cochrane Library	
Budesonide	200-400	X2	X4
Fluticasone	100-250		
Ciclesonide	80-160		5-10 mg? Prednisone

Eur Respir J 2008;31:143–78

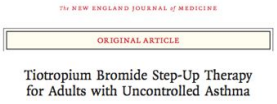


Specific Label Changes for Long-Acting Beta-Agonists (LABAs).

1. Contraindicate the use of LABAs for asthma in patients of all ages without concomitant use of an asthma-controller medication such as an inhaled corticosteroid.
2. Stop use of the LABA, if possible, once asthma control is achieved and maintain the use of an asthma-controller medication, such as an inhaled corticosteroid.
3. Recommend against LABA use in patients whose asthma is adequately controlled with a low- or medium-dose inhaled corticosteroid.
4. Recommend that a fixed-dose combination product containing a LABA and an inhaled corticosteroid be used to ensure compliance with concomitant therapy in pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid.

NEJM 2010 - 10.1056/nejmp1002074

Data from 110 trials (60,954 pts) including 11% adolescents and 6% children.
For the primary end-point of asthma-related death, intubation, and hospitalization
Statistically significant increase of 2.8 extra events per 1000 asthmatic patients treated with LABA inhalers - Number needed to harm (NNH) was 358
Tools For Practice - Edmonton, Alberta



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

Three-way double blind triple dummy crossover - funded by NHLBI

210 patients with asthma

On ICS (80 mcg beclomethasone BID) and randomized to

1.LABA (salmeterol)

2.doubling of ICS

3.tiotropium

14 weeks on each therapy

Predetermined secondary outcome measures

the number of asthma-control days, asthma symptoms, rescue-bronchodilator use, asthma exacerbations, use of health care services, biomarkers of airway inflammation, and results of validated questionnaires

NEJM 2010;Sept 19

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

Tiotropium – of the clinical endpoints all but the albuterol use was improved from baseline

LABA - all were improved for salmeterol

Double dose ICS – only improvement was proportion of asthma controlled days

The average change in the questionnaires were all less than the minimum importance difference

Tiotropium=salmeterol >double dose of ICS

Not enough patients to see a difference in exacerbations

NEJM 2010;Sept 19

Two studies - real world effectiveness - open label

2 years - average age 45-50 - 40-50% male

Initiation - LTRA or ICS

Add-on - ICS (12 weeks) then LTRA or LABA

LTRA (montelukast or zafirlukast); inhaled glucocorticoid (beclomethasone, budesonide, or fluticasone); LABA (salmeterol or formoterol)

"Study results at 2 months suggest that LTRA was equivalent to an inhaled glucocorticoid as first-line controller therapy and to LABA as add-on therapy for diverse primary care patients. Equivalence was not proved at 2 years"

"Exacerbation rates and ACQ scores did not differ significantly between the two groups."

N Engl J Med 2011;364:1695-707

288 patients with mild persistent asthma - 44 week trial - average age 11- 55% male

4 treatments - placebo controlled

Beclo = beclomethasone 80 micrograms a day total

1 - COMBINED - BID beclo PLUS beclo/salbutamol for rescue

2 - DAILY - BID beclo PLUS salbutamol for rescue

3 - RESCUE - No maintenance PLUS beclo/salbutamol for rescue

4 - NO MAINTENANCE - just salbutamol for rescue

Rescue for all groups was two puffs as needed for symptom relief

Lancet 2011, 377:650-7

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Lancet 2011, 377:650-7

	Exacerbations (%) - required prednisone	Treatment failure (%) - two courses of prednisone
Combined	31	5.6
Daily	28	2.8
Rescue	35	8.5
No maintenance	49	23

Asthma control days - no difference between the groups

Children in the regular beclomethasone group grew 1.1 cm less

Children in the rescue group used 15-25% of the total beclomethasone used in the daily group

ASTHMA ACTION PLAN (EXAMPLE 1)

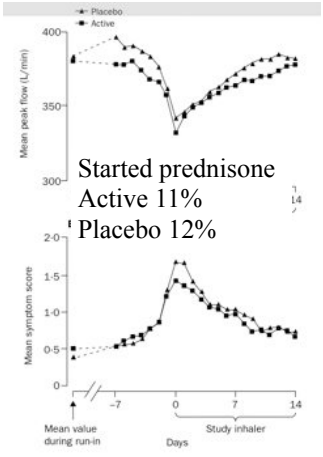
390 patients with asthma followed for 1 year

Instructed to double their dose if FEV dropped by >15% or symptoms increased by more than 1 point on a 4 point scale

Approx - 50% had an "exacerbation"

Lancet 2004; 363: 271-5

"In adults with asthma on daily maintenance ICS, a self-initiated ICS increase to 1000 to 2000 mcg/day at the onset of an exacerbation is not associated with a statistically significant reduction in the risk of exacerbations requiring rescue oral corticosteroids" Cochrane Library



Quadrupling the Dose of Inhaled Corticosteroid to Prevent Asthma Exacerbations: A Randomized, Double Blind, Placebo Controlled, Parallel Group, Clinical Trial

Am J Respir Crit Care Med. 2009 Jul 9. [Epub ahead of print

The right approach?

Salbutamol used when symptomatic and preventing exercise-induced asthma

"all patients with mild persistent asthma deserve the opportunity to decide whether the benefit from their use (ICS) is worth the effort of taking a very safe medication, usually once daily" Am J Res Crit Care Med 2005;172:410-2

Maybe use ICS seasonally or situationally?

Start with a low dose of inhaled corticosteroids - 200-400 mcg beclomethasone equiv - daily, twice daily? - always reassess

Then a LABA - but maybe LTRA / tiotropium - INDIVIDUALIZED

Combination product used if individual agents used together improved control

Exacerbations - use more salbutamol - maybe quadruple dose of ICS?

COPD

Ask: "Are you willing to try quitting?"

YES:

- **S** ...Set a quit date
- **T** ...Tell family & friends
- **A** ...Anticipate challenges
- **R** ...Remove tobacco items
- **T** …Tobacco replacements?

NO:

Here to help if you change your mind

Slide stolen from Adil Virani

Smoking cessation

Physician advice - baseline 2-3% increases it by - 1-3%

"How do you feel about stopping smoking?"; and listening empathetically for just 30-40 seconds)

Abstinence for at least 6 months		
Baseline/placebo	10-15%	
Motivational interviewing	1.27	
Nicotine (overall)	1.58	
Nicotine gum	1.43	2 and 4 mg
Oral lozenges	1.9	1,2, 4 mg
Inhaler	1.9	
Nicotine patch	1.66	7,14, 21 mg 24h patch
Nasal spray	2.02	
Nortriptyline	2.03	10 mg up to 100 mg/day
Bupropion	1.69	150 mg/day **
SSRI	ND	
Nicotine plus bupropion/nortriptyline	ND	
Bupropion vs varenicline	0.66	Varenicline 0.5 mg BID**

likelihood of cessation is greater when motivated, self-referred patients are treated

** different than in CPS

The correct dose for bupropion

Bupropion

Study design

1 year RCT – 742 patients

Dose

Placebo or bupropion SR 100, 150 or 300mg/day for seven weeks

New Engl J Med 1998; 337:1195-202

The correct dose for bupropion is 150 mg daily

Point prevalence smoking cessation rates

Percentage of subjects not smoking -daily dose

	Plac	100mg	150mg	300mg	p value
6 weeks	19.0	28.8*	38.6*	44.2*	< 0.001
3 months	14.4	24.2*	26.1*	29.5*	< 0.001
6 months	15.7	24.2	27.5*	26.9*	0.02
12 months	12.4	19.6	22.9*	23.1*	0.01

* Versus placebo

New Eng J Med 1998; 337:1195-202

Is bigger better? An argument for very low starting doses

James P. McCormack PharmD, G. Michael Allan MD, Adil S. Virani PharmD

Oct 4, 2010

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Placebo-Controlled Trial of Cytisine for Smoking Cessation

Cytisine (extracted from the seeds of Cytisus laborinum L.)

vs placebo - 25 days - 740 smokers

six 1.5-mg tablets per day (one tablet every 2 hours) for 3 days (days 1 through 3), five tablets per day for 9 days (days 4 through 12), four tablets per day for 4 days (days 13 through 16), three tablets per day for 4 days (days 17 through 20), and two tab- lets per day for the final 5 days (days 21 through 25). The target quit date was scheduled for the fifth day.

Abstinence for 12 months - 8.4% vs 2.4%

Any gastrointestinal event - 14% vs 8%

N Engl J Med 2011; 365:1193-1200

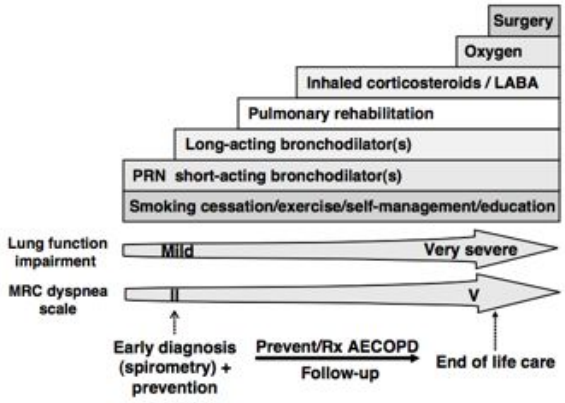
Smoking cessation

	Harm	
Nicotine gum	Dyspepsia (9%), Nausea (9%), Hiccups (10%), Headache (11%), Jaw pain, Denture issues, Throat irritation (5%)	
Nicotine Inhaler	Throat irritation, Sneezing, Coughing, Rhinitis, Pharyngitis	
Nicotine patch	Headache, Disturbed sleep, Site rash	
Nortriptyline	Dry mouth blurred vision, Constipation, Sedation, Confusion, Urinary retention	Least expensive
Bupropion	Insomnia (20%), Dry mouth (10%), Disturbed concentration (9%), Nausea (9%), Constipation (8%), Seizures (1%), Angioedema	
Varenicline	Nausea (30%), Headaches, Abnormal dreams, Constipation, Suicidal ideation?	

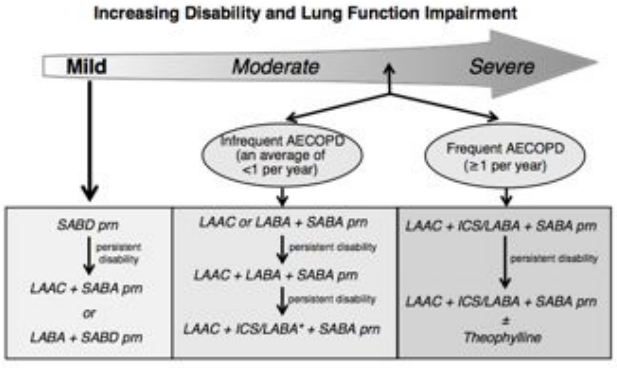
Benefit vs Harm vs Cost vs inconvenience

ACUTE COPD EXACERBATION

	BENEFIT	HARM	Costs (choose least expensive)	Inconvenience
O_2 (but be careful-may need low pO2 to breath)	Immediate relief	SEE ASTHMA		
SABA	Immediate relief			
SAAC	Not many trials comparing SABA and SAAC			
Corticosteroids	Fewer treatment failures - 20% vs 10% 1.5 days less hospitalization			
Methylxanthines	Don't work			
Systemic Antibiotics	If moderate/severe Mortality 14% vs 3% Treatment failure 58% vs 28%	More adverse events 8% vs 22% - diarrhea, skin rash	ABXs used in studies - amoxicillin, amoxicillin/clavulanate, TMP/SMX, ampicillin, penicillin, chloramphenicol, cefaclor, ofloxacin	Oral, IM, IV



Can Respir J Vol 15 Suppl A January/February 2008



Can Respir J Vol 15 Suppl A January/February 2008

Salbutamol is effective for patients with COPD

Beta agonists do produce significant improvements in symptoms of dyspnea and wheezing in patients with moderate to severe COPD

In studies, the risk of dropping out (i.e. treatment failure) when on treatment with placebo was almost twice that of patients on treatment with beta-2 agonists 22% versus 46%

Patients preferred beta-2 agonist therapy more frequently than placebo 57% versus 9%

Main endpoints - usually 1-3 years

	Exacerbations		Mortality	Hospitalized	Pneumonia	ΔSGRQ -100 Δ in score of 4 = small clinical difference	Candidiasis other SE
	Per year	Patients					
Baseline/placebo	1.4	45%	10-15 %	10%	6-7%	≈ 50	1-2%
ICS	0.81 RR	ND	ND	?	?	-1.22	2.49 RR 1.95 Hoarseness
ICS vs LABA	ND	ND	ND	ND	1.42 RR	-0.74 favours ICS	?
ICS/LABA	0.74 RR	ND	0.79 RR	?	1.83 RR	-2.9	5.73 RR
ICS/LABA vs ICS	0.91 RR	ND	0.76 RR	?	ND	-1.3 favours combo	ND
LABA/ICS vs LABA	0.82 RR	ND	ND	ND	1.58 RR	ND	4.28 RR
Tiotropium (LAAC)	?	0.74 RR	ND	0.64 RR	?	-3.28	5.08 RR dry mouth
Add ICS to LAAC/LABA	?	?	?	?	?	?	?
Add ICS/LABA to LAAC	ND	ND	ND	ND	ND	-2.49	?
Pneumococcal vaccine	ND	?	ND	?	?	?	?
Influenza vaccine	0.75 RR	?	ND	?	?	?	12% local reactions
Oral corticosteroids	?	?	?	?	?	?	?
Roflumilast	0.83 RR	?	ND 2%	ND	ND	ND different scale	diarrhea (5%)and weight loss (10%)

Breathlessness (scale of 1-3) - difference of 0.1 to 0.2
Change in SABA puffs a day - typically 1 less per day

? = data not reported
ND - no statistical difference

Minimally important clinical difference "definition"

Change of 4

1. No longer takes a long time to wash or dress, can now walk up stairs without stopping and go out for entertainment.
2. Things no longer seem to require too much effort, no longer has to stop for rests while doing housework and can now carry things upstairs.
3. No longer has to walk more slowly than other people, no longer breathless on getting washed and dressed or on bending over
4. BUT 4 also = slightly effective

Eur Respir J 2002;19:398–404

AVERAGE CHANGE COMPARED TO PLACEBO
Inhaled CS - 1.22
ICS/LABA - 2.9
Tiotropium - 3.3
LABA - 1.3

Other studies

"There is only a modest benefit of ICS in preventing COPD exacerbations, which is not related to the level of baseline lung function on metaregression analysis. The benefits of ICS in preventing COPD exacerbations thus seem to be overstated"

Chest 2010;137:318–325" – 18% relative reduction in exacerbations

"Withdrawal of FP in COPD patients using SFC resulted in acute and persistent deterioration in lung function and dyspnoea and in an increase in mild exacerbations and percentage of disturbed nights. This study clearly indicates a key role for ICS in the management of COPD as their discontinuation leads to disease deterioration, even under treatment with a LABA"
Thorax 2005;60:480–487

Combined salmeterol and fluticasone versus tiotropium in the treatment of COPD (INSPIRE)

Patients

1,323 patients with COPD - mean age 64, male (81%)– smokers (38%), on ICS (50%) - RDBPC, FEV1 39% predicted

Treatment

stopped all therapy (given pred 30mg and salmeterol BID)

randomised to salmeterol/fluticasone BID or tiotropium once daily

Duration

2 years

Am J Respir Crit Care Med 2008;177:19-26

Clinical Endpoints

	Exacer-bations per year	Exacerbations (%)	Hosp for exacerbations (%)	Mortality (%)	Pneumonia (%)	Withdraw from study (%)	Withdraw due to lack of efficacy (%)	SGRQ Δ in score of 4 (Score out of 100)
Salmeterol/ fluticasone	1.28	62	16	3	8	35	5	46
Tiotropium	1.32	59	13	6	4	42	6	48

Colors indicate SS

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 9, 2008 VOL. 359 NO. 15

A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

"overall mean between-group difference in the SGRQ total score at any time point was 2.7 (95% confidence interval [CI], 2.0 to 3.3) in favor of tiotropium"

"A higher proportion of patients in the tiotropium group than in the placebo group had an improvement of 4 units or more in the SGRQ total scores from baseline at 1 year (49% vs. 41%), 2 years (48% vs. 39%), 3 years (46% vs. 37%), and 4 years (45% vs. 36%)

Table 3. Exacerbations of COPD and Related Hospitalizations.*

Variable	Tiotropium	Placebo	Relative Risk for Tiotropium vs. Placebo (95% CI)	P Value
Exacerbation†				
Per patient-year — no.	0.73±0.02	0.85±0.02	0.86 (0.81–0.91)	<0.001
Leading to hospitalization — no. per patient-year	0.15±0.01	0.16±0.01	0.94 (0.82–1.07)	0.34
Days per patient-year	12.11±0.32	13.64±0.35	0.89 (0.83–0.95)	0.001
Hospitalization days per patient-year	3.17±0.17	3.13±0.17	1.01 (0.87–1.18)	0.86
Patients with exacerbation — no. (%)‡				
Total	2001 (67.0)	2049 (68.2)	NA	0.35
Leading to hospitalization	759 (25.4)	811 (27.0)	NA	0.18

N Engl J Med 2008;359:1543-54

Long-term Erythromycin Therapy Is Associated with Decreased Chronic Obstructive Pulmonary Disease Exacerbations

Terence A. R. Seemungal[1,2*], Tom M. A. Wilkinson[2*], John R. Hurst[2], Wayomi R. Perera[2], Ray J. Sapsford[2], and Jadwiga A. Wedzicha[2]
[1]Department of Clinical Medical Sciences, St. Augustine Campus, University of the West Indies, St. Augustine, Trinidad and Tobago; and [2]Academic Unit of Respiratory Medicine, University College London, London, United Kingdom

250 mg PO BID -12 months
Baseline exacerbations - 2 exacerbations/yr (median)
0.65 RR
Hospitalizations reduced from 11 to 7% - SS?
No difference in side effects

Am J Respir Crit Care Med 2008;178:1139-47

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 25, 2011 VOL. 365 NO. 8

Azithromycin for Prevention of Exacerbations of COPD

250 mg PO BID -12 months
Baseline exacerbations - 1.83 exacerbations/yr
0.73 RR
SGRQ - 2.8 points
Hospitalizations - no difference
Death - no difference
5% increase in audiogram hearing decrement

N Engl J Med 2011;365:689-98

7,376 patients with moderate to very-severe COPD
75% male, 48% smokers, avg age 63 - one year
Tiotropium 18 mcg daily
Salmeterol 50 mcg twice daily

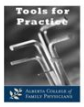
Annual rate of exacerbations
Exacerbation - an increase in or new onset of more than one symptom of COPD (cough, sputum, wheezing, dyspnea, or chest tightness), with at least one symptom lasting 3 days or more and leading the patient's attending physician to initiate treatment with systemic glucocorticoids, antibiotics, or both (criterion for moderate exacerbation) or to hospital- ize the patient (criterion for severe exacerbation).

N Engl J Med 2011;364:1093-1103

	Annual rate of exacerbations	% with > 1 exacerbation	% severe exacerbations	% serious adverse events (Resp)
Tiotropium	0.64	34.4	7.1	8.1
Salmeterol	0.72	38.5	9.2	10.0

No difference in mortality

April 30, 2012



Which is the best puffer for initial therapy in COPD?

Clinical Question: Which puffer has the greatest impact on clinical outcomes as the first-line long-acting inhaled treatment for COPD?

Bottom-line: "The available evidence indicates that tiotropium is likely the best initial long-acting therapy for COPD, followed by a LABA (like salmeterol)"

Triple Therapy for Moderate-to-Severe Chronic Obstructive Pulmonary Disease

"There was insufficient evidence to determine if triple therapy is clinically superior to dual bronchodilator therapy or combination (LABA plus ICS) therapy. More studies comparing these therapies are needed. The use of triple therapy decreases the number of COPD hospitalizations, improves lung function, and improves the quality of life of patients with moderate-to-severe COPD, compared with tiotropium alone."

Glasgow supported self-management trial (GSuST) for patients with moderate to severe COPD: randomised controlled trial

"Participants in the intervention group were trained to detect and treat exacerbations promptly, with ongoing support for 12 months"

"Supported self management had no effect on time to first readmission or death with COPD"

BMJ 2012;344:e1060

Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies

16 RCTs AND 7 OBSERVATIONAL STUDIES - over 3 years - 20-25% INCREASE IN FRACTURES - an NNH of 83

Thorax 2011;66:699-708

The right approach?

FIRST - don't smoke - if you do - nortriptyline low dose - patient ultimately chooses the way however

"At this stage, people with COPD should use the bronchodilator that gives them the most improvement in their symptoms - Cochrane Library 2006

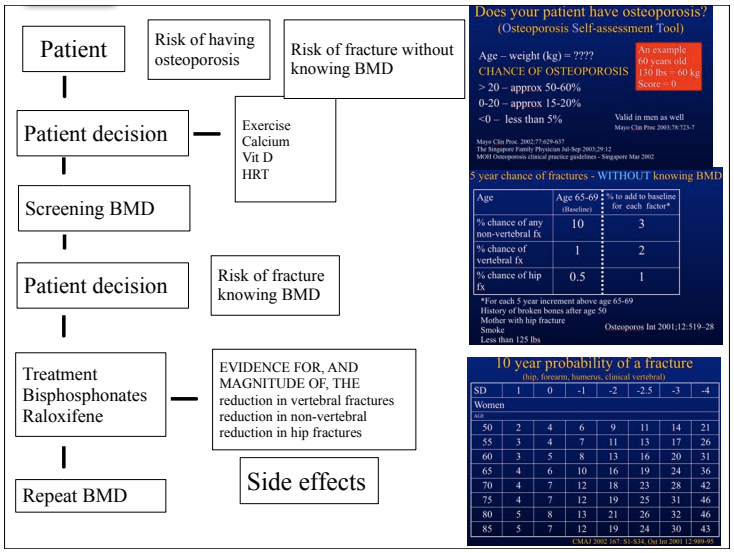
"considering that, historically, the severity of COPD has been classified according to FEV1, which may not correlate directly with symptoms and, consequently, a symptomatic approach to therapy using clinical stages may be more useful, physicians should individualize treatment and try an additional type of drug if the patient symptomatically needs for something else to be tried, and yet stop the additional drug if it does not seem to help" - Chest 2008;134;223-5

If I had COPD I would use a SABA then try either a LABA or tiotropium, then ICS or ABX

Exacerbation - salbutamol, steroids (prednisone), basically any antibiotic

Osteoporosis : The Benefits and Harms of Treatment - Making No Bones About It

James McCormack, B.Sc. (Pharm), Pharm.D.
Professor
Faculty of Pharmaceutical Sciences
University of British Columbia



Decisions that can be made without a BMD

Exercise
Calcium
Vitamin D
HRT?

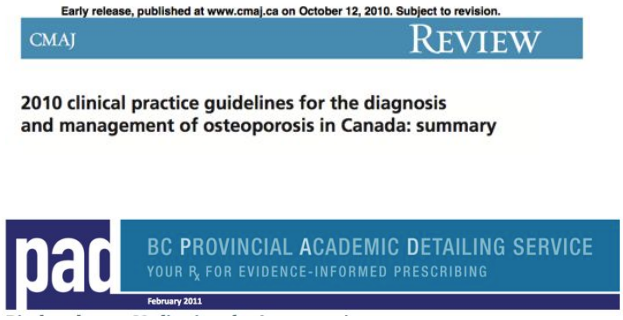
Exercise Evidence

"In summary, routine physical activity appears to be important in preventing loss of bone mineral density and osteoporosis, particularly in postmenopausal women. The benefits clearly outweigh the potential risks, particularly in older people."

CMAJ 2006;174:801-9

Talk to your patient

Before you do a BMD ask patient if they would take therapy – cost, benefit, side effects etc.



A simple tool for assessing the chance of your patient having osteoporosis

Does your patient have osteoporosis?

(Osteoporosis Self-assessment Tool)

Age – weight (kg) = ????

CHANCE OF OSTEOPOROSIS

> 20 – approx 50-60%

0-20 – approx 15-20%

<0 – less than 5%

An example
60 years old
130 lbs = 60 kg
Score = 0

Valid in men as well

Mayo Clin Proc 2003;78:723-7

Mayo Clin Proc. 2002;77:629-637
The Singapore Family Physician Jul-Sep 2003;29:12
MOH Osteoporosis clinical practice guidelines - Singapore Mar 2002

A simple tool for estimating chance of fractures without a BMD

5 year chance of fractures - WITHOUT knowing BMD

Age	Age 65-69 (Baseline)	% to add to baseline for each factor*
% chance of any non-vertebral fx	10	3
% chance of vertebral fx	1	2
% chance of hip fx	0.5	1

*For each 5 year increment above age 65-69
History of broken bones after age 50
Mother with hip fracture
Smoke
Less than 125 lbs

Osteoporos Int 2001;12:519–28

TABLE 5. Ten-Year Absolute Risk of Hip Fracture in Women, ≥60 yr of Age Among Different Levels of the Risk Score

	*Number of risk factors**			
	0	*1*	*2*	*3 of 4*
60–69 yr	1.4%	3%	6%	NA
70–79 yr	6%	8%	15%	22%
80+ yr	15%	22%	29%	25%
Corticosteroid use	NA			

Gray area means at high risk.
* Number of the following four risk factors: any prior fracture since age 50, body weight <64 kg, use of a walking aid, and smoking.
NA, not applicable because of too low power.

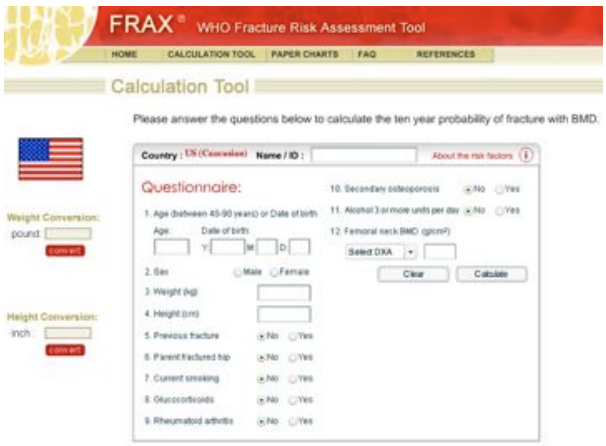
TABLE 6. Ten-Year Absolute Risk of Fragility Fracture in Women, ≥60 yr of Age Among Different Levels of the Risk Score

	*Number of risk factors**			
	0	*1*	*2*	*3 of 4*
60–69 yr	5%	6%	8%	NA
70–79 yr	11%	12%	20%	29%
80+ yr	12%	24%	35%	31%
Corticosteroid use	NA			

Gray area means at high risk.
* Number of the following four risk factors: any prior fracture since age 50, body weight <64 kg, use of a walking aid, and smoking.
NA, not applicable because of too low power.

J Bone Min Res 2009;24;768-74

http://www.shef.ac.uk/FRAX/



Simple is better

"Simple models based on age and BMD alone or age and fracture history alone predicted 10-year risk of hip, major osteoporotic, and clinical fracture as well as more complex FRAX models"

Arch Intern Med 2009;169:2087-94

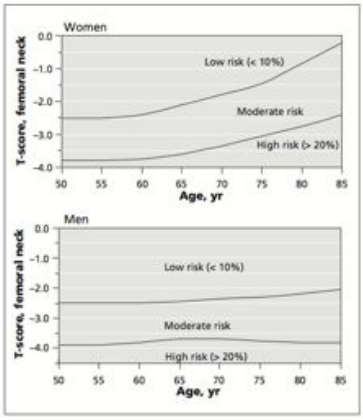
A simple tool for estimating chance of fractures with a BMD

10 year probability of a fracture

(hip, forearm, humerus, clinical vertebral)

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, Ost Int 2001 12:989-95



2010 tool of the Canadian Association of Radiologists and Osteoporosis Canada

CMAJ 2010. DOI:10.1503/cmaj.100771

Drugs for osteoporosis/fracture prevention

Nutritional	calcium	Oral daily
	vitamin D	Oral daily
Anabolic agents	teriparatide (Forteo)	Daily SC
Bisphosphonates	alendronate (Fosamax, generics)	Oral daily and weekly
	etidronate (Didrocal, generics)	Oral daily x 14 days Q3months
	risedronate (Actonel, generics)	Oral daily, weekly, monthly
	zoledronic acid (Aclasta)	Yearly IV infusion
RANK Ligand inhibitors	denosumab (Prolia)	Q6M SC
Selective estrogen receptor modulators	raloxifene (Evista, generics)	Oral daily
Calcitonin	calcitonin salmon (Miacalcin, Calcimar, Caltine, generics)	daily intranasal daily or Q2 days SC

A simple table describing the benefits of treating osteoporosis

• Osteoporosis Drugs Benefit - 2-3 years •

RELATIVE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~ 50%	~ 20%	~40%
Raloxifene	~ 40%	NS	NS
Teriparatide	~ 70%	~ 40%	NS
Vitamin D usually with calcium	~15-25%	~15-25%	~15-30%
Denosumab	~ 70%	~ 20%	~40%
Strontium	~40%	~ 15%	NS
ALL DRUGS	~50%	~20%	~25%

ABSOLUTE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~4-8%	~2%	~0.5-1%
Raloxifene	~4%	NS	NS
Teriparatide	~10%	~4%	NS
Vitamin D usually with calcium	1-2%	1-2%	~1%
Denosumab	~5%	~2%	~0.5%
Strontium	~8%	~2%	NS
ALL DRUGS	~5%	~2%	~0.5%

*~ 50% of the studies enrolled patients with a history of fractures with the exception of the VitaminD/calcium studies where this was ~ 50%
** etidronate has only been shown to reduce vertebral fractures in secondary prevention

"There is good evidence from randomized controlled trials (RCTs) that alendronate, etidronate, ibandronate, risedronate, calcitonin, 1-34 PTH, and raloxifene prevent vertebral fractures compared with placebo.

There is good evidence from RCTs that risedronate and alendronate prevent both nonvertebral and hip fractures compared with placebo.

There is good evidence that zoledronic acid prevents vertebral and nonvertebral fractures, and fair evidence that it prevents hip fractures."

Agency for Healthcare Research and Quality - report #12
December 2007

Benefit of treatments for hip fractures

Meta-analysis - 12 trials, 18,667 patients - over 3 years hip fractures are reduced by 0.5%

J Bone Miner Res 2006;21:340-9

Zoledronic acid after hip fracture

Patients

1,065 patients with a surgical repair of a hip fracture, 91% white, 76% female, mean age 75, T score 2.5 or less - 41%, -2.5 to -1.5 - 35%, more than -1.5 11%

Treatment

Zoledronic acid 5mg IV yearly or placebo

Duration

Median follow up of 1.9 years

Results

Bone density differences (total hip) - drug vs placebo

12 months 2.6% inc vs 1% dec

24 months 4.7% inc vs 0.7% dec

36 months 5.5% inc vs 0.9% dec

N Engl J Med 2007;357

Zoledronic acid results

	Any fracture(%)	Hip fracture (%)	Nonvertebral fracture (%)	Death (%)	Serious A Fib (%)	Any serious adverse event(%)
Zoledronic acid 5 mg	8.6	3.5	7.6	9.6	1.3	38.3
Placebo	13.9	2.0	10.7	13.3	0.5	41.2
Relative risk	38	NSS		35	250	NSS
Absolute risk	5.3		3.1	4.7	0.8	
Number needed to treat/harm	19		29	21	125	

Muscle aches and/or pyrexia increased by 3-6% within 3 days of infusion

Compliance/adherence

"almost three-quarters of all women initiating osteoporosis drug therapy-regardless of the medication received-are no longer adherent with treatment 12 months following therapy initiation, and almost one-half have discontinued such therapy by this time."

"compliance with weekly bisphosphonate therapy appears to be generally no better than that with medications requiring more frequent dosing."

Osteoporos Int 2006;17:1645-52

Bisphosphonates and atrial fib

Meta-analysis of all Merck-conducted placebo controlled trials of alendronate

32 studies - 9,518 alendronate, 7,773 placebo

RR for all AF events

1.16 (CI = 0.87, 1.55) p = 0.33

Osteoporos Int 2010 DOI 10.1007/s00198-011-1546-9

Bisphosphonates and Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women

A population-based, nested case-control study to explore the association between bisphosphonate use and fractures in a cohort of women aged 68 years or older from Ontario

52,595 women with at least 5 years of bisphosphonate therapy

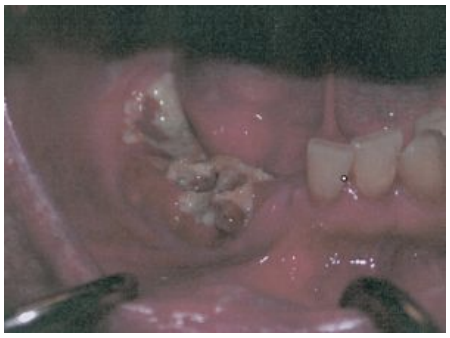
subtrochanteric or femoral shaft fracture 0.13% during the subsequent year - 0.22% within 2 years

JAMA 2011;305:783-9

Jaw osteonecrosis from bisphosphonates

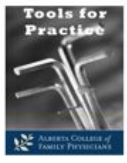
More often occurs after dental procedures reported A minimum and maximum frequency of ONJ in patients receiving oral BPs as one in 2,030 and one in 950, respectively, and a minimum and maximum frequency of patients receiving oral BPs who have undergone extractions as one in 270 and one in 125, respectively

J Oral Maxillofac Surg 2007;65:415-23



Very good review

The American Journal of Medicine 2009;122:S33–S45



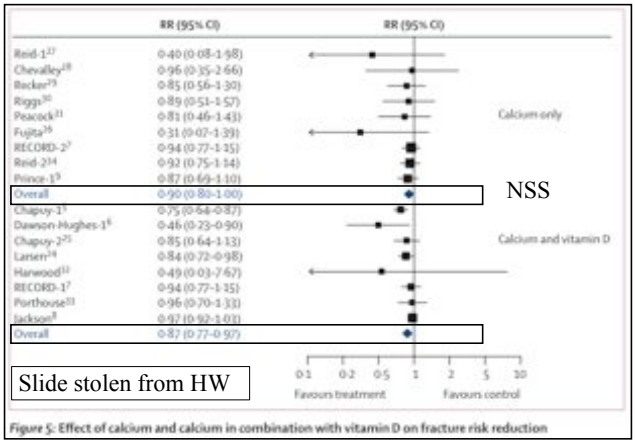
February 7, 2011

Does Calcium Supplementation Increase the Risk of MI?

Clinical Question: Does calcium (Ca+) supplementation contribute to increased risk of myocardial infarction (MI) and other cardiovascular disease (CVD)?

Bottom-line: The present evidence suggests that calcium supplementation, particularly ≥1000mg/day, may lead to an increase risk of MI. This evidence is poor and the risk, if present, is likely <1%

Effect of Calcium and Ca + Vitamin D on Fracture Risk Reduction



NSS

Slide stolen from HW

Figure 5: Effect of calcium and calcium in combination with vitamin D on fracture risk reduction

Tang, BMP et al. Lancet 2007;370:657-66

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:c3691doi: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			

RCT evidence of Vitamin D

Fracture (19 trials) - High dose (>400IU/day)
2-4 years?
reduced Non-vertebral fractures 1.1%
reduced Hip fractures by 0.6%
Arch Intern Med 2009;169:551-61

Falls (5 trials)
Reduced falls by 7%
JAMA 2004;291:1999-2006

Mortality (18 trials) - 6 years
reduced overall mortality by 0.4-0.5%
Arch Intern Med 2007;167:1730-7

BUT!!

BMJ RESEARCH

Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe

The DIPART (vitamin D individual Patient Analysis of Randomized Trials) Group

"This individual patient data analysis indicates that vitamin D given alone in doses of 400-800 IU is not effective in preventing fractures. By contrast, calcium and vitamin D given together reduce hip fractures and total fractures, and probably vertebral fractures, irrespective of age, sex, or previous fractures"

OVER THREE YEARS
ANY FRACTURE
0.5% REDUCTION
0.9% IF >70 - 0.4% (hip)
1.2% if previous fracture - 0.2% (hip)

BMJ 2010;340:b5463

Calcitonin injections

5 RCTs - 264 patients

"Pain at rest was reduced as early as 1 week into treatment (weighted mean difference [WMD] =3.08; 95% confidence interval [CI]: 2.64, 3.52) and this effect continued weekly to 4 weeks (WMD = 4.03; 95% CI: 3.70, 4.35). A similar pattern was seen for pain scores associated with sitting, standing, and walking."

Osteo Int 2005;16:1281-90

Calcitonin

Meta-analysis of 30 trials and 3993 pts

- 4 RCT vertebral Fracture: RR 0.46 (0.25-0.87)
  - Relative risk reduction = 54%
- 3 RCT non-vertebral Fracture: RR 0.52 (0.22-1.23)
  - Not significant
- Concerns: Lots of heterogeneity and Bigger trials find less benefit

US Agency of Healthcare Research and Quality

- Reduced vertebral fracture: Fair Evidence
- No change in non-vertebral: Good Evidence

Endocr Rev 2002 23: 540-551, Ann Intern Med 2008;148:197-213

PTH

Meta-analysis 13 RCTs (but not all have # data)
7 RCTs (4359 pts) Vertebral Fracture:
RR 0.36 (0.28-0.47), Relative risk reduction 64%
5 RCTs (2377 pts) Non-vertebral Fracture:
RR 0.62 (0.48-0.82), Relative risk reduction 38%
Note: unclear if RR or Odds Ratio, if latter, not interpretable.

US Agency of Healthcare Research and Quality
Reduced vertebral fracture: Good Evidence
Reduced non-vertebral: Fair Evidence

Osteoporos Int 200718:45–47, Ann Intern Med2008;148:197

Bottom-Line PTH and Calcitonin

The evidence for PTH and Calcitonin is not as robust as bisphosphonates.

Calcitonin reduces vertebral fracture rates (and the degree is likely < 50%) but does not improve non-vertebral fracture rate.

PTH reduces vertebral & non-vertebral fracture rates but the reliability of the data is somewhat uncertain.

Strontium

"pooled data from SOTI and TROPOS indicate that strontium ranelate therapy is associated with a significant reduction in the risk of vertebral fracture [relative risk (RR) compared with placebo 0.60, 95% confidence intervals (CI) 0.53 to 0.69, p < 0.001] and non-vertebral fracture (RR 0.84, 95% CI 0.73 to 0.97, p = 0.01). The studies were not powered to identify a statistically significant difference in the incidence of fracture at any specific peripheral fracture site"

Thromboses were "found to be significantly higher in patients receiving strontium ranelate compared with placebo (RR 1.42, 95% CI 1.02 to 1.98, p = 0.036)"

Health Technology Assessment 2007;Vol 11:number 4

Densoumab

- Sample: 7868 women
  - mean age 72, BMD 26, 80% European, mean T-score = -2.8 spine, -1.9 total hip, & -2.16 femoral neck, 23.5% vertebral fractures
- Outcomes at 36 months mean

Outcome	Denosumab	Placebo	Diff (NNT)	Relative Risk Reduction	P-value
Vertebral	2.3%	7.2%	4.8% (21)	68%	<0.001
Non-vertebral	6.5%	8%	1.5% (67)	20%	0.01
Hip	0.7%	1.2%	0.3% (333)	40%	0.04
Clinical Vertebral	0.8%	2.6%	1.7% (59)	69%	<0.001

Notes: The clinical vertebral NNT much higher than overall. Hip AR reported in trial worse than my calculation (Diff = 0.44%, NTT 228). Still not very impressive

Hormone replacement issues

Hormone replacement therapy (HRT) helps with the symptoms of menopause

The best designed trials to date have shown that HRT does more harm than good on average

Likely "safe" for 3-4 years

Use the lowest dose to decrease symptoms

JAMA 2002;288:321-33

Lower doses of estrogen

2,673 postmenopausal women

1 year of placebo, 0.625, 0.45, 0.3 mg/d or 0.625/2.5, 0.45/2.5, 0.45/1.5, 0.3/1.5mg/d

Benefits

Number and severity of hot flushes were reduced to a similar degree in all groups compared to placebo

Fertil Steril 2001;75:1065-79

Lower doses of estrogen

Harm

- Breast pain – 26% in 0.625/2.5 group, 7% in 0.3 group
- Vaginal hemorrhage – 14% in 0.625 group, 6% in 0.625/2.5 group, 2% in 0.3 group
- Breast enlargement, vaginal moniliasis, leg cramps, dysmenorrhea and vaginitis also more common in higher dose groups

Fertil Steril 2001;75:1065-79

Harms from hormone replacement

	CHD (%)	Stroke (%)	DVT (%)	PE (%)	Total CVD (%)	Breast CA (%)	Global Index (%)
Estr/prog	1.9	1.5	1.4	0.8	8.2	2.0	8.8
Placebo	1.5	1.0	0.6	0.4	6.7	1.5	7.7
RRI	27	50	133	100	22	25	14
ARI	0.4	0.5	0.8	0.4	1.5	0.5	1.1
NNH	250	200	125	250	67	200	91

JAMA 2002;288:321-33

Benefits from hormone replacement

	Colorectal CA (%)	Hip fractures (%)	All fractures (%)	Deaths (%)
Estr/prog	0.5	0.5	7.6	2.7
Placebo	0.8	0.8	9.7	2.7
RRR	38	38	22	NSS
ARR	0.3	0.3	2.1	
NNT	333	333	48	

JAMA 2002;288:321-33

Outcomes per 10,000 woman-years

	Estrogen PLUS progestin	Estrogen alone
Fractures	46 less	56 less
Invasive breast cancer	8 more	8 less
Stroke	9 more	11 more
Death	-	2 fewer
DVT	12 more	7 more
PE	9 more	-
Lung cancer death	5 more	-
Gallbladder disease	20 more	33 more
Dementia	22 more	-
Urinary incontinence	872 more	1271 more

Annals of Internal Medicine - 29/05/2012

• Osteoporosis Drugs Benefit - 2-3 years •

RELATIVE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~ 50%	~ 20%	~40%
Raloxifene	~ 40%	NS	NS
Teriparatide	~ 70%	~ 40%	NS
Vitamin D usually with calcium	~15-25%	~15-25%	~15-30%
Denosumab	~ 70%	~ 20%	~40%
Strontium	~40%	~ 15%	NS
ALL DRUGS	~50%	~20%	~25%

ABSOLUTE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~4-8%	~2%	~0.5-1%
Raloxifene	~4%	NS	NS
Teriparatide	~10%	~4%	NS
Vitamin D usually with calcium	1-2%	1-2%	~1%
Denosumab	~5%	~2%	~0.5%
Strontium	~8%	~2%	NS
ALL DRUGS	~5%	~2%	~0.5%

*~ 50% of the studies enrolled patients with a history of fractures with the exception of the VitaminD/calcium studies where this was ~ 50%
** etidronate has only been shown to reduce vertebral fractures in secondary prevention

How long do we treat?

Fracture Intervention Trial (FIT)

- Women who had taken alendronate for 4.5 yr - randomly given alendronate or placebo for 5 years
- No difference in the number of clinical fractures or morphometric vertebral fractures between the two groups

J Bone Mineral Res 2004;10(Suppl 1):S45

- Two other alendronate trials showed similar results

N Engl J Med 2004;350:1189–1199

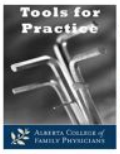
How long do we treat?

Fracture Intervention Trial (FIT) - second report

Women who had taken alendronate for 4.5 yr - randomly given alendronate or placebo for 5 years

No difference in overall clinical fractures but a 3% reduction in clinical vertebral fractures

JAMA 2006;296:2927-38



Bisphosphonates: Forever or Five Years and stop?

Clinical Question: Can patients with osteoporosis who have been on bisphosphonates for 5 years discontinue treatment without increasing future fracture risk?

"Available evidence suggests that after 5 years of treatment, discontinuation of bisphosphonates carries little to no increased future fracture risk. Choosing appropriate patients to continue therapy beyond 5 years and determining when or if to reinitiate therapy in those discontinued, remains uncertain."

An example of what should be told to patients

Your risk of NOT having a hip fracture in the next 3-5 years is 97%

The non-Rx measures are exercise, calcium, Vitamin D, preventing falls, stopping drugs (benzo's antihypertensives)

If you take this drug for the next 3-5 years your risk of NOT having a fracture will be approximately 98.5%

The side effects are not much different than placebo – approximately 1% chance of esophageal side effects (JAW OSTEONECROSIS)

Take a pill every day – glass of water, can't lie down etc

Costs

American Family Physician letter

May 15, 2001

Physicians don't talk to their patients with these conditions in the terms proposed by Dr. McCormack

We tell our patients, "Your blood pressure is too high; you should be on medication to reduce it;" or "Your cholesterol level remains elevated despite diet and exercise; we need to add medication to bring it down."

If …Dr. McCormack takes the approach he advocates for patients … I doubt that many of his patients opt for therapy

NELSON B. WATTS, M.D.
Emory University School of Medicine
Atlanta, Georgia

American Family Physician letter

May 15, 2001

I agree with the request for including more complete information about the results of clinical trials

I strongly disagree with his proposal for using this information in clinical practice

I tell patients who have low bone density or a fragility fracture that they have osteoporosis … I tell them that patients who have osteoporosis should be treated

Most patients want my advice, not a lesson in data analysis

NELSON B. WATTS, M.D.
Emory University School of Medicine
Atlanta, Georgia

CMAJ REVIEW

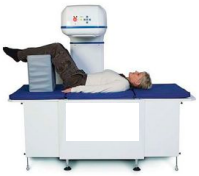
2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary

"For patients who are undergoing treatment, repeat measurement of bone mineral density should initially be performed after one to three years; the testing interval can be increased once therapy is shown to be effective"

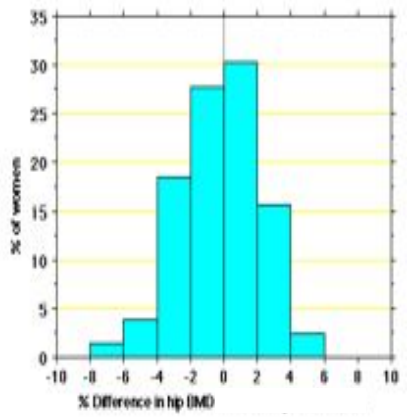
"For individuals with low risk of fracture and without additional risk factors for rapid loss of bone mineral density, a testing interval of 5–10 years may be sufficient"

Evidence for Targets

BONE DENSITY
There are NO studies that have looked at getting patients to different BMDs and seeing if that makes a clinically important difference



Follow-up bone density measurements after treatment



Stolen from

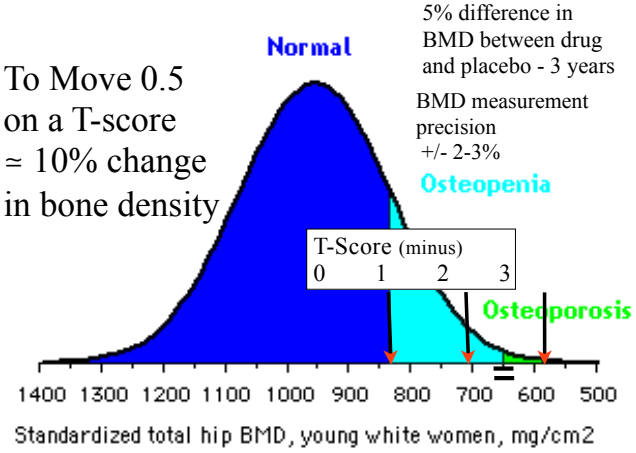
Susan Ott, MD
Associate Professor
Department of Medicine
University of Wash

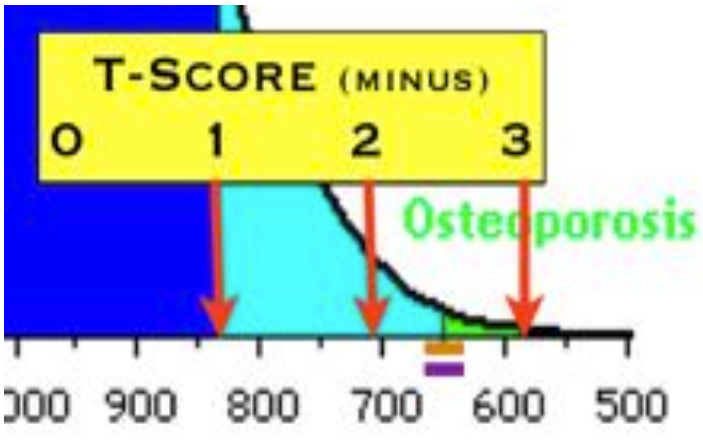
Bone density reports that state a change in bone density has been seen

"Lumbar spine measurements have increased by 3.5%"

"Right total femur measurements have decreased by 4.1%"

To Move 0.5 on a T-score ≃ 10% change in bone density





Other Smarter People

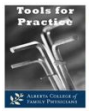
Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data

Katy J L Bell, Andrew Hayen, Petra Macaskill, Les Irwig, Jonathan C Craig, Kristine Ensrud and Douglas C Bauer

BMJ 2009;338;b2266;

"Monitoring BMD in the first 3 years after starting treatment with a bisphosphonate is unnecessary and may be misleading"

BMJ 2009;338;b2266

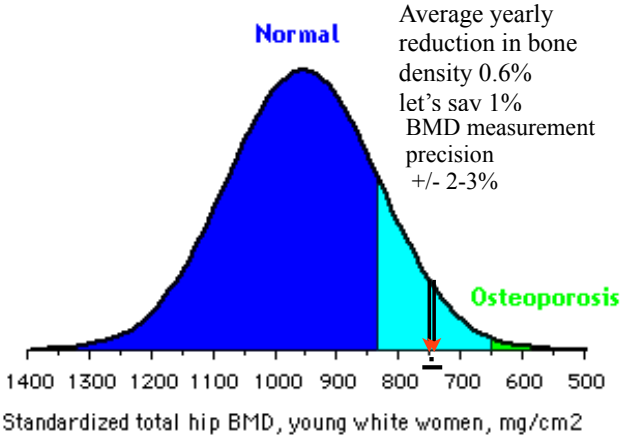


Bone Mineral Density – Too much of a good thing?

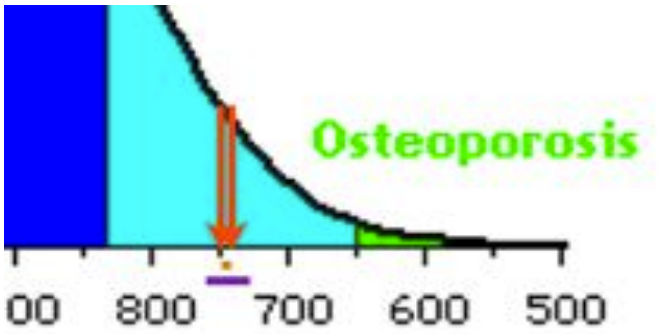
Clinical Question: Once we have initiated bisphosphonate therapy, how frequently should we check bone mineral density (BMD)?

Christina Korownyk & Michael R. Kolber

Follow-up bone density measurements for assessment of "risk"



Average yearly reduction in bone density 0.6%
let's sav 1%
BMD measurement precision
+/- 2-3%



Other Smarter People

Evaluating the Value of Repeat Bone Mineral Density Measurement and Prediction of Fractures in Older Women

The Study of Osteoporotic Fractures

Teresa A. Hillier, MD, MS; Katie L. Stone, PhD; Doug C. Bauer, MD; Joanne H. Rizzo, MS; Kathryn L. Pedula, MS; Jane A. Cauley, DrPH; Kristine E. Ensrud, MD, MPH; Marc C. Hochberg, MD; Steve R. Cummings, MD

Arch Intern Med. 2007;167(2):155-160.

"repeat BMD [8 years] measurement provides little additional benefit as a screening tool"
Average bone loss/year 0.6%

Arch Intern Med 2007;167:155-60

DXA measurements of +/- 2%

What does a measurement error/precision error/ coefficient of variation of +/- 2% really mean?

Changes in BMD from previous measurement

What you can say with reasonable confidence (whatever that means)

+/- 2.0%

impossible to know if this is random variation or a change in bone density

+/- 2.0% to 4%

if you saw this difference in 100 patients 5-32% of the time this difference would be due to chance

+/- > 4%

if you saw this difference in 100 patients less than 5% of the time this difference would be due to chance

in other words you can say the change is likely real and unlikely to be due to machine error but you can't be all that certain as to the amount of change

What should we recommend

PROBABLY BUT NOT FOR EVERYONE?

1. Calcium - 1500 mg daily elemental calcium
2. Vitamin D - 800 units per day

A recent meta-analysis suggests you need to use Vitamin D with calcium
J Clin Endocrinol Metab 2007;92:1415-23

SOUNDS REASONABLE

3. Weight bearing exercise she enjoys
4. Discuss the risks and benefits of bisphosphonates, raloxifene and other drugs for osteoporosis

The Hierarchy of Evidence for Therapy Studies

632 JAMA, Feb 23, 1963

Effectiveness of Estrogens for Therapy of Myocardial Infarction in Middle-Age Men

10 mg versus placebo - over 5 years
Cardio/renal event - first 3 months - 22% vs 5% - but mortality lower at 5 years
"Feminizing effect" - 40% vs 30%

JAMA 1963;183:106-12

The Coronary Drug Project

Initial Findings Leading to Modifications of Its Research Protocol

The Coronary Drug Project Research Group

Terminated early

5 mg versus placebo - over 18 months
Definite non-fatal MI - 6.2% vs 3.2%
Pulmonary embolism - 1.5% vs 0.4%
Excessive shopping - 80% vs 3%

JAMA 1970;214:1303-13

Adverse events associated with testosterone administration

6 months - blinded

Baseline		Placebo 103 subjects	Testosterone gel 100 mg once daily 106 subjects	Add group	Labs		
Average Age	74 yr				A1c	6.2 %	
Black	8 %				Avg DBP	76 mmHg	
Caucasian	90 %				Avg SBP	137 mmHg	
HTN	82 %				BMI	30	
Prev CVD	52 %				HDL	47 mg/dL	
Previous Smokers	69 %				Hyperlipidemia	57 %	
Smokers	9 %				LDL	91 mg/dL	
Type 2 diabetics	26 %				Total chol	168 mg/dL	
					Total testosterone	243 ng/dL	
					Triglycerides	151 mg/dL	
					ARR (%)	RRR (%)	NNT/NNH
Comparator		○	◉				
Control		◉	○				
Adverse cardiac events		1.0 n = 1	9.4 n = 10		-8.5	-872	-12
Atherosclerosis-related events		1.0 n = 1	6.6 n = 7		-5.6	-580	-18
Overall CVD		4.9 n = 5	21.7 n = 23		-16.8	-347	-6
Skin reactions at gel application site, itching, erythema, psoriasis, foot ulcers, and increased hair growth		7.8 n = 8	17.9 n = 19		-10.2	-131	-10

Hormone replacement and heart disease

Observational data – heart disease is reduced by 35-50% by estrogen use - Nurses Health Study

Healthy woman selection bias?

Arch Intern Med 2000;160:2263-72

Lowers LDL, raises HDL, increases bone density

Symptom control

Estrogen plus progestin for secondary prevention of CHD in postmenopausal women- the HERS trial

Patients

2763 women with coronary heart disease, postmenopausal with an intact uterus - mean age 66.7

Treatment

0.625 mg of CEE plus 2.5 mg of medroxyprogesterone daily

Duration

4.1 years

JAMA 1998;280;605-13

Estrogen plus progestin for secondary prevention of CHD in postmenopausal women- the HERS trial

Results

11% decrease in LDL, 10% increase in HDL

No difference in:

CHD, CHD death, cancer, fractures, all cause mortality

but a 1.6% increase in both DVT/PE and gallbladder disease

Risk and benefits of estrogen plus progestin in healthy postmenopausal women

Patients

16,608 women mean age 63 – treated for diabetes (4%), treated for hypertension (36%), treated for elevated cholesterol (13%), smoker (11%)

Treatment

CEE 0.625 mg CEE PO daily PLUS medroxyprogesterone 2.5 mg PO daily or placebo

Duration

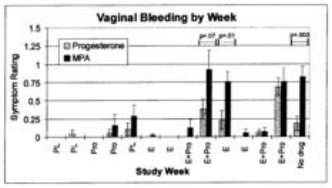
5.2 years (study stopped early due to health risks exceeding benefits)

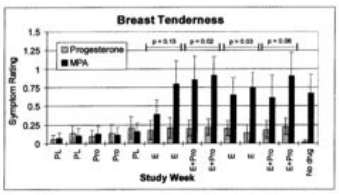
JAMA 2002;288:321-33

The Bioidentical Hormone Debate: Are Bioi Hormones (Estradiol, Estriol, and Progesterone or More Efficacious than Commonly Used Syn Versions in Hormone Replacement Therapy?

"With respect to the risk for breast cancer, heart disease, heart attack, and stroke, substantial scientific and medical evidence demonstrates that bioidentical hormones are safer and more efficacious forms of HRT than commonly used synthetic versions"

	Synthetic progestins vs progesterone
Symptoms	2 RCT's showing no difference
Tolerability	1) Cross sectional survey of 176 women who were currently being treated with HRT including micronized progesterone for a period of 1–6 months and had been treated previously with MPA - advantage to progesterone 2) RCT of 23 women - no differences in symptom control - ? differences in tolerability 3) RCT - CEE + MPA cyclical vs CEE +MP cyclical # of women who had episodes of excess bleeding for each 6 month interval (total 3 years)
Breast CA	"Synthetic progestins clearly associated ... with breast CA" - WHI (RCT), NHS (cohort) etc 1) Lots of surrogate data - cell proliferation and level association 2) Two cohort trials - same one presented twice (one was an update) - cases of invasive breast CA Estrogen +progesterone/dydrogesterone 129/40,537PY = .32% Estrogen and other progestagens = 527/104,243PY = 0.51% 3) "no randomized, controlled trials were identified that directly compared the risks for breast cancer between progesterone and synthetic progestins"
CVD	"MPA.. substantial increas in risk of heart attack and stroke - WHI (RCT) 1) Lots of lipid/surrogate data /animal data 2) One RCT cross over Estrogen and progesterone vs MPA on exercise induced MI ischemia exercise time significantly increased in the progesterone group 3) One case control - progesterone no risk of VTE but there was with synthetic
	Estrogen vs estriol
Breast CA	1) Population based cased cohort trial - 30,000 women Similar rates of endometrial cancer Estrogen but not estriol increased risk of breast CA compared to non-users - BUT no ss difference between estrogen and estriol 2) Case control study - 3,345 women Estrogen increased breast CA but low potency estrogens (oral estriol or topical) did not 3) "Large-scale randomized control trials are needed to quantify the effects of estriol in the risk of breast cancer"





0 = none
1 = slight/a little
2 = some
3 = extreme

23 non-depressed early postmenopausal women

Overall symptom control/ Mood - no difference

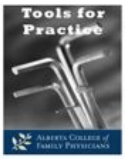
Side effects
1) mpa vs progesterone - no difference
2) When combo was used there was a difference - 0.5 on a 3 point scale
3) Breast tenderness - difference was there when just CEE was used
4) PEPI study - showed no difference in breast tenderness

Menopause 2002;9:253-63

Bioidentical vs synthetic - the evidence

	Symptom control		Tolerability		Breast Ca		CVD	
	P	E	P	E	P	E	P	E
RCT	2 no diff	0	2 ? 1 diff 11% vs 4% - 1 to 1.5 episodes of exc bleeding	0	0	0	1 surrogate end point	0
Cohort/case control	0	0	0	0	1 0.2%/yr diff	2 Topical Head to head?	1 VTE	0
Case series/ case reports	0	0	0	0	0	0	0	0
Expert opinion	+++	+++	+++	+++	+++	+++	+++	+++

March 5, 2012



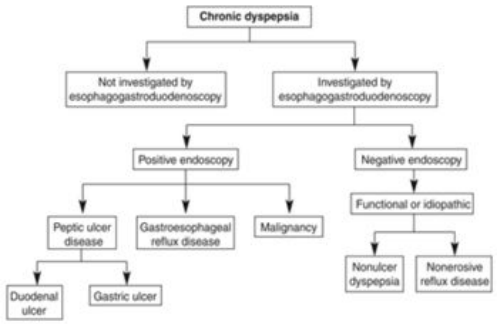
Bioidentical Hormone Replacement: Are We Missing The Boat?

Clinical Question: Does "bioidentical hormone" micronized progesterone (MP) instead of "synthetic hormone" medroxyprogesterone acetate (MPA) result in improved menopausal symptom control and/or reduction in harm?

Bottom-line: "The theory behind bioidentical hormone use is appealing; however its clinical advantage is not supported by reliable evidence. Long-term safety is largely unknown"

GERD

James McCormack, Pharm.D.
Professor
Faculty of Pharmaceutical Sciences, UBC



Dyspepsia/GERD

Dyspepsia: All male and non-pregnant female adults with pain or discomfort felt to arise in the upper GI tract with symptoms of greater than 25% of days over the past 4 weeks

GERD: Dominant symptom is heartburn or acid regurgitation, does not include atypical manifestations

Goals of Treatment

to ameliorate signs and symptoms, especially heartburn, because complications can occur with even mild symptoms

to prevent irritation of the distal esophagus, which could produce strictures, perforations, or cancers

When to Consider Drug Therapy

Drug therapy should be considered in all patients with symptoms of reflux (substernal sensation of warmth or burning, regurgitation, or dysphagia) who:

1) have no response to nondrug measures such as avoidance of foods that reduce lower esophageal sphincter pressure or worsen symptoms avoidance of lying down directly after meals, ingestion of smaller meals, elevation of the head of the bed by 4−6 inches, smoking cessation, and loss of weight

2) avoidance of drugs that worsen reflux (calcium channel blockers, NSAIDs, theophylline, tricyclic antidepressants, tetracyclines, bisphosphonates) doesn't help

Lifestyle Intervention

Cohort/case control studies - change in symptoms
Tobacco cessation - no effect
Weight loss - improvement
Elevation of the head of the bed - improvement
Insufficient evidence
Coffee and caffeine
Chocolate
Spicy foods
Citrus
Carbonated beverage
Fatty foods
Mint
Late-evening meal

Arch Intern Med 2006;166:965-971

Acid suppressing therapy

Antacids

Sodium bicarbonate (Alka-Seltzer), aluminum hydroxide, magnesium hydroxide (most), calcium carbonate (Tums), magaldrate (Riopan), alginic acid (Gaviscon)

Simethicone (Ovol) - no effect

H_2RA

Cimetidine, ranitidine, famotidine, nizatidine

PPI

Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole

Maalox versus Ranitidine 75mg

94 patients

Single episode of heartburn

Evaluated symptoms every 2-5 minutes

Results

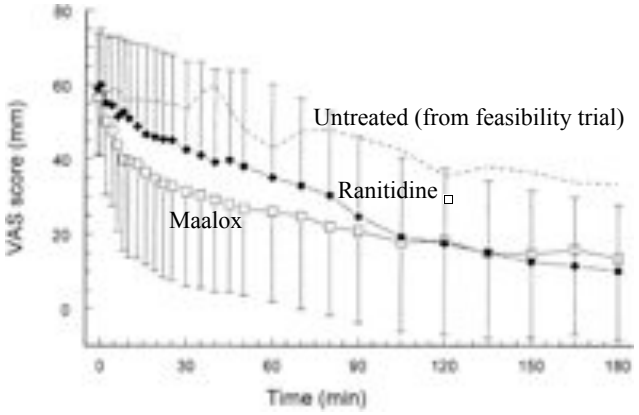
Onset of pain relief (<75% of baseline)

Maalox - 19 minutes

Ranitidine - 70 minutes

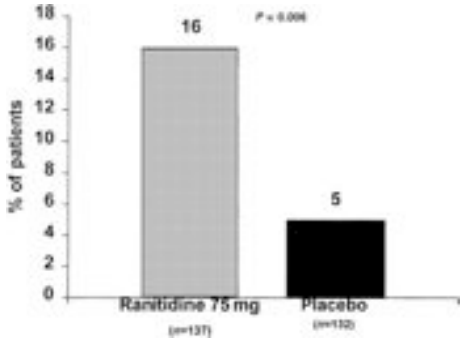
Alimentary Pharmacology & Therapeutics 1999;13:1605-10

Visual analogue scores of heartburn



Alimentary Pharmacology & Therapeutics 1999;13:1605-10

Percentage of patients with complete prevention of heartburn



284 patients after receiving a test meal

Alimentary Pharmacology & Therapeutics 1999;13:467-473

Percentage of patients experiencing overall adequate heartburn relief

Episode*	Placebo	Ranitidine 25 mg	Ranitidine 75 mg	Ranitidine 125 mg
First	54	72§	76¶	73¶
Last†	50	70**	72¶	71¶
All‡	50	67¶	71¶	71¶

* For first and last episodes, based on Cochran–Mantel–Haenszel test, adjusted for investigator; for all episodes combined, based on Generalised Estimating Equations (GEE).
† Last episode for each patient.
‡ Rates and *P*-values have been adjusted for correlation between episodes within a patient by using GEE methods.
§ *P*-value = 0.002 vs. placebo.
** *P*-value = 0.004 vs. placebo.
¶ *P*-value ≤ 0.001 vs. placebo.

566 patients with heartburn episodes

25 mg
=
125 mg

Alimentary Pharmacology & Therapeutics 1999;13:475-481

PPIs

HOW WELL DO THEY WORK?

Healing/symptoms heartburn

Relapse rate

Prevention of NSAID induced ulcers

Stress ulcers

PPI withdrawal

HOW BAD ARE THE PROBLEMS?

Interactions

Fractures

Pneumonia

C.difficile

iron and B12 deficiencies

Cancer

Table 1. Proton pump inhibitors: Approximate equivalent doses and cost.

Drug	Brand name (formulation)	Available doses (mg)	Usual daily dose range (mg)	Average daily cost*
Omeprazole	Losec® (tablet)	10, 20	10 – 40	$1.13^ – 4.52
Esomeprazole	Nexium® (tablet)	20, 40	10 – 40#	$0.55^ – 2.20
Pantoprazole	Pantoloc® (capsule)	20, 40	20 – 80	$1.02^ – 4.08
Lanzoprazole	Prevacid® (capsule)	15, 30	15 – 60	$2.09 – 4.20
Rabeprazole	Pariet® (tablet)	10, 20	10 – 40	$0.70 – 2.80

Switching from omeprazole at the same dose leads to a 70-90% increase in serum concentration
* Prices are based on average PharmaNet cost for 2001 or wholesale price plus 7%.
^ assumes cutting tablets to halves or quarters when possible to minimize cost.

"ACUTE" Heartburn

HEALING SYMPTOM/RESOLUTION

Patients who respond in the PPI group

≈ 65% at 4 weeks, 85% at 8 weeks - DOUBLE DOSE ANOTHER 5%?

Patients who respond to H_2RA

≈ 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 H_2RA

Cochrane Library CD003244

Chronic

relapse rate at 1 year

PPI
- Placebo ~ 80%
- PPI ~ 25%
- Low dose PPI ~ 28%
- Full dose ~15%

H_2Ra
- Placebo ~ 50%
- Full dose ~15%

H_2RA vs PPI
- H_2RA ~60%
- PPI ~ 20%

http://www.cks.nhs.uk/dyspepsia_proven_gord/evidence/supporting_evidence/no_response_to_initial_therapy/extending_treatment_duration#-330424

"Rebound" after PPI withdrawal in healthy people

120 healthy volunteers

12 weeks of placebo or

8 weeks of esomeprazole 40 mg daily and then 4 weeks of placebo

Reporting dyspepsia, heartburn or acid regurg during weeks 9-12

Placebo ~ 5%

PPI ~ 20%

Gastroenterology 2009;137:80-7

PPI withdrawal in asymptomatic GERD patients

71 patients - tried to titrate dose down over 3-6 months
42% still on PPI - median reinstitution time 14 days
34% ended up on H2RA
7% on prokinetic agent
1% on both
16% no-drugs

Gastroenterology 2001;121:1095–1100

223 patients on lansoprazole 30mg BID
50% ended up on rabeprazole 20mg daily
10% off all drugs

56% with erosive esophagitis failed
31% of those with endoscopic-negative failed

Aliment Pharmacol Ther 2007;25:709–714

On-demand PPI use

"Patients with severe esophagitis (e.g., Los Angeles grades C and D), those with Barrett's esophagus, and those with extra-esophageal manifestations should not be considered for on-demand therapy."

"The available data support the use of on-demand therapy for GERD in uninvestigated reflux disease, non-erosive reflux disease, and possibly mild esophagitis as well"

Am J Gastroenterol 2007;102:642–653

Interactions

Information for Healthcare Professionals: Update to the labeling of Clopidogrel Bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC)

Nov 17, 2009

"The concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel's active metabolite levels and anti-clotting activity. Patients at risk for heart attacks or strokes, who are given clopidogrel to prevent blood clots, may not get the full protective anti-clotting effect if they also take prescription omeprazole or the OTC form (Prilosec OTC)."

The Evidence on CVD

3 - large observational studies - 30-50% inc CVD

5 - similar design - no difference

1 - RCT - hazard ratio - 0.99 95% CI (0.68–1.44) AND a decrease in bleeding

Chance, confounders, publication bias

"Lack of a specific association and the discrepancy between findings of the analyses between and within people suggests that the interaction between proton pump inhibitors and clopidogrel is clinically unimportant"

BMJ 2012;345:e4388 doi: 10.1136/bmj.e4388

Fractures

Mechanism - Calcium malabsorption

FDA Consumer Health Information

Possible Increased Risk of Bone Fractures With Certain Antacid Drugs

FDA: May 25, 2010

FDA has determined an osteoporosis and fracture warning on the over-the-counter (OTC) proton pump inhibitor (PPI) medication "Drug Facts" label is not indicated at this time. Following a thorough review of available safety data, FDA has concluded that fracture risk with short-term, low dose PPI use is unlikely.

Update: 3/23/2011

A couple of meta-analyses of cohort and case-control studies suggests an increased risk
If it is real - conflicting data
Hip fracture per year - 1/2500
Vertebral fracture per year -1/350

Drugs 2012; 72 (4)

Pneumonia

Mechanism - reduce acid - organisms survive in the stomach - reflux - micro-aspiration - pneumonia

data not really strong

2004 - 4.5 times higher - 1 per 226 patients

2009 - 1.3 times higher - 2.5% absolute increase

Cleveland Clinic J Med 2011;78:39-49

C. difficile infections

C difficile - 23 studies - case control and cohort studies
Overall RR is 1.69 (1.40–1.97)

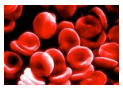
Am J Gastroenterol advance online publication, 19 June 2012; doi:10.1038/ajg.2012.179

42 studies - case control and cohort studies
1.74 (1.47-2.05)
Am J Gastroenterol 2012;107:1011-9

Hospitalized - chance of C.difficile infection
Non-PPI users ~1.5%
PPI users ~ 3% - likely less (2-2.5%) on H_2RA
Community patients - risk about 1/1000

Am J Gastroenterol 2012; 107:1011–1019; doi:10.1038/ajg.2012.108; published online 24 April 2012

Iron and B12



Mechanism - hydrochloric acid assists in the absorption of iron and Vitamin B12

"most individuals in the population consuming a normal diet probably would not experience any significant B12 deficiency from PPI use"
"the available evidence does not justify routine B_{12} screening for long-term PPI users"
"At this time, there are not enough data to recommend routine screening for iron deficiency in patients receiving PPI therapy who are otherwise healthy"

Cancer

"no cohort study to date has demonstrated an increased risk of gastric cancer in H. pylori-infected patients treated with acid suppressants"

"There are theoretical and in vitro data suggesting a potential relationship between hypergastrinemia and increased risk for developing colorectal cancer, but clinical studies to date have not supported this"

Dig Dis Sci 2011;56:931–50

PPIs	Absolute Number Differences
THE GOOD	
Healing/symptoms	~ 55% over placebo ~ 30% over H_2RA
Reduce relapse at 1 year	~ 55% over placebo ~ 35% over H_2RA
Prevent NSAID-induced ulcers	~20% over placebo - endoscopic ?? clinical ulcers
Reduce stress ulcers	~ 8% over placebo ~ 0% over H_2RA
Withdrawal - rebound	~ 15% rebound symptoms ~ 50% can lower dose ~ 33% go on H_2RA ~ 10-20% off drugs
THE BAD	
Interactions	Clopidogrel - likely 0% Other drugs?
Fractures/year	If real 0.3% vertebral and 0.025% hip
Pneumonia	If real 0.25%?
C difficile	~ 1.5% in hospital ~ 0.1% in community
Iron/B12	??
Cancer	??

H. pylori test and treat versus placebo in *H. pylori* positive patients with non-ulcer dyspepsia

"global improvement" at 3-12 months 63% of the heartburn patients improved with placebo compared with 71% on eradication therapy

The Cochrane Library 2009

Peptic Ulcer Disease

Goals of Treatment

to ameliorate symptoms of peptic ulcer disease

to promote ulcer healing

to prevent complications of peptic ulcer disease (hemorrhage or perforation)

to prevent recurrences of peptic ulcer disease

to prevent complications of stress ulcers

HP or Not

Urea Breath Test
– < 50 years old and no alarm symptoms (vomiting, bleeding, anemia, weight loss)

Gastroscopy and biopsy
– > 50 years old or new or alarm symptoms

Blood: IGG previous (not current) infection

H. pylori test and treat plus ulcer healing drug versus ulcer healing drug (UHD)

overall healing no difference (around 80%)

no difference in recurrence of H. pylori therapy versus chronic UHD (around 10%)

H. pylori therapy vs placebo - decreased recurrence (15% versus 65%)

The Cochrane Library 2009

H.pylori eradication in patients with GI bleeds

Rebleeding in H.pylori eradication group 2.9% versus 20% in no treatment group

Rebleeding in H.pylori eradication group 1.6% versus 5.6% in long-term acid suppression group

The Cochrane Library 2005;4

Issues to consider when selecting an H pylori eradication regimen

percent eradication of H. pylori - all roughly 80%

patients with symptoms should receive a regimen that contains an acid suppressor like an H2 antagonist or proton pump inhibitor

all H2 antagonists are equally effective so choose the least expensive of cimetidine, ranitidine, famotidine, nizatidine

all proton pump inhibitors are equally effective so choose the least expensive of omeprazole, pantoprazole, lansoprazole, esomeprazole. rabeprazole

Issues to consider when selecting a regimen

regimens containing amoxicillin cannot be used in patients with penicillin allergies

alcohol must be avoided with metronidazole regimens

more resistance with metronidazole (20%) than amoxicillin (1%) BUT..

convenience of twice a day versus three or four times a day dosing

duration of therapy 7 days to 2 weeks - no real difference if look at high quality trials

quadruple vs triple therapy - no real difference - Bismuth subcitrate not commercially available

sequential therapy PPI+amoxil bid x 5days,THEN
PPI + clarith 500 mg + metro 500 bid x 5 days - SR of 10 studies - Eradication rates (93% ST vs 77% TT)

ten fold variation in cost

approximately 1/3 of patients will have side effects primarily gastrointestinal (diarrhea, upset stomach) but only 3% will experience side effects severe enough to require withdrawal of therapy

1. H2 antagonist, metronidazole, amoxicillin
2. Bismuth subsalicylate, metronidazole, amoxicillin
3. Bismuth subsalicylate, metronidazole, tetracycline
4. Proton pump inhibitor, bismuth subsalicylate, metronidazole, tetracycline -7 days
5. Proton pump inhibitor, clarithromycin, amoxicillin (Hp-PAC, Losec 1-2-3 A, Nexium 1-2-3 A) -7 days
6. Proton pump inhibitor, amoxicillin, metronidazole
7. Proton pump inhibitor, clarithromycin, metronidazole (Losec 1-2-3 M) - 7 days

Testing for eradication

Only if a complicated ulcer (bleeding), or if symptoms return

PUD if negative H. pylori test

Cimetidine, ranitidine, famotidine, nizatidine

Omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole

Sucralfate

Misoprostol

Prevention of NSAID - induced ulcers

Misoprostol

Cimetidine, ranitidine, famotidine, nizatidine, omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole

Screen for H. pylori and treat if positive

Eradicating Hp prior to long term NSAIDs ↓ PUD

In those with dyspepsia or previous UGI bleed

10% (Erad + PPI) vs 31% (PPI)

ARR = 19% or NNT = 5

Lancet 2002;359:9

Treatment of NSAID-induced ulcers

If H. pylori positive

treat with H. pylori regimen

If H. pylori negative and NSAID can be stopped

treat with acid suppressing therapy

If H. pylori negative and NSAID cannot be stopped

Omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole

Misoprostol