23rd ANNUAL DRUG THERAPY DECISION MAKING COURSE

Encouraging Healthy Skepticism

April 20th and 21st, 2012

Fairmont Waterfront Hotel
Vancouver, B.C.

Friday Syllabus

SKEPTICEMIA

When skepticism gets into your blood

There is no cure

Sponsored by

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

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

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

- Dresden James

Course Directors

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

Guest Faculty

G. Michael Allan, Assoc. Prof., Family Practice, University of Alberta
& Director, Evidence and CPD Program, Alberta College of Family Physicians
Mike Kolber, Assoc. Prof., Family Medicine, University of Alberta
Tina Korownyk, Asst. Prof., Family Medicine, University of Alberta
Stephen Setter, Assoc. Prof., Pharmacy, Washington State University, Spokane WA

Local Faculty

Roxane Carr, Clinical Pharmacy Specialist, CWHC
Peter Chan, Clin. Prof., Medicine, Psychiatry, UBC
Tom Elliott, Clin. Assoc. Prof., Medicine, Endocrinology, VGH
Rob Enns, Clin. Prof., Medicine, Gastroenterology, UBC & PHC
Jonathan Fleming, Assoc. Prof., Medicine, Psychiatry, UBC
Shahin Jamal, Clin. Asst Prof., Medicine, Rheumatology, UBC & VA
Jason Kong, Clin. Asst. Prof., Medicine, Endocrinology, UBC & VA
Peter Loewen, Assoc. Prof., Pharmaceutical Sciences, UBC & VCH
Andrew Merkur, Clin. Asst. Prof., Dept. of Ophthalmology and Visual Sciences, UBC & VA
Val Montessori, Clin. Assoc. Prof., Medicine, Infectious Diseases, UBC & PHC
Natasha Press, Clin. Assoc. Prof., Medicine, Infectious Diseases, UBC & PHC
Kam Shojania, Clin. Prof., Medicine, Head, Division of Rheumatology, UBC & PHC
Johanna Trimble, BC Patient Voices Network, Patient Safety Advisory Council, VCH
Adil Virani, Assoc. Prof, Pharmaceutical Sciences, UBC, & Director, LMPS

CWHC - Children's and Women's Health Centre
FHA – Fraser Health Authority
PHC – Providence Health Care
UBC – University of British Columbia
VA - Vancouver Acute
VCH - Vancouver Coastal Health
LMPS - Lower Mainland Pharmacy Services, FHA, PHSA, PHC, VCH

23rd Annual
Drug Therapy Decision Making Course
Friday April 20, 2012

Counting on the evidence

07:00 Registration (Muffins & Coffee)

Chair - Bob Rangno and James McCormack

"Counting by numbers"

08:00	Welcome and Introduction	Bob Rangno
08:10	5 things I've learned and actually remembered	Bob Rangno
08:20	The WHO, what, why, where and when of therapeutics – top 10 things you can count on	James McCormack

"Joints - 230 and still counting"

08:50	The 11 out of 10 pain of acute gout?	Kam Shojania
09:10	Questions	
09:20	"Toe" - phaceous gout – more deposits than in your bank account	Kam Shojania
09:40	RA – making your joint counts, count?	Shahin Jamal
10:00	Questions	
10:20	Refreshment Break	

"Making number 2 number 1"

10:40	IBS – not just another 4 letter word	Mike Kolber
11:00	IBD – the clue is in number "2"	Rob Enns
11:20	Questions	
11:30	H pylori treatment – is 4 better than 3?	Mike Kolber
11:50	Hepatitis C – ABC 123	Adil Virani
12:10	Questions	
12:30	Lunch	

"Once, twice, three times a lady"

13:20	Covering HPV strains – 2, 4 or maybe more	Natasha Press
13:40	Acetaminophen in children - is Tylenol a #1, 2 or 3?	Roxane Carr
14:00	Zoster vaccine - counting the chicken pox before they hatch	Val Montessori
14:20	Questions	
14:40	Refreshment Break	

"Stopping drugs – which 1 is 2 many?*"*

15:00	Delirium – what to do if it's "relative"	Johanna Trimble
15:20	Delirium – making the relative absolutely better	Peter Chan
15:40	Drugectomy - count on a 90% success rate	Stephen Setter
16:00	Can you count on new anticoagulants?	Peter Loewen
16:20	Questions	
16:40	Adjourn	

Robert Rangno and James McCormack

Welcome

to the

23rd Annual

Drug Therapy Decision Making Course

An interactive course on common and new drug therapy issues from an evidence based perspective

To get a pdf version of the handouts go to http://therapeuticseducation.org/dtc
Only registered TEC members (FREE) will have access to the pdfs

5 things we've learned - well maybe 9

1. Conflict of interest
2. Scepticism
3. Low dose
4. Genetic Mongrels - N=1
5. Old drugs
6. Outcomes vs surrogates
7. NNT/NNH
8. Re-evaluation
9. Patient values!!!!!!

What guidelines should Offer

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

The chance of "X" with no treatment

The chance of "X" with treatment

Baseline risk
RRR, ARR, NNT
Difference between groups

Fracture risk over 2-3 years

Bisphosphonates	Baseline (%)	RR/OR (%)	Absolute benefit (%)
Non-vertebral	10	20	2
Vertebral	10	50	5
Hip	2	25	0.5
Wrist	3	20	0.6

BMC Musculoskeletal Disorders 2011;12:209

You can't be too rich or too low: Targets

Lipids: There are NO studies that have looked at getting patients to different lipid levels

BP[1]: current evidence for BP targets of 130/80 is inconsistent, even for patients with diabetes, renal disease, or existing cardiovascular disease

A1C[2]: Over five years, non-fatal MI NNT=117-150 and microalbuminuria NNT=32-142 patients

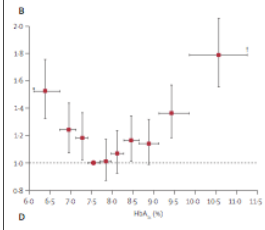
- None if only high quality studies
- For severe hypoglycemia NNH=15-52

Rate Control[3]: No difference between <80 or <110 HR

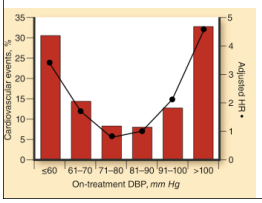
1) Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD004349. N Engl J Med. 2010 Apr 29;362(17):1575-85. Lancet 2009; 374: 525–33. N Engl J Med 2010;363:918-29. 2) BMJ 2011;343:d4169 doi: 10.1136/bmj.d4169 3) N Engl J Med 2010;362:1363-73.

What goes down must come up

A1C[1]



Diastolic BP[2]



BMI[3] over 65

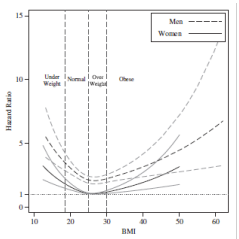


Figure 1. Hazard ratios of all-cause mortality according to body mass index (BMI) in men and women aged 70 to 75 (lines are 95% confidence intervals).

1) Lancet 2010; 375: 481–89
2) Curr Hypertens Rep (2010) 12:290–295
3) J Am Geriatr Soc 2010; 58:234–241

Robert Rangno and James McCormack

Surrogates: The Never-ending Consistently Inconsistent Story

The Marker	The Treatment
HDL	Torcetrapib[1] LDL down, HDL up CVD & mortality up Niacin
LDL	Ezetimibe
Trigly	Fibrates
BP	Atenolol Aliskiren Doxazosin
A1c	Rosiglitazone Almost any diabetes medications except Metformin
Homocysteine	Folate
CRP in CVD	Vitamin E, Rosiglitazone, etc.

N Engl J Med 2007;357:2109-22

12 Recent Trials

Lipids
- AIM-HIGH (niacin)
- ACCORD (fibrates)

Blood Pressure
- ALTITUDE (aliskiren)
- VALISH, AASK, ACCORD (aggressive BP lowering)

Diabetes
- ACCORD, ADVANCE, VADT (aggressive A1c lowering)
- ROADMAP (olmesartan)

General
- ACTIVE (irbesartan/afib)
- CRESCENDO (rimonabant)

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

Golden Pill Award

PRESCRIRE AWARDS

	Major therapeutic advance	Clear advantage	Modest improvement
2011	0	0	0

Table 1 Performance measures for the various groups

Measure	Martirosyan *et al* prescribing quality indicators	Medicare PQRI	National quality forum endorsed	OECD	NCQA
HbA1c					
Percentage with HbA1c >9					✓
Percentage with A1c <7.0	✓*				✓
Lipids					
Percentage with ≥1 LDL measure					✓
Percentage with LDL <100					✓
Percentage with LDL <100 or on statin					
Percentage with LDL <130					
Percentage with LDL <130 or on statin					
Percentage on a statin	✓				
BP control					
Percentage with BP <140/80	✓*				✓
Percentage with BP <140/90					✓
Percentage with BP <130/80					✓
Nephropathy					
Percentage with ≥1 urine microalbumin					
Percentage with microalbumin or on ACEI/ ARB	✓*				
Aspirin use					
Percentage receiving aspirin ≥75 mg/day	✓*		✓		

ACTIVITY - not exercise
NUTRITION - not diet
WEIGHT (Obese)
STOP SMOKING
FEEL BETTER

Qual Saf Health Care 2008 17: 315-7

Adding "value" to clinical practice guidelines

5 Canadian Guidelines for blood pressure, cholesterol, glucose, and bone density

OBJECTIVE To determine the degree to which current Canadian clinical practice guidelines (CPGs) for common

197 pages - 90,000 Words

99 words - relevant to the issues of patients' values and preferences

determining the probability that an individual patient will experience an end point without and with implementation of the therapeutic intervention, and the number of descriptions of specific or comparative costs

79 drugs available in Canada

Only for

- ATORVASTATIN, SIMVASTATIN, STATINS (as a group)
- ALENDRONATE
- HORMONE REPLACEMENT

could one use the information presented in the guidelines to estimate a potential benefit

Robert Rangno and James McCormack

Patient preference for autonomy: does it change as risk rises?

Timothy Kenealy[a,*], Felicity Goodyear-Smith[a], Susan Wells[b], Bruce Arroll[a], Rod Jackson[b] and Margaret Horsburgh[c]

"No combination of predicted risk, demographics or attitudes strongly predicted the preference of an individual patient. Clinicians should therefore seek to understand and confirm each patient's preferences"

"One factor affecting willingness to make decisions is the desire to avoid regret caused by negative outcomes from one's own decision"

Family Practice 2011; 0:1–4 doi:10.1093/fampra/cmr022

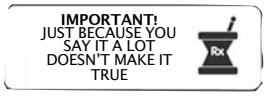
Helping Patients Decide: Ten Steps to Better Risk Communication

Angela Fagerlin, Brian J. Zikmund-Fisher, Peter A. Ubel

USE

1. Plain language
2. Absolute risks - not relative risks, NNTs or comparative risks
3. Pictographs/bar graphs
4. Frequencies (5 out of 100) versus percentages (5%) ??
5. Incremental risks (changes from baseline)
6. Summary table(s)
7. Decision information not all information
8. Time frames

J Natl Cancer Inst 2011;103:1–8



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

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

James McCormack *professor*[1], G Michael Allan *associate professor*[2]

"THE ADMONITION TO MAKE SURE [PATIENTS] FINISH THE "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" DIRECTED BY PRESCRIBER" SHOULD BE DISCOURAGED

CMAJ ANALYSIS

Is bigger better? An argument for very low starting doses

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

CMAJ, January 11, 2011

25 mg sildenafil (Viagra)	effective dose for erectile dysfunction
25 mg sumatriptan (Imitrex)	works as well as 100 mg
5 mg daily fluoxetine (Prozac)	similar effects to those seen at 20 mg and 40 mg daily
0.25 mg ezetimibe (Ezetrol)	1/40th of the recommended initial starting dose provides 50% of the LDL lowering effect
15 mg 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 bupropion (Zyban) 0.5 mg BID varenicline (Champix)	produces the same rate of smoking cessation at one year as 300 mg daily (1.0 mg BID)
25 mg ranitidine (Zantac)	as effective as 125 mg for heartburn relief
1.8 mg colchicine	as effective as 4.8mg for acute gout with less adverse events

ADVANTAGES OF STARTING WITH "VERY" LOW DOSES

1) GET THE POTENTIAL "PLACEBO GROUP EFFECT"

2) PATIENTS ARE ENGAGED IN THE PROCESS OF FINDING THE BEST DOSE FOR THEM

3) COST SAVINGS CAN BE CONSIDERABLE AND REDUCED ADVERSE EVENTS

4) MOST CLINICALLY RELEVANT DRUG INTERACTIONS CAN BE AVOIDED

ACTIVITY

ADDITIONAL BENEFITS NOT SEEN WITH BP/CHOL/DIABETES MEDS

LOTS OF STUDIES ON POSITIVE SURROGATES BP, LIPIDS, ETC

EXERCISE SEEMS TO IMPROVE SLEEP QUALITY & FATIGUE

COCHRANE DATABASE SYST REV. 2002;(4):CD003404. J GERONTOL A BIOL SCI MED SCI. 2008 SEP;63(9):997-1004. J SPORTS MED PHYS FITNESS. 2007 DEC;47(4):462-7

IMPROVES DEPRESSION

COCHRANE DATABASE SYST REV. 2008 OCT 8;(4):CD004366

IMPROVES OA PAIN AND FUNCTION

COCHRANE DATABASE SYST REV. 2008 OCT 8;(4):CD004376

ETC

Kam Shojania

11/10 pain of acute gout

Dr. Kam Shojania
Clinical Professor and Head,
UBC Division of Rheumatology

With thanks to Drs Koehler and Kherani
for some of the slides in this presentation

Division of Rheumatology

Learning Objectives

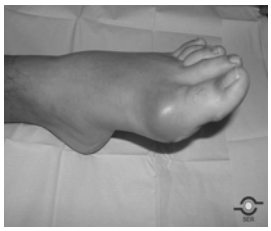
- By the end of this presentation, participants will
- Understand how to recognize acute gout - clinical presentation
- Review the differential diagnosis of monoarthritis
- Understand the approach to the diagnosis of gout, including use of:
  - Blood
  - Synovial fluid
  - X-ray
  - DECT
- Review the approach to treatment of acute gout

Full Disclosure

- Takeda (maker of Febuxostat) has provided research funding for at least two of my division members - investigator-initiated imaging DECT studies but not clinical trials.
- Takeda has also provided honoraria for some talks I have given and I once was at an advisory meeting for them in 2010 where I also had a very nice meal (with wine).
- I really like DECT scans to diagnose gout but they have not yet been generally accepted as a diagnostic modality
- There are no slides from industry but I did take some from Drs. Koehler and Kherani

Case 1

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



Is gout painful?

From Bywaters Collection

Kam Shojania

Differential Diagnosis: Acute Monoarthritis

Infection

Infection

Infection

Crystal (Gout, Pseudogout)

Trauma (hemarthrosis)

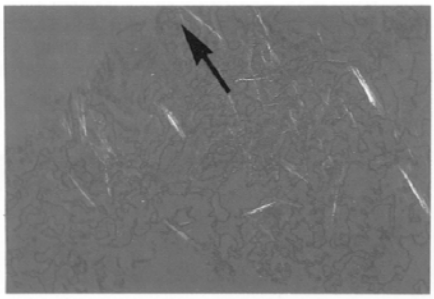
Psoriatic arthritis

Reactive Arthritis

What investigations would you do?

- **ASPIRATION** "To inject is human, to aspirate divine" – Barry Koehler
- Blood work
  - Hematology
  - Serum uric acid and serum creatinine
  - ESR
- X-ray(s)

Urate Crystals: Polarized Microscope with Red Compensator



Diagnosing gout

- Clinical awareness
  - Not always the big toe and not always a single joint
  - Serum uric acid may be normal
  - Gout can occur in the presence of other types of arthritis
    - Osteoarthritis
    - Other inflammatory arthritides (but not often with rheumatoid disease)
    - Even septic arthritis
- But there is only one way to be sure that it is gout …
  - Aspirate the joint!

Diagnosis of gout (continued)

- What if you cannot obtain fluid from - or around - the joint?
  - You may miss a septic arthritis so maintain clinical vigilance. Remember that you have sinned.
  - Consider the circumstantial evidence - joint involved, systemic complaints, serum uric acid, age and sex of patient.

What about serum uric acid levels?

- What is normal?
  - ≤ 360 males
  - ≤ 340 females
- What if it's normal during the episode of acute arthritis?
- Why not treat, based on the clinical presentation and the uric acid level?

Kam Shojania

No-touch gout diagnosis

Hein J. E. M. Janssens, MD; Jaap Fransen, PhD; Eloy H. van de Lisdonk, MD, PhD; Piet L. C. M. van Riel, MD, PhD; Chris van Weel, MD, PhD; Matthijs Janssen, MD, PhDA Diagnostic Rule for Acute Gouty Arthritis in Primary Care Without Joint Fluid Analysis ARCH INTERN MED/ VOL 170 (NO. 13), JULY 12, 2010

Variable	Score
Male sex	2.0
Previous patient-reported arthritis attack	2.0
Onset within 1 day	0.5
Joint redness	1.0
Involvement of 1st MTP	2.5
Hypertension or ≥ cardiovascular disease*	1.5
Serum uric acid > 350	3.5

*History of MI, angina pectoris, CHF, CVA, TIA, PVD

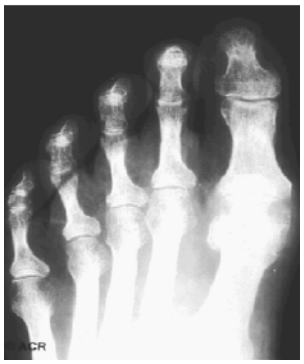
4 or less Not gout
8 or more Probable gout

- All patients had diagnosis confirmed by joint aspiration
- 17% false positive with score of ≥8
- Only 30% of midrange had gout
- Nearly all ≤4 did not have gout

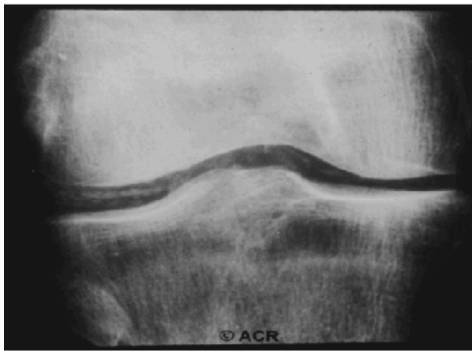
Diagnosis of gout (continued)

X-rays
- Do they help?

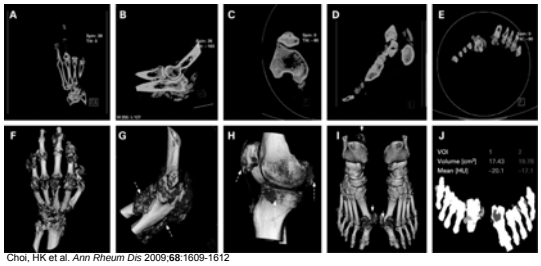
Gout



Chondrocalcinosis



DECT
Dual energy computed tomography



Choi, HK et al. *Ann Rheum Dis* 2009;**68**:1609-1612

Treatment of <u>acute</u> gouty arthritis

- Any NSAID will do, not just Indomethacin
- If NSAID contraindicated, consider corticosteroid, intra-articular or systemic
- Don't forget local measures, such as ice, splinting, rest, elevation
- Add analgesic prn

Kam Shojania

What about colchicine?

- The good
- The bad
- And the ugly

What about colchicine?

- The good
  - –Effective for treatment of of acute gout, if started in 1st 1-2 days

What about colchicine?

The bad

- – Diarrhea
- – Nausea and vomiting
- – Bloating

What about colchicine?

And the ugly

- – Myopathy
- – Cardiomyopathy
- – Pancreatitis
- – Renal failure
- – Severe dermatitis

Treating gout
-The acute attack

- NSAID's
  - o But beware of the side effects
  - o Use caution in those with hypertension or renal failure
- Corticosteroids
  - o Oral bolus
  - o Parenteral
    - ▪ Intramuscular
    - ▪ Intra-articular – probably the safest and best route
- Colchicine
  - o Oral
  - o Intravenous

What we've talked about

- o Understand how to recognize gout - clinical presentation
- o Review the differential diagnosis of monoarthritis
- o Understand the approach to the diagnosis of gout, including use of:
  - ▪ Blood
  - ▪ Synovial fluid
  - ▪ X-ray
  - ▪ DECT
- o Review the approach to treatment of acute gout

Kam Shojania

"Toe" – phaceous gout – more deposits than in your bank account

Dr. Kam Shojania
Clinical Professor and Head,
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With thanks to Drs Koehler and Kherani
for some of the slides in this presentation

Division of Rheumatology

Learning Objectives

- By the end of this presentation, participants will
- Understand how to recognize chronic gout
- Understand the approach to the diagnosis of gout, including use of:
  - Blood
  - Synovial fluid
  - X-ray
  - DECT
- Review the approach to treatment of acute gout

Full Disclosure

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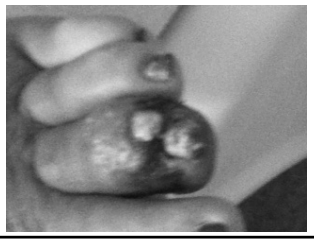
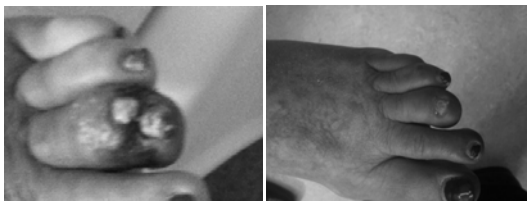
- Takeda has also provided honoraria for some talks I have given and I once was at an advisory meeting for them in 2010 where I also had a very nice meal (with wine).
- Blah blah blah

Case 2

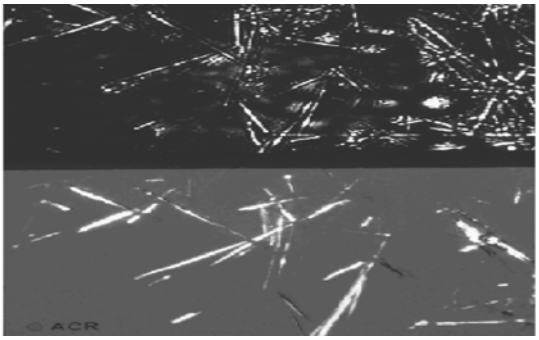
- A 65 year old nurse is admitted for cellulitis of her 3rd toe which was red, painful and had been draining. An x-ray is done and rheumatology is consulted for the possibility of osteomyelitis. She had fractured this toe in the past.



Before and after a few months of allopurinol



Urate crystals from tophus

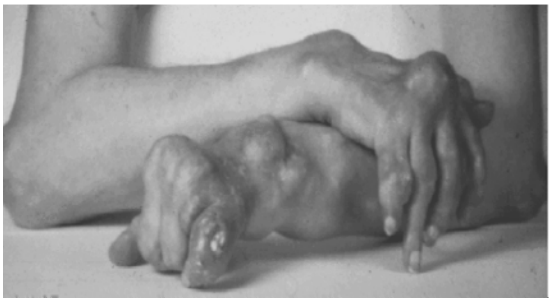


Kam Shojania

A few rules for gout

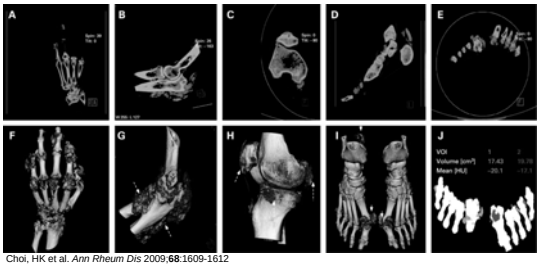
- Do not treat asymptomatic hyperuricemia
- Chronic toe pain does not make a diagnosis of gout
- Diagnose gout with joint aspiration (not serum uric acid).
- **Premenopausal women (with normal renal function) will almost never have gout.**
- Treat gout with allopurinol to aim for a serum uric acid of less than 360
- Treat 'mobilization gout' prophylactically with low dose NSAIDs, colchicine or prednisone for the first few months of allopurinol therapy.

Chronic tophaceous gout



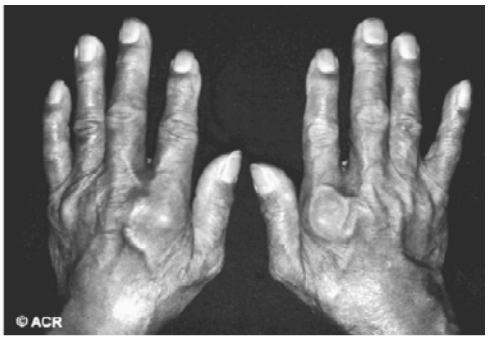
From Bywaters Collection

DECT
Dual energy computed tomography

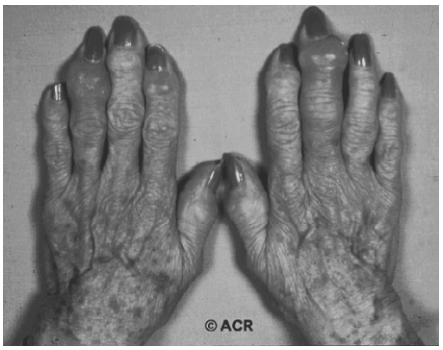


Choi, HK et al. *Ann Rheum Dis* 2009;**68**:1609-1612

Gout or rheumatoid arthritis?



Gout or osteoarthritis?



Kam Shojania

What's a diet for gout?

- **Dr. Alexander Haig 19th century**
  - "Cut out the butcherer, and live by the baker, the dairyman and the fruiterer."
- **Purine-rich foods, dairy and protein intake, and the risk of gout in men.** Choi HK; Atkinson K; Karlson EW; Willett W; Curhan G. N Engl J Med 2004 Mar 11; 350 (11), pp. 1093-103.
  - Higher levels of meat and seafood consumption are associated with an increased risk of gout, whereas a higher level of consumption of dairy products is associated with a decreased risk. Moderate intake of purine-rich vegetables or protein is not associated with an increased risk of gout.
- Alcohol
  - Beer, liquor; not wine Choi et al
  - Mechanism – decreased excretion, ? Increased production, dehydration

Why do we get gout?

- Mainly a metabolic disorder
- Contributing factors
  - Diet
  - Medications
  - Metabolic syndrome
  - Dehydration/physical stress

Medications that increase uric acid levels

- Diuretics, especially thiazides
- Low dose ASA

Why do we get gout?

- Mainly a metabolic disorder
- Contributing factors
  - Diet
  - Medications
  - Metabolic syndrome
  - Dehydration/physical stress

Gout is a metabolic syndrome

There is an increased incidence of gout in persons with:

- Obesity
- Diabetes mellitus
- Hypertension
- Renal failure
- Hypothyroidism

Why do we get gout?

- Mainly a metabolic disorder
- Contributing factors
  - Diet
  - Medications
  - Metabolic syndrome
  - Dehydration/physical stress

What is a common reason for stress and dehydration?

After surgery

Treatment of recurrent gouty arthritis

- Urate-lowering agents
  - Xanthine oxidase inhibitors
    - Allopurinol 300mg daily – can titrate up
    - Febuxostat 80mg daily
  - Uricosuric agents - Probenecid, Sulfinpyrazone
    - This is the only time for a 24 hr urine uric acid
    - **Nobody actually prescribes or takes these however – QID? Gimme a break**
- Diet
- Education, education, education!!!

How to use uric acid lowering agents

Wait for acute attack to resolve

Initiate Allopurinol or febuxostat along with colchicine 0.6mg daily or a low dose NSAID daily (for the first 6mo).

Monitor serum uric acid (and creatinine) monthly for a few months until sUA < 360.

If sUA not below target, question compliance. If compliant, increase allopurinol by 100mg/month until sUA<360

Would usually use allopurinol

- Dose as per renal function – watch for rash
- Rarely severe rash or Steven Johnsons Syndrome
- If patient develops a rash, stop allopurinol and initiate febuxostat.
- For patients with moderate renal dysfunction, I would choose febuxostat first if patient can afford it.
- Remember there are potential drug interactions with both drugs so please check when initiating. Most common AZATHIOPRINE, WARFARIN

Costs?

- Allopurinol 300 mg $20/month
- Febuxostat 80 mg od $60-70/month
- Pharmacare will cover if patient allergic to allopurinol.

TOTAL RECALL: Treating gout -The acute attack

- NSAID's
  - But beware of the side effects
  - Use caution in those with hypertension or renal failure
- Corticosteroids
  - Oral bolus
  - Parenteral
    - Intramuscular
    - Intra-articular
- Colchicine
  - Oral
  - Intravenous

Kam Shojania

Treating gout- Prevention I

- General principles
  - Not until after the second attack
  - Preventative treatment never stops
  - Diet alone is rarely sufficient, even if the patient adheres to it, no matter what his naturopath says.
- Cautionary note
  - Attacks of gout will often increase during the first few months of prevention therapy.

Treating gout - Prevention II

- Treat with goal of lowering serum uric acid below 360
- Give concomitant “anti-flare agent” until no attacks for 6 months
  - Low dose colchicine
  - NSAID
  - Low dose corticosteroid
- Educate, educate, educate!

What we’ve talked about

- Understand how to recognize gout - clinical presentation
- Review the differential diagnosis of monoarthritis
- Understand the approach to the diagnosis of gout, including use of:
  - Blood
  - Synovial fluid
  - X-ray
  - DECT
- Review the approach to treatment of gout
  - When to start
  - Acute
  - Chronic/tophaceous
  - Education

Shahin Jamal

The Use of Biologics in Rheumatology

Shahin Jamal, MD, FRCPC
April 20, 2012

Outline

- Introduction to Biologics
- Biologics Used in Rheumatology
- Efficacy of Biologics
- Biologic Safety – what do we monitor?
- Practical Considerations with Biologics
- Common Subcutaneous Injectors

What are Biologics?

- First used in rheumatology in 1998
- Genetically engineered drugs
  - Human genes are used in non-human cell cultures to produce large amounts of natural human proteins
- Have specific targets
- Copy the effects of substances naturally made by the body's immune system

How do biologics work?

- Most biologics act as inhibitors of cytokines (eg. TNFα, IL6, etc)
- Cytokines → messenger molecules
  - Act to excite other immune system cells
  - Propagate inflammatory response
- Biologics specifically attach to these cytokines and inactivate them.

Practical issues with Biologics

- Expensive to make → Expensive to buy
- Must be given by injection, subcutaneously or intravenously
- Must be stored in a refrigerator and warmed to room temperature before use
- Work quickly to relieve inflammatory symptoms

Biologics Used in RA

- TNF α Inhibitors:
  - Adalimumab (Humira ®)
  - Certolizumab (Cimzia ®)
  - Etanercept (Enbrel ®)
  - Golimumab (Simponi ®)
  - Infliximab (Remicade ®)
- B Cell Modulator:
  - Rituximab (Rituxan ®)
- CTLA 4 Agonist:
  - Abatacept (Orencia ®)
- Interleukin 6 Inhibitor:
  - Tocilizumab (Actemra ®)

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Things to know:

Prior to initiating therapy:

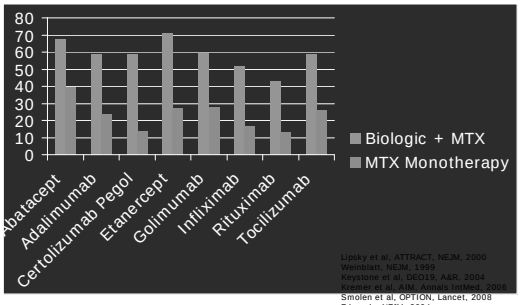
- Rule out previous exposure to TB
- Screen for viral hepatitis
- Ensure vaccinations are up to date, including pneumovax

During treatment:

- CBC and liver tests every 3-6 months
- Annual flu shot
- No live vaccines (yellow fever, BCG, rubella, polio, cholera, typhoid, varicella)

Benefits and Adverse Effects

Efficacy Data – ACR20 at 24 weeks



Lipsky et al, ATTRACT, NEJM, 2000
Weinblatt, NEJM, 1999
Keystone et al, DE019, A&R, 2004
Kremer et al, AIM, Annals IntMed, 2006
Smolen et al, OPTION, Lancet, 2008
Edwards, NEJM, 2004
Keystone et al, GO FORWARD, ARD, 2008
Keystone et al, RAPID 1, A&R, 2008

Benefits of Biologics

- Rapid suppression of inflammation
- Improvement of pain and swelling
- Improvement of function
- Inhibit radiographic damage and destruction (even when incomplete clinical benefit)
- Potent inhibition of inflammatory markers
- Improvement of cardiovascular outcomes

Biologics: Common adverse effects

- Upper respiratory infections (colds, sinusitis, bronchitis, etc.)
- Injection site reactions (SC agents)
- Infusion reactions (IV agents)– itching, hives, headache, palpitations
- Skin rash
- Dizziness
- Nausea, diarrhea
- Headache

Biologics: Rare / serious toxicities

- Bacterial infections (pneumonia, joint)
- Unusual infections (TB, fungal, PML)
- Leukopenia, neutropenia, thrombocytopenia, anemia, pancytopenia
- ?Malignancy

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TNF α Inhibitors: Adverse Events

- Optic neuritis
- Multiple sclerosis and other nerve disorders
- Worsening of heart failure
- Development of autoantibodies – lupus-like syndrome or autoimmune hepatitis

Rituximab: Adverse Effects

- Hypercholesterolemia
- Hypertension
- Tumor lysis syndrome
- Bowel obstruction and perforation
- Progressive multifocal leukoencephalopathy (PML)

Tocilizumab: Adverse Events

- Elevated liver tests
- Elevated lipids and triglycerides
- Neutropenia
- ? Cardiac and vascular events
- ? GI perforation

Abatacept:

- May react with GDH-PQQ based blood glucose monitoring systems for false high reading

Special Considerations

- Pregnancy and Breast Feeding
- Surgery
- Immunizations

Canadian Rheumatology Association has guidelines on these being published this summer!

TNF α Inhibitors

Properties of Anti-TNF Agents

	Infliximab	Adalimumab	Golimumab	Etanercept	Certolizumab
					
Dosage	3-10mg/kg q4-8weeks	40mg q2weeks	50mg qmonthly	50mg qweekly	200mg q2w OR 400mg qmonthly
Form	Lyophilized IV Infusion	0.8mL Pre-filled pen Pre-filled syringe	0.5mL Auto-injector Pre-filled syringe	1.0mL Auto-injector Pre-filled syringe	Lyophilized 200 mg/ml SC
Half-life	8 – 10 days	~14 days	14 days	4 days	~14 days

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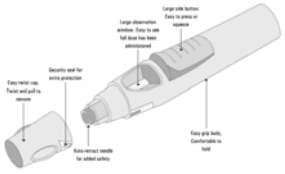
Adalimumab

HUMIRA® Pen

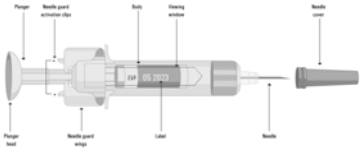
HUMIRA®
Pre-Filled Syringe

Golimumab



SMARTJECT™ AutoInjector

Pre-filled Syringe

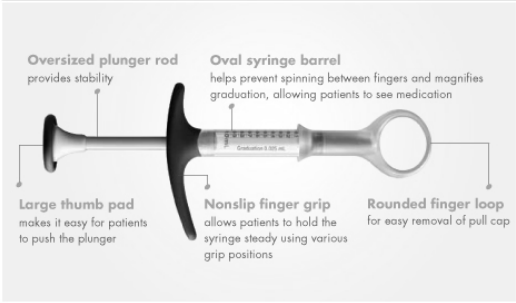


Etanercept

SURECLICK™ AutoInjector

Pre-filled Syringe

Certolizumab Pegol



Diseases with Approved Indications for TNFi

- Rheumatoid Arthritis
- Psoriatic Arthritis
- Ankylosing Spondylitis
- Juvenile Arthritis
- IBD and associated arthritis
- Psoriasis

Non-TNF Biologics

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Rituximab: Characteristics

Inhibits what?	CD 20 molecule on B cells
Type of biologic	Chimeric Antibody
Dose	1000mg IV x 2 given two weeks apart With methylprednisolone 100mg IV
Re-treatment	Initial response At least 6 months after initial dose
Half-life	20.8 days

Rituximab: Areas of Investigation

- Sjogren's Syndrome
- Castleman's Disease
- Systemic Lupus Erythematosis
- **ANCA positive vasculitis**
- Membranous Glomerulonephritis/ Nephropathies
- Refractory Polymyositis
- Dermatomyositis
- Multiple Neuropathies
- Thrombocytopenic Purpura
- Multiple Sclerosis & Neuromyelitis Optica
- Post-Transplant (liver, heart)

Abatacept: Characteristics

Inhibits what?	Co-stimulation modulator Binds CD80/86 on APC and prevents interaction with CD28 on T cell
Type of biologic	Fully human soluble receptor fusion protein
Dose	Under 60 Kg = 500 mg 60 to 100 Kg = 750 mg Over 100 Kg = 1,000 mg
Frequency	Monthly IV infusion
Half-Life	16.7 days

Abatacept: Indications

- Rheumatoid Arthritis
- Juvenile Rheumatoid Arthritis

Clinical Development Program:

- SLE
- Psoriatic Arthritis
- IBD (Crohns, UC)
- Vasculitis (GCA, Takayasu's Arteritis, Wegeners)
- Sarcoidosis
- Ankylosing Spondylitis
- Scleroderma
- Recent Onset Type 1 Diabetes Mellitus

Tocilizumab: Characteristics

Inhibits what?	Interleukin 6
Type of biologic	Humanized Monoclonal Antibody
Dose	4mg or 8mg / kg
Frequency	Monthly IV infusion

Tocilizumab: Indications

- Rheumatoid Arthritis

<u>Developing Programs:</u>

- Juvenile Idiopathic Arthritis
- Castleman's disease
- Scleroderma

Shahin Jamal

Changes in Rheumatology

- Revolutionized management of many rheumatologic diseases
- We are now treating patients earlier and more aggressively
- We are now able to achieve high targets:
  - Remission
  - Drug free remission
  - Cure!

Conclusion

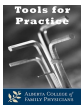
- Biologics work well and have revolutionized how we treat patients
- They are generally well tolerated – infection is most significant concern
- Major barriers to use:
  - Long term toxicity unknown
  - Access to medication due to high cost

"I go home today. They cured me using this new miracle drug. I'm afraid it'll be years before it's approved for humans."

"Take the green pill to feel hunky, the yellow pill to feel dory."

All you need to know about Irritable Bowel Syndrome in 20 minutes!

Michael Kolber BSc, MD, CCFP, MSc
DTC April 2012



Conflict of Interest

Decision Making 201

- Take studies (on populations of patients) and formulate a decision / treatment plan for the patient in front of you who seeks your help

IBS Overview

- Why important: prevalence, QOL
- Diagnosis, competing diagnosis
- Treatments
  - Diets: fibre, elimination, FODMAPs
  - anti-spasmodics, peppermint oil
  - anti-depressants
  - Exercise
  - Others: 5-HT ANTs, probiotics, antibiotics..

Prevalence of IBS

- 7% -20% prevalence in N. America[1]
  - 12-13% of 1200 Canadians surveyed
- 1.5Xs – 4Xs more likely in women*
- Work absenteeism 20% > non-IBS[1]
- Disproportionate health care and indirect costs[2]

[1]*Brandt, AJG 2009 (1): S8-35* [2]*Thompson, Dig Dis Sci 2002; 47 (1): 225*

Self perceived health and Activity Limitations: IBS vs IBD, Canada

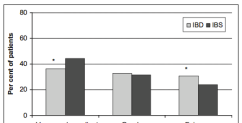


Figure 1) *Self-perceived general health of inflammatory bowel disease (IBD) patients versus irritable bowel syndrome (IBS) patients in a Canadian household population aged 19 years and older, 2005. *IBD estimate differs significantly from that of IBS (P<0.01). Data from the 2005 Canadian Community Health Survey (Statistics Canada)*

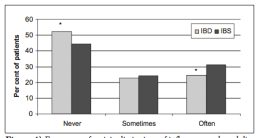


Figure 4) *Frequency of activity limitations of inflammatory bowel disease (IBD) patients versus irritable bowel syndrome (IBS) patients in a Canadian household population aged 19 years and older, 2005. *IBD stimate differs significantly from that of IBS (P<0.01). Data from the 2005 Canadian Community Health Survey (Statistics Canada)*

Tang, Can J Gastro 2008;22(5):475-483.

IBS Definition

- Abdominal pain…that occurs in association with altered bowel habits over a period of at least three months
  - Do not need ROME (I,II, or III) or Manning…
- Individual symptoms not great for predicting → constellation of symptoms
  - Highest sensitivity: lower abdominal pain
  - Highest specificity: abdominal distension

Brandt, Am J Gastro 2009 (1): S8-35

What is the diagnosis?

- 21 yo frequents ER with recurrent post choly chronic abdominal pain, plays "good doc / bad doc" and threatens to sue GI (for assault) after ERCP.
- 29 yo female: 5 years of abd. pain, bloating and constipation. Admitted to hospital: numerous investigations, all negative. Previously 3 anti-depressant trials. Mom has similar, 20 years later dx with CVD and believes "it was CVD all along".
- 44 yo female that sustains 2' burns on abdomen after using hot water bottles for severe abdominal cramping. Wishes for colectomy.

What is the diagnosis?

- 34 yo female: chronic diarrhea, (stops on side of road), nocturnal BMs. One episode painless rectal bleeding.
- 62 yo male: 2 years of urgent, loose BMs, fecal incontinence. Post choly, no better with cholestyramine.
- 47 year old 'biker chick' with chronic abd. pain, intermittent loose stools. Colon normal, ATTG elevated

Colonoscopy on IBS patients

- 466 consecutive IBS-D patients (no alarm sx) had colonoscopy
  - Average age 41 yo, 69% female
- IBS diagnosis changed in 9 / 466 (1.9%) patients
  - 2 IBD cases
  - 7 microscopic colitis
- Microscopic colitis: mean age 49 yo (all > 35 yo) 6/7 females

Chey, Am J Gastro 2010 doi:10.1038/ajg.2010.55

Are they hiding something bad?

Table 3. Prevalence of organic diseases in patients meeting symptom-based criteria for IBS

Organic GI disease	IBS patients (%)	General population (%)
Colitis/IBD[a]	0.51–0.98	0.3–1.2
Colorectal cancer[a]	0–0.51	0–6 (varies with age)
Thyroid dysfunction[b]	4.2	5–9
Gastrointestinal infection[b]	0–1.5	NA
Celiac sprue[b]	3.6	0.7
Lactose maldigestion[b]	38	26

[a]Data from Cash *et al.* (67). [b]Data courtesy of Moayyedi, *et al.* (personal communication, unpublished).

Brandt, Am J Gastro 2009 (1): S8-35
Ford, Arch Intern Med. 2009;169(7):651-658

What investigations?

- Constipation predominant:
  - Inadequate data to recommend routine labs[1,2]
  - CBC, TSH, FBS, +/- calcium
- Diarrhea predominant:
  - ATTG recommended[3,4]
  - CBC, stool O+P: low yield → not recommended[3,4]
    - CRP / ESR: elevated in 3/300 IBS patients → all 3 IBD[5]

[1]*Rao, Am J Gastro 2005;100:1605–1615*
[2]ACG Constipation Task Force, Am J Gastro 2005(100); S1
[3]*Brandt, Am J Gastro 2009 (1): S8-35*
[4]*Cash, Am J Gastro 2002;97:2812*
[5]*Sanders, Lancet* 2001; 358: 1504–08

Do they all need colonoscopy?

- No alarm features*:
  - bleed, nocturnal, weight loss
- No 'new' symptoms in patients < 50 years
  →No endoscopy[1]
- Real life:
  - 25% of US colonoscopies < 50 years for 'IBS'[2]
  - 50% of US IBS patients end up having colon[3]
- If do colon → random bx. for microscopic colitis

1Brandt, Am J Gastro 2009:
2Lieberman, Gastro Endosc 2005;62:875, [3]Talley, Gastro 1995; 109:1736 (Cash Am J Gastro 2002)

Treatment Principles

- All IBS patients are different
- No one treatment for all IBS patients
- Treat predominant GI symptom
- Treat non-GI associated conditions
- Nothing really alters long term outcome of the condition (no DMARDs)

Patient / physician disconnect

- Most bothersome symptoms:
  - Both: pain, bloating
- Etiology:
  - GP: lack of fibre
  - Patient: food intolerance
- Treatment:
  - GPs: dietary advise, counseling
  - Patients: reassurance, meds (and do not appreciate dietary advise)

Bijkerk, Can J Gastro 2003;17(6):363-368

Issues with IBS studies

- High placebo rate[1,2]
- Errors in systematic reviews: missing studies, including studies should have excluded, calculating errors, changes point estimates and NNS results to SS (and vice versa)[3]

[1]Ford, Aliment Pharm Ther 2010; 32: 144
[2]Ladabaum, Clin Gastro Hep 2010;8:42
[3]Ford, Am J Gastro 2010; 105:280–288

High Fibre Diet and IBS Systematic Review 2011

- 12 studies, 621 patients[1]
- No benefit over placebo in:
  - Abdominal pain, global assessment, IBS symptom score
  - No difference soluble vs. insoluble fibre
- Limitations: no primary care studies
- 5 other SRs: two showed benefit
  - Ford 2008[2]: pp analysis, dichotomous outcome
    - ITT and high quality studies → no benefit
    - Sub-group: psyllium benefit
  - Bijkerk 2004[3]: included studies w/o placebo arms, ? errors in outcome measurement

[1]Ruepert, Cochrane 2011 : CD003460, [2]Ford, BMJ 2008;337:a2313
[3]Bijkerk, Aliment Pharm Ther 2004;19:245

Dutch Primary Care Fibre study

- 275 primary care IBS patients
- 94% white, 78% female, 34 years, 56% IBS-C
- RCT: psyllium (10g), bran (10g) or placebo x 12 weeks
- 1' Outcome: Adequate relief of abdo pain in 2/4 preceding weeks
- 40% LTFU at 3/12 (mainly perceived lack of benefit)
  - Bran early droppers (made worse)
- Worst case analysis: (LTFU = not responders)
  - Psyllium > placebo at 1, 2 (but not 3 months)
  - Bran = placebo
- No change in QOL

Bijkerk BMJ 2009; 339:b3154

Fibre and IBS

WHAT IS ALREADY KNOWN ON THIS TOPIC

Increasing dietary fibre (either insoluble or soluble) is almost universally advocated for th treatment of irritable bowel syndrome

No trial has assessed its effects in the primary care setting, where the vast majority of the patients are managed

WHAT THIS STUDY ADDS

The addition of soluble fibre (psyllium) but not insoluble fibre (bran) was effective in the clinical management of patients with irritable bowel syndrome in primary care

The benefit of psyllium may be somewhat greater in patients who fulfil the Rome II criteria Irritable bowel syndrome

Bran may worsen symptoms of irritable bowel syndrome, especially at the beginning of treatment, and should be advised only with caution

page 6 of 7

Elimination Diets

- 60-70% patients: IBS symptoms food related
- 12-60% positive response with elimination diets

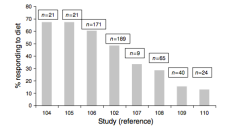


Figure 1. Proportion of irritable bowel syndrome (IBS) patients responding to exclusion diets.

Brandt Am J Gastro 2009

Elimination vs 'sham' elimination diet

- 150 IBS patients: UK, X age 44, dx 10 years, 80% female
- Food allergy testing, then randomized:
  - Elimination: remove foods allergy testing identified
  - Sham: removed same # of foods (but not the ones they tested +'ve for)
- IBS symptom scores improved 39 points
  - 50 points MCID
- No difference: 'significant improvement', QOL scores, anxiety, depression
- Many per protocol analysis
- Conclusion: "food elimination diets may be effective"

Atkinson, Gut 2004;53:1459–1464

Elimination Diets

Low FODMAPs diet

(Fermentable Oligo- Di- and Mono-saccharides And Polyols)

- ? Low FODMAP diet ↓ GI symptoms in IBS patients
- ? 2 ' to fructose malabsorption (low fructose, sorbitol)
- Limitations of studies:
  - Most from one site[1,2]
  - short in length[1] (one had 2 days on diets)
  - small numbers[1,2,3]
  - patients 'run in' (responded to low FODMAP → put back on high FODMAP and did worse)[2]
  - observational[3]

[1]*Ong, Journal of Gastro and Hepat 2010; 25: 1366*
[2]Shepherd, Clin Gastro Hepatol 2008;6:765
[3]*Staudacher, J Hum Nutr Diet 2011;24: 487*

FODMAP diet

Table 1 Food sources of FODMAPs (where FODMAPs are problematic based on standard serving size) and suitable alternatives

FODMAP	Excess fructose	Lactose	Oligosaccharides (fructans and/or galactans)	Polyols
Problem high FODMAP food source	*Fruits*: apples, pears, nashi pears, clingstone peaches, mango, sugar snap peas, watermelon, tinned fruit in natural juice *Honey* *Sweeteners*: fructose, high fructose corn syrup *Large total fructose dose*: concentrated fruit sources; large serves of fruit, dried fruit, fruit juice	*Milk*: cow, goat and sheep (regular & low-fat), ice cream *Yoghurt* (regular & low-fat) *Cheeses*: soft & fresh (e.g. ricotta, cottage)	*Vegetables*: artichokes, asparagus, beetroot, Brussels sprout, broccoli, cabbage, fennel, garlic, leeks, okra, onions, peas, shallots. *Cereals*: wheat & rye when eaten in large amounts (e.g. bread, pasta, couscous, crackers, biscuits) *Legumes*: chickpeas, lentils, red kidney beans, baked beans *Fruits*: watermelon, custard apple, white peaches, rambutan, persimmon	*Fruits*: apples, apricots, cherries, longon, lychee, nashi pears, nectarine, pears, peaches, plums, prunes, watermelon *Vegetables*: avocado, cauliflower, mushrooms, snow peas *Sweeteners*: sorbitol(420), mannitol(421), xylitol(967), maltitol (965), isomalt (953) & others ending in "-ol"
Suitable alternative low-FODMAP food source	*Fruit*: banana, blueberry, carambola, durian, grapefruit, grape, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, paw paw, raspberry, rockmelon, strawberry, tangelo. *Honey substitutes*: maple syrup, golden syrup *Sweeteners*: any except polyols	*Milk*: lactose-free, rice milk *Cheese*: 'hard' cheeses including brie, camembert *Yoghurt*: lactose-free *Ice cream substitutes*: gelati, sorbet *Butter*	*Vegetables*: bamboo shoots, bok choy, carrot, celery, capsicum, choko, choy sum, corn, eggplant, green beans, lettuce, chives, parsnip, pumpkin, silverbeet, spring onion (green only), tomato *Onion/garlic substitutes*: garlic-infused oil *Cereals*: gluten-free & spelt bread/cereal products	*Fruits*: banana, blueberry, carambola, durian, grapefruit, grape, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, paw paw, raspberry, rockmelon *Sweeteners*: sugar (sucrose), glucose, other artificial sweeteners not ending in "-ol"

Exercise and IBS RCT Sweden

- 102 IBS patients (all subtypes): 79% women, 39 yo
  - Exercise: physical activity advice 2xs / month (PT) with diary and cycling test at 6 weeks
  - Control: maintain current lifestyle, call from PT q 1/12
- Outcomes at 12 weeks:
  - 1' IBS-SSS change: PA ↓ 51 points (pp) (SS) and 37 points (mod ITT)*
  - 2' IBS QOL: sleep, energy, fatigue, physical function improved (PP), physical function (ITT)
  - SF-36, Depression scale: no change
- Gut physiologist review of the paper:
  - "Begs the question about how it works"

Johannesson, Am J Gastro 2011; 106:915
Chey, Gastro 2011; 5: 1941

Anti-spasmodics

- Compared to placebo, antispasmodics improve[1]:
  - Abdo pain: 58% vs 46% placebo (NNT = 8)
  - Global assessment: 57% vs 39% (NNT = 5)
  - Symptom score: 37% vs 22% (NNT 7)
- Meds that work: dicyclomine (Bentyl) peppermint oil, pinaverium (Dicetel), trimebutine
- Earlier SR: otilonium, hyoscine, peppermint work[2]
- Nothing from primary care

[1]*Ruepert, Cochrane 2011, Issue 8. Art. No.: CD003460*
[2]*Ford, BMJ 2008;337:a2313*
[3]*Brandt, AM J Gastro 2009*

Peppermint Oil

- 4 placebo controlled RCTs, 392 patients,
- 1 trial reported IBS subtype (IBS-D 75%)
- Quality: ¾ studies 4 weeks, no N. Am.
- Persistent IBS symptoms:
  - 52/197 (26%) peppermint vs 127 / 195 (65%) placebo
  - NNT = 2.5

[1]*Ruepert, Cochrane 2011,CD003460* [2]*Ford,* BMJ 2008;337:a2313

Anti-depressants

- Compared to placebo, anti-Ds improve:
  - Abdo pain: 54% vs 37% placebo (NNT = 6)
  - Global assessment: 59% vs 39% (NNT = 5)
  - IBS symptom score: 53% vs 26% (NNT 4)
- SSRIs: improve global assessment
- TCAs: improve abdo pain, global asessment and symptom score

Ruepert, Cochrane 2011, Issue 8. Art. No.: CD003460.
Brandt, Am J Gastro 2009

Anti-depressants

- SSRIs: ? Better for IBS –C
- TCAs: ? Better for IBS-D
- "No head to head trials of SSRI, TCAs"


VOLUME 104 SUPPLEMENT 1 JANUARY 2009 nature publishing group

An Evidence-Based Systematic Review on the Management of Irritable Bowel Syndrome

American College of Gastroenterology IBS Task Force:
Lawrence J. Brandt, MD, MACG, Chair[1], William D. Chey, MD, FACG[2], Amy E. Foxx-Orenstein, DO, FACG[3], Eamonn M.M. Quigley, MD, FACG[4], Lawrence R. Schiller, MD, FACG[5], Philip S. Schoenfeld, MD, FACG[6], Brennan M. Spiegel, MD, FACG[7], Nicholas J. Talley, MD, PhD, FACG[8] with Paul Moayyedi, Epidemiologist-Statistician, BSc, MB ChB, PhD, MPH, FRCP (London), FRCPC, FACG[9]

RCT: TCA vs SSRI vs Placebo

- 51 IBS patients with IBS (mostly IBS-D)
  - Excluded if on anti-Ds
- Imipramine 50 mg, citalopram 40 mg, or placebo x 12 weeks
- 1' outcomes: adequate pain relief in week prior
  - Imipramine 100%, citalopram 69%, placebo 69%
- Appears beneficial in abd pain, depression, disability, QOL
- Problems: ↓ recruitment ("anti-Ds, but I'm not depressed"), no multiple comparison adjustment, ↑LTFU (? LOCF)
- Conclusion: "Neither imipramine nor citalopram significantly improved global IBS endpoints over placebo".

Talley, Dig Dis Sci 2008; 53:108

Probiotics and IBS

- May be beneficial as add on therapy
- Probiotics differ → difficult to analyze all types and generalize about benefit[1]
- SR 2010 Gut: dichotomized outcomes[2]
  - RR 0.71 (0.57, 0.88)
  - NNT = 4
  - Significant heterogeneity, ? Publication bias

[1]Brant Am J. Gastro 2009 [2]Moayyedi, Gut 2010;59:325e332

Additional Therapies

- Alostron (Lotronex): 5-HT3 Ant
  - Ischemic colitis → removed
- Tegaserod (Zelnorm): 5-HT4 Ant
  - Cardiac → removed
- Additional therapies: Lubiprostone (IBS-C), Rifaximin, accupuncture, CBT

What is needed

- "High quality, larger, RCT, primary care trials[1]" OR
- "Try something reasonable and let your patients tell you if it works (n of 1 trials)"[2]

[1]Ford, Evidence-Based Medicine 2012. doi:10.1136

[2]Kolber, DTC 2012, personal communication

Summary

- Common disease with ↓ QOL, burden
- Make positive diagnosis with limited tests
  - Rule out celiac, +/- microscopic colitis
- Every patient is different: IBS-D ≠ IBS-C
  - Treat predominate symptoms (GI and non GI)
  - Use what works for them
- Exercise
- Hold off newer agents (or let your partners try and see how it goes)

Thank you

- mkolber@ualberta.ca

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) typically encompasses two major disease processes; ulcerative colitis (UC) and Crohn's disease (CD). Although in theory many other immune mediated inflammatory disorders may affect the gastrointestinal tract (celiac disease, ulcerative jejunoilieitis, microscopic colitis) when we use the term IBD most discussions are centering around either UC or CD. The two diseases are distinctly different, likely with different etiologies but with some similarities in their phenotypic presentation and management.

Ulcerative colitis affects only the colon. In theory, since the colon can be removed as a treatment option- it can be cured. However, the benefits of the 'cure' have other quality of life issues that may in fact counterbalance the perceived benefit of the colitis being cured. Ulcerative colitis usually presents with bloody diarrhea. The disorder is usually classified as mild, moderate or severe depending on the clinical presentation (i.e. weight loss, frequency of bowel movements, nocturnal symptoms, anemia). The disorder is also classed depending on extent of bowel involved – rectum (proctitis), left sided (as more amenable to topical therapies) or pancolitis.

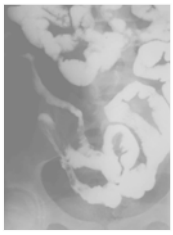
Therapy of UC depends on the extent and severity of disease. Topical therapies are usually considered early in the course for left sided disease and include 5-ASA enemas and/or steroid enemas. Oral 5-ASA therapies are used for mild-moderate disease. Immunosuppressive agents (azathioprine) and anti-TNF agents are usually reserved for patients with moderate to severe disease (par;ticularly those who have been oral steroid requiring). Hospitalized patients are treated with intravenous corticosteroids and if an adequate response is not seen in 3-5 days anti- TNF agents.

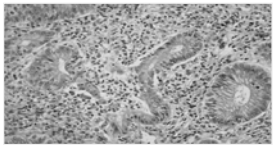
Crohn's disease typically affects the terminal ileum but can affect all areas of the GI tract from the mouth to the anus. The severity of disease can be measured using clinical (weight loss, diarrhea frequency) and laboratory (albumin, Hb, CRP) parameters. The presenting symptoms usually are affected by which portion of the bowel is affected (i.e. if isolated colonic disease diarrhea predominates, if perianal fistulous disease drainage may be a significant issue, if ileal stenosis is significant then obstructive symptoms occur).

The management of CD has dramatically changed. Oral 5-ASA therapies are not usually considered effective therapy. For perianal disease oral antibiotic therapy and immunosuppressive agents are used combined with surgery. For ilealcolonic disease immunosuppressive therapies such as azathioprine, methotrexate and anti-TNF agents are typically used. A trend towards early and aggressive immunosuppression- particularly in those with high risk disease has been demonstrated to be more effective. The use of regular corticosteroids is strongly discouraged. These patients need to be managed through Gastroenterologists comfortable with aggressive treatment paradigms.

Because immunosuppression is such a common therapeutic management strategy that requires a great deal of counseling and discussion many other primary care issues are often neglected. These include regular vaccinations (including influenza and pneumococcal), regular pap smears (increased proliferation of HPV), skin evaluation (slightly increased risk of BCC and SCC) and bone densitometry (CD is an independent risk factor for osteoporosis). These issues are best managed in primary care and should be addressed in all patients with IBD.

Rob Enns





Inflammatory Bowel Disease

Robert A. Enns MD, FRCP
Clinical Professor of Medicine
Department of Medicine, St. Paul's Hospital, UBC

Outline

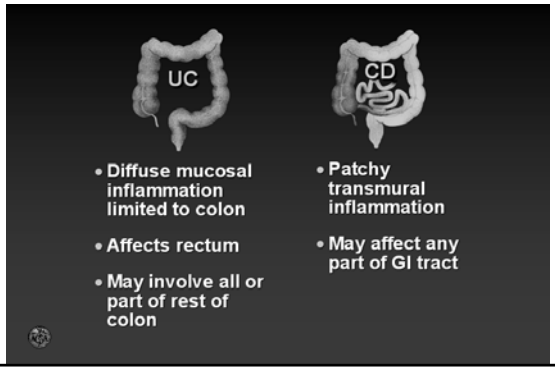
- IBD- What is it?
- What are the possible etiologies?
- What are the available therapies?
- What are the issues with biologics?
- Endoscopic issues

Characteristics of UC and CD

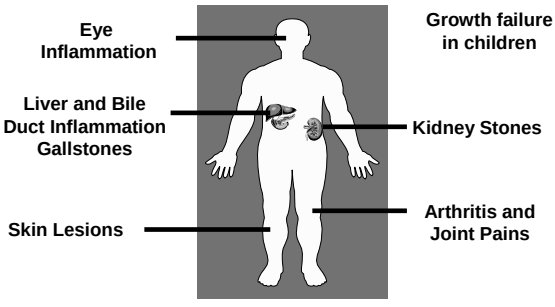
	UC	CD
Location	Colon	Entire GI tract
Extent of inflammation	Mucosal and submucosal	Transmural
Peak age of onset (years)	15–25	15–25
Prevalence (per 100,000)	35–100	10–100
Surgery/ resection	Curative	Not curative

Stenson WF. In: *Textbook of Gastroenterology*. 2nd Ed. 1995:1748-1805.

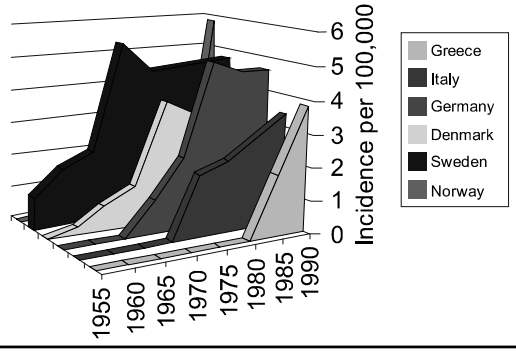
What is Crohn's Disease



Systemic Complications of IBD



Rising Incidence of CD



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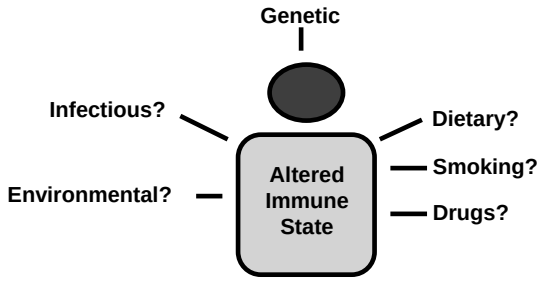
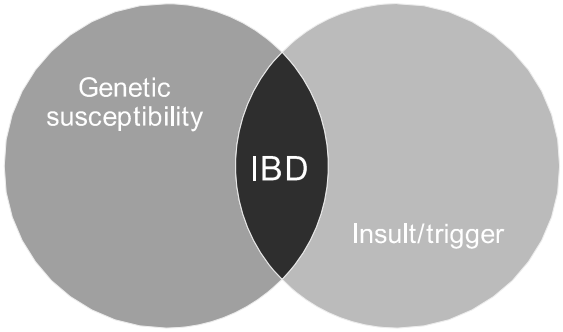
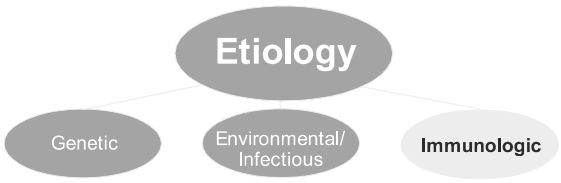
Proposed Etiological Factors



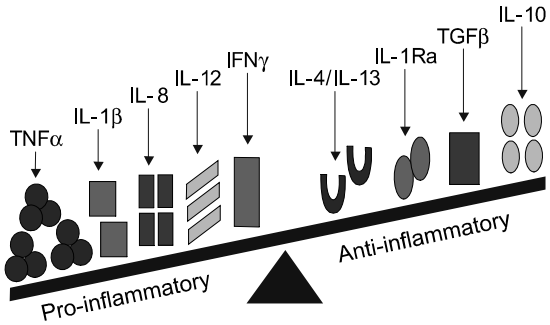
Development of IBD



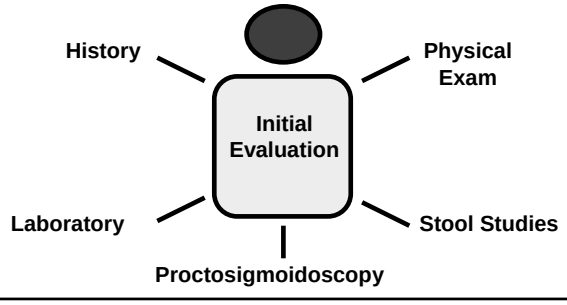
Current Etiologic Theories of IBD



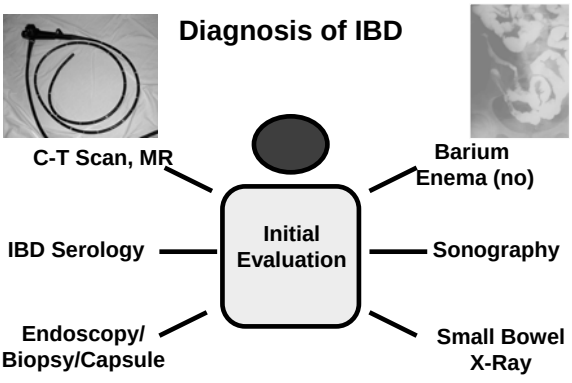
Chronic Inflammation: Imbalance Between Mediators



Diagnosis of IBD



Diagnosis of IBD



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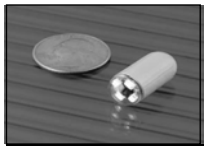
Capsule Endoscopy/PillCam



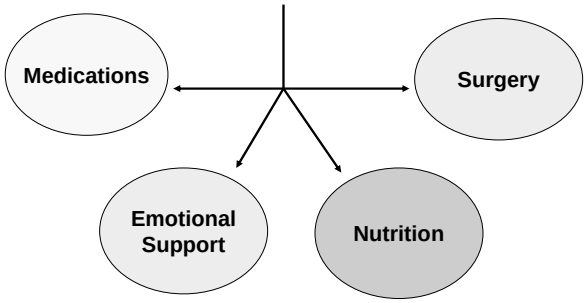
What are Treatment options for Crohn's Disease

- Clearly Depends on what area of the bowel is affected
- UGI
  - Stomach/esophagus: acid suppression
- Perianal
  - Antibiotics/sitz baths

Goals of Therapy

- Inducing remission
- Maintaining remission
- Healing mucosa
- Restore and maintain nutrition
- Maintain quality of life
- For those requiring surgery, select optimal timing for surgical intervention

Treatment of IBD



What Treatment options are Available For CD?

- Symptomatic therapy
  - Agents for diarrhea
    - i.e. codeine, imodium, other binders
  - Agents for pain control
    - Anti-inflammatories, tylenol, narcotics
  - Agents more specific for CD

Crohn's Disease Activity Index: Variables

- Number of liquid or very soft stools during the previous week
- Severity of abdominal pain/cramping
- General well-being
- Extraintestinal manifestations
- Presence of abdominal mass
- Use of antidiarrheal drug therapy
- Hematocrit
- Body weight

Best WR et al. *Gastroenterology.* 1976;70:439-444.

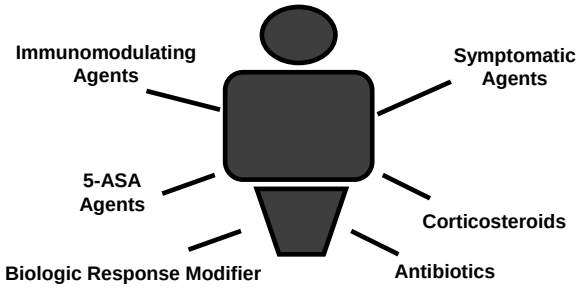
Rob Enns

Crohn's Disease Activity Index

- Scoring
  - Maximum score 600
  - Remission < 150
  - Moderate activity 200 – 450
  - Severe activity > 450

Best WR et al. *Gastroenterology.* 1976;70:439-444.

Drug Therapy

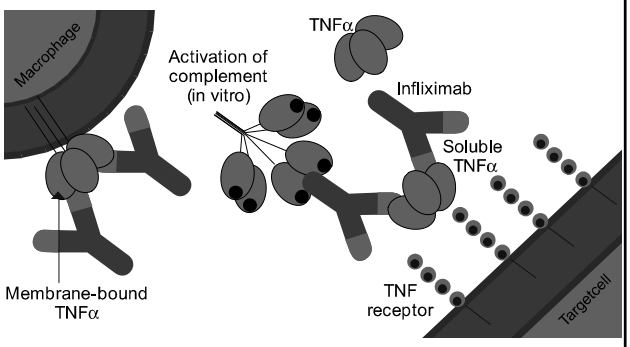


Long-term Maintenance of Remission in CD

Oral aminosalicylates	±
Topical aminosalicylates	–
Systemic corticosteroids	–
Corticosteroids with low systemic bioavailability (budesonide)	+
Immunosuppressants	
Cyclosporine	–
Methotrexate	+
Azathioprine/6-mercaptopurine	+++
Biologics	+++

±, questionable; +, weak; ++, moderate; +++, strong; –, none.

Infliximab Mechanism of Action



Conclusions With Anti- TNF

- Anti-TNFs rapidly reduced signs and symptoms of Crohn's disease
  - 2/3 demonstrated a clinical response
  - 1/3 achieved clinical remission
- Clinical benefit associated with mucosal healing
- Consistent benefit in all patient subgroups
- 5 mg/kg infusion produced a high degree of benefit lasting at least 8 weeks for induction and long term

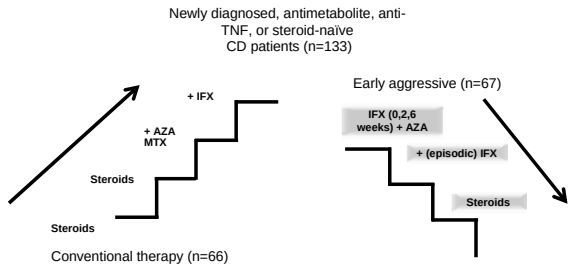
Predictors of a Bad Course of Disease: Colectomy

- **Strong predictors**
  - **Steroid use**
  - **Hospitalisations**
  - **Mucosal lesions**
  - **Undetectable IFX**
  - **"noisy" pts**
- **"a trend towards value"**
  - **Inflammation; CRP levels**
- **Contradictory evidence**
  - **Disease location**
  - **Disease duration**

IFX has proven efficacy despite any predictor

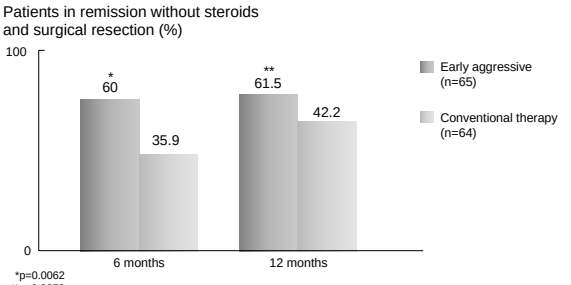
Rob Enns

Early Aggressive Biologic Therapy *vs.* Conventional Management of Crohn's Disease



D'Haens *et al. Lancet* 2008;371:660

Early Aggressive Biologic Therapy *vs. C*onventional Management of Crohn's Disease



*p=0.0062
**p=0.0278

D'Haens *et al. Lancet* 2008:371:660

Safety Data From the TREAT Registry

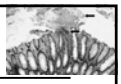
Cox proportional hazard regression (multivariate)

Adverse event	Hazard ratio	95% CI
Death		
Current use of IFX	1.1	0.6–1.8
Current use of AZA/6-MP/MTX	0.8	0.5–1.2
Current use of GCS	2.0	1.3–3.0*
Current use of narcotic analgesics	2.1	1.3–3.2†
Serious infection		
Current use of IFX	1.4	1.0–2.1
Current use of AZA/6-MP/MTX	0.9	0.6–1.3
Current use of GCS	2.0	1.4–2.9**
Current use of narcotic analgesics	2.2	1.5–3.1†

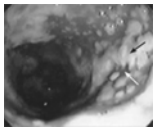
*p=0.002; **p<0.001; †p<0.0001
6-MP = 6-mercaptopurine; AZA = azathioprine; CI = confidence interval; GCS = glucocorticoid steroids; IFX = infliximab; MTX = methotrexate

Lichtenstein *et al. Gastroenterology* 2006;130:A-71
Lichtenstein *et al. Gastroenterology* 2007;132: A-178

C. difficile Complicating IBD



- **3 fold increase in *C. difficile* infection rates 2004-2005[1]**
- **Majority contacted infection as outpatients, 61% antibiotic exposed[1]**
- **Immunosuppressives and colonic involvement were independent risk factors[1]**
- **Infected hospitalized patients four times greater mortality[2]**
- **Burden of illness greater in UC than CD[2]**



"Treat Empirically for CD in Acutely ill!"

1. Issa M, *et al*. Impact of Clostridium difficile on inflammatory bowel disease. *Clinical Gastroenterology and Hepatology* 2007;5(3):345-51
2. Ananthakrishnan AN, *et al*. Excess hospitalisation burden associated with *Clostridium difficile* in patients with inflammatory bowel disease. *Gut* 2008;57(2):205-10

Poor prognostic factors for Crohn's disease patients-Selecting Pts

Disease location and behaviour

- **Extensive small bowel disease[1]**
- **Severe upper gastro-intestinal disease[1-4]**
- **Rectal disease[3]**
- **Perianal lesions[5,6]**
- **Early stricturing / penetrating disease[1,2,6]**
- **Deep ulcers[7]**

Risk factors

- **Smoking[1]**
- **Young age at diagnosis[1,2]**
- **Genetic and serological profile (to identify patients at risk in the future?)**

1. Louis E, *et al. Gut* 2003;52:552–7; 2. Romberg MJ, *et al. Am J Gastroenterol* 2009;104:371–83; 3. Henckaerts L, *et al. Clin Gastroenterol Hepatol* 2009;7:972–80; 4. Chow D, *et al. Inflamm Bowel Dis* 2009;15:551–7; 5. Hellers G, *et al. Gut* 1980;21:525–7; 6. Beaugerie L, *et al. Gastroenterol* 2006;130:650–6; 7. Allez M, *et al. Am J Gastroenterol* 2002;97:947–53

What is an individual's risk?

- **Rectal disease**
  - **92% risk of perianal lesions over disease course[1]**
- **Ileal Crohn's disease**
  - **38% risk of surgery over 10 years[2]**
- **Stricturing or penetrating complications**
  - **Associated with ileal and perianal disease[3]**
  - **82% risk of surgery within 6 months of developing complications[3]**
- **Deep colonic ulcer**
  - **62% risk of colectomy over 8 years[4]**

1. Hellers G, *et al. Gut* 1980;21:525–7; 2. Solberg IC, *et al. Clin Gastroenterol Hepatol* 2007;5:1430–8; 3. Thia KT, *et al. Gastroenterol* 2010;139:1147–55; 4. Allez M, *et al. Am J Gastroenterol* 2002;97:947–53

Concepts about Vaccination

- **Inactivated vaccines may be given e.g. adjuvanted pH1N1.**
- **Live vaccines must be avoided.**
- **Toxoids may be given.**
- **Responses may be attenuated.**
- **Permissible vaccines:**
  - **Influenza**
  - **Pnemococcal vaccine**
  - **Tetanus**
  - **etc.**

H. Pylori Update
Is 4 better than 3?

Mike Kolber BSc, MD, CCFP, MSc
DTC April 2012

Hp Objectives

- Background, associated illnesses
- Testing for Hp
- Treatment options
  - Triple Therapy (TT)
  - Quadruple Therapy (QT)
  - Sequential Therapy
- What if your first line fails?

H. Pylori: Background

- 20-30% of Canadians[1]
- Higher in:
  - Developing countries (China, India, Pakistan) 70-90% [2]
  - Canadian First Nations / Inuit 55-95%[1,4]
- Contracted first few years of life
- Transmitted fecal-oral
  - Risk factors: ↓SE status (at childhood), crowding, poor sanitation

[1]Jones, Can J Gastro 2012; 97, [2]Braden, BMJ 2012;344:e828
Mccoll, NEJM 2010;362:1597 [4]Bernstein, Dig Dis Sci 1999; 4:668

Hp Associated Illnesses

- Peptic ulcer disease
- Gastric Cancer
- Dyspepsia
- MALT Lymphoma

Peptic Ulcer Disease and Hp

- 10% of Hp + patients → PUD[1]
- 90% duodenal ulcer, 70% gastric ulcer HP +
- OR of PUD in Hp + vs Hp - = 4[2]

[1]Ford, Cochrane 2006, CD003840,
[2]Papatheodoridis, Clin Gastro Hepatol 2006; 4:130

NSAIDs, Hp and PUD
Synergistic Effect

- PUD[1,2]
  - Hp + / Hp - OR = 2-4
  - NSAID + / NSAID - OR = 3-5
  - Hp + PLUS NSAID + / Hp – PLUS NSAID - OR = 17-19

- Eradicating Hp prior to LT NSAIDs ↓ PUD
  - In those with dyspepsia or previous UGI bleed[3]
    - 10% (Erad + PPI) vs 31% (PPI), ARR = 19%, NNT = 5

[1]Papatheodoridis, Clin Gastro Hepatol 2006; 4:130
[2]Huang, Lancet 2002; 359: 14, [3]Chan, Lancet 2002; 359: 9

Gastric Cancer and Hp

- 1% patients HP + → gastric cancer[3]
- #2 worldwide cancer death, # 9 Canada[1]
- SR: Eradicating Hp → ↓ gastric cancer rates[4]
  - 1.7% to 1.1% (ARR = 0.6, NNT = 167)
    - 0.65 (0.43, 0.98) p = 0.04
  - Calculation error → 0.65 (0.42, 1.01) p = 0.05

  → benefit but NSS[5]

[1]*Canadian Cancer Stats 2011*
[3] *Ford, Best Pract Research Clin Gastro 2011; 25: 581*
[4]*Fuccio, Ann Intern Med. 2009;151:121*
[5]*Ford, Ann Int Med 2009; 151: 513*

Dyspepsia and Hp Eradication: Cadet-HP study

- 294 CAN patients > 18 yo uninvestigated dyspepsia
- RCT: TT (PMC) or PPI + placebo for 7 days
  - After 7 days, GP determined treatment (not mentioned)
- Outcome: % no / minimal symptoms at 1 year
  - Likert scale 1-2/7
- TT 50% vs PPI 36% (ARR = 14%, NNT = 7)
  - Persisting Hp had ↑ symptoms
- 90% had overlapping symptoms: 'ulcer like', 'GERD like' and 'dysmotility like'

Chiba, BMJ 2002;324:1012

Dyspepsia and Hp Eradication: Brazil 2012

- 404 patients with dyspepsia
- Gastroscopy = gastritis, duodenitis (other endo diagnosis excluded)
  - RCT Triple therapy (TT) or Omeprazole + placebo x 10 days
- Outcomes:
  - 50% ↓ symptoms: 49% (TT) vs 36.5%, NNT = 8
  - Global improvement: 78% vs 65%, NNT = 8
  - Complete symptom relief 18% vs 14% (NSS)
- HP +'ve who received placebo → 3% PUD

Mazzoleni, Arch Intern Med. 2011;171:1929

Dyspepsia Hp eradication vs. PPI therapy

- SR of 3 trials, 1547 patients, mean age 42 yo
  - All 3 primary care (UK Denmark)
  - Did not include CADET-Hp study?
- Dichotomized symptoms (pain, nausea, GERD)
  - If any symptom present → classified as having symptoms
- Any symptoms at 1 year: 83% TT, 84% PPI
  - No difference (go figure)!

Ford, Aliment Pharm Ther 2008; 28: 534

Who should be checked for Hp?

- Dyspepsia
- Documented PUD, gastric cancer, MALT lymphoma
- Long term NSAID users[4]
- Family history of gastric cancer[3,4]
- Iron deficiency anemia, chronic ITP[3]

[2]Chey, Am J Gastro 2007;102:1808, [3]Gut 2007;56:772 [4]Hunt, Can J Gastro 2004; 18:547

Diagnosing Hp

- Urea Breath Test
  - < 50 years old and no alarm symptoms
- Gastroscopy and biopsy
  - > 50 years old or new or alarm symptoms
- Stool antigen: (not another stool test!)
- Blood: IGG previous (not current) infection

Urea Breath test
Instructions Dynacare Oct. 2010

- Antibiotics: none x 4 weeks
- Bismuth: none x 2 weeks
- **PPI: none x 3 days**
- **H2ANT: none x 1 day**

Hp therapy options

- Triple (TT): 7, 10, 14 days
  - PAC: PPI, amoxil, clarithro
  - PMC: PPI, metronidazole, clarithro
- Quadruple (QT)
  - PPI bid+ metro 500 mg tid + tetra 500mg qid + bismuth subcitrate 120 mg qid x 10 -14 days
- Sequential (ST)
  - PPI + amoxil 1 gr bid x 5 days, THEN PPI + clarithro 500 mg + metro bid x 5 days
- Concomitant: amoxil 1 g, clarithro 500 mg, metronidazole 500 mg + PPI bid for 10–14 days
- Hybrid: sequential (2 drugs), then concomitant (4 drugs)

Graham, CMAJ 2011;183(9): 506

Canadian patient Hp Eradication Rates

- 17 trials involving Canadian patients
  - differing treatment lengths
- Eradication Rates:
  - Standard TT (PAC): 84% (79-90)
  - TT (PMC): 82% (76-88)
  - QT: 87% (80-95)
    - no stats re: different or not
- Adherence (> 75% of meds taken)
  - 91-94% QT ~ TT

Rogers, Can J. Gastro 2007; 21(5): 295

Hp Resistance in Canada

- Clarithromycin resistance: important in treatment failures[2,3]
  - Avoid Clarithromycin if resistance rates > 20%
  - Resistance rates ↑ with ↑ macrolide usage[3]
- Largely unknown as sensitivities not normally run
- Previously not problem, but no recent data[1]
- Metronidazole: in vitro resistance ≠ in vivo[3]

[1]Can J Gastro 2000;14(10):879 [2]Fuccio, BMJ 2008;337:a1454
[3]Malfertheiner, Gut 2007;56:772–781

Triple Therapy Treatment Length
Slightly Longer = Slightly Better?

- Triple Therapy Eradication rates[1]:
  - 7 days (77%) vs 10 days (81%)
  - 7 days (73%) vs 14 days (78%)
- Higher quality studies: NSS difference

- Hp Guidelines:
  - American[2]: 14 days
  - European[3]: 7 -14 days
  - Canadian[4]: 7-10 days

[1]*Ann Intern Med. 2007;147:553,*
[2]Chey, Am J Gastro 2007;102:1808, [3]Gut 2007;56:772,[4]Hunt, Can J Gastro 2004; 18:547

QT vs. TT
Systematic Review

- QT: PPI bid+ metronidazole 500 tid + tetracycline 500mg qid + bismuth subcitrate 120 mg qid
- TT: standard PAC
- 9 RCTs (1700 patients)[1]
  - Overall eradication rates: 77% TT / 78% QT
  - No difference across geography, length of tx.
  - No difference in AE rates, compliance
- N American study: 83% vs 88% (NSS)[2]

[1] Luther, Am J Gastroenterol 2010;105:65
[2] Laine, Am J Gastroenterol 2003;98:562

10 day QT vs 7 day TT

- Non- inferiority study (per protocol analysis)
- Quadruple tx PPI + 3 in 1 pill (metro, tetra, bismuth)
  - Erad rate superior (93%) to triple (68%)
  - ARR 25% NNT = 4
  - Adverse events similar between groups
- Industry funded: Canadian, no Canadian patients
- Justified 7 vs 10 day therapy:
  - 7 day quad tx has not been tested
  - 7 vs 10 vs 14 day tx not stat significant

Malfertheiner, Lancet 2011; 377: 905

Problems with Quad therapy

- Bismuth subcitrate not commercially available
- More complex → less adherence?
  - Not according to previous research[1,2]
  - In 'real life' could be different

[1] Luther, Am J Gastroenterol 2010;105:65
[2]Rogers, Can J. Gastro 2007; 21(5): 295

Sequential therapy (ST)

- PPI + amoxil 1 gr bid x 5 days, THEN
  PPI + clarith 500 mg + metro 500 bid x 5 days
- SR of 10 studies (including 1 pediatric)
- Eradication rates (93% ST vs 77% TT)
- Italian studies with some US patients

Ann Intern Med. 2008;148:923

Sequential Therapy University of Alberta

- Retrospective study 177 Hp +'ve patients
- Eradication rate: 60% 1st attempt (mostly TT(PAC))
  - TT (PAC)= 55% (51/93) 1st line, 52 % total
  - ST = 89% (24/27) 1st , 87% total
  - QT = 100% (3/3) 1st, 72% total
- Limitations: single GI, tertiary care, not RCT, small numbers

Pinchbeck, van Zanten, CDDW 2012

How to choose Hp treatment

- Avoid macrolide if previously used
- Local resistance rates:
  - Clarithro resistance determines resistance
- Compliance:
  - QT vs TT?
- Cost:

Hp eradication in 2012

- 1st line
  - TT (PAC or PMC): 7-14 days
  - QT: 10 days*
- Second line
  - TT with different antibiotic
  - Sequential
  - Quadruple

Ensure Eradication

- H. pylori +'ve PUD
- Recurrent functional dyspepsia
- MALT lymphoma
- Resected gastric cancer

Fuccio, BMJ 2008;337:a1454 , Gut 2007;56:772

Summary

- Current evidence: Canadians:
  - Standard TT still likely reasonable, but resistance likely increasing
  - QT: difficult getting bismuth subcitrate
  - Sequential: await further RCTs in N. America
- If fail 1st line: use different antibiotics
- Confirm eradication: PUD, gastric cancer

Thank you!

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New treatments for Hepatitis C: Are they worth the costs?

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April 20, 2012

Disclosure

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

Outline

* Test your knowledge
* Hepatitis background
* Efficacy of protease inhibitors
* Safety issues
* CDR recommendation
* Questions

What is the prevalence of Hepatitis C Infections in Canada?

A. <0.5%
B. 0.5-1%
C. 2%
D. π % (3.1415…)
E. 5%

What percentage of those infected with Hepatitis C will spontaneously clear the virus?

A. 2-5%
B. 10%
C. 25%
D. 50%

What percentage of treatment naïve patients receiving Boceprevir or Teleprevir (+ Interferon & Ribavirin) get a sustained virologic response ?

A. 25%
B. 40%
C. 50%
D. 70%
E. 90%

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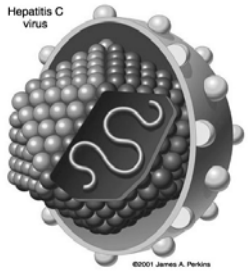
Hepatitis Background

- Hepatitis C can be a serious and potentially life---threatening liver disease
- About 250,000 Canadians (<1% of the population; Remis 2007; Sherman 2007). In 2007, the annual incidence of Hepatitis C viral infections was ~ 7,000, (most from injection drug use)
- World wide prevalence rates are 2-3%
- Of those infected:
  - **~ 25% spontaneously clear the infection** (range 15% to 45%)
  - ~ 15-25% develop significant liver disease (esophageal bleeding, ascites, and encephalopathy)
- Risk factors for disease progression: Males, ethanol use, HIV co-infection, obesity and increasing age
- CHC is a leading cause of chronic liver disease and transplants

HCV Basics



•http://people.rit.edu/japfaa/infectious.html

- ☐ HCV has surface proteins that recognize the liver
- ☐ HCV has an icosohedral core (like HIV)
- ☐ HCV contains single-stranded positive RNA.(hence, similar to mRNA & host cell can immediately create protein via translation)

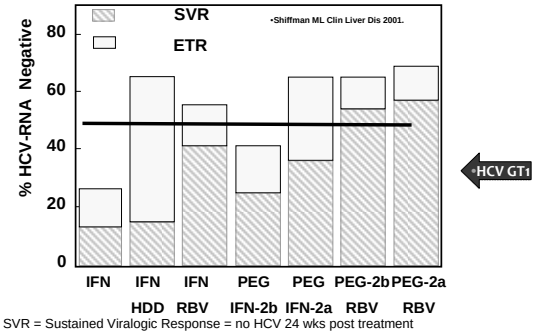
Hepatitis Background

- Six Chronic Hepatitis C (CHC) genotypes
- Genotype 1 (G1) is most frequent (55 - 65%) and least responsive to therapy
- The gold standard treatment for CHC G1 is a 48 week course of PEGylated interferon (PEG IFN) with ribavirin (RBV)
  - Difficult to adhere to this treatment course
- Adverse effects associated with PEG INF + RBV:
  - anemia, sleep loss, depression, mood swings, joint pain, rashes, skin sores, hair loss, headaches, chills, nausea, severe fatigue and weight loss (Ghany, 2009)

Interferons and Ribavirin

- Interferons (IFN) are glycoproteins which stimulate the immune system
- PEG INF-α has improved pharmacokinetics (solubility & T1/2) and is a core treatment for CHC G1
- Ribavirin is a prodrug resembling RNA nucleotides
  - MoA of ribavirin is unknown – believed to interfere with viral RNA production and thereby prevents HCV replication

Efficacy of IFN-based therapy



SVR = Sustained Viralogic Response = no HCV 24 wks post treatment

ETR = Early Treatment Response

Term	Definition
Rapid virological response (RVR)	HCV RNA negative at treatment week 4 by a sensitive PCR based quantitative assay with a lower limit of detection of 50 IU/mL.
Extended rapid virologic response (ERVR)	HCV RNA negative at treatment weeks 4 and 12 (definition as per ADVANCE trial (telaprevir)).
Early virological response (EVR)	≥ 2 log reduction in HCV RNA level compared to baseline HCV RNA level (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR).
End-of-treatment response (ETR)	HCV RNA negative by a sensitive test at the end of 24 or 48 weeks of treatment.
Sustained virological response (SVR)	HCV RNA negative for 24 weeks after cessation of treatment
Virological breakthrough	Reappearance of HCV RNA in serum while still on therapy. Achievement of an undetectable HCV RNA and subsequent occurrence of an HCV RNA level greater than 1000 IU/mL (definition as per SPRINT-2 trial (boceprevir)).
Relapse	Reappearance of HCV RNA in serum after therapy is discontinued
Nonresponder	Failure to clear HCV RNA from serum after 24 weeks therapy
Null responder	Failure to decrease HCV RNA by at least 2 logs after 2 week of therapy
Partial responder	Two log decrease in HCV RNA but still HCV RNA positive at week 24

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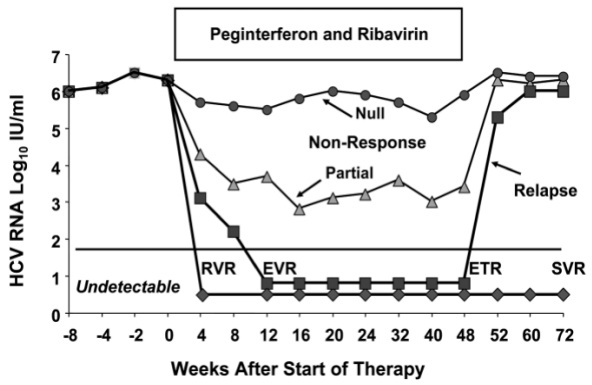


SVR Rates with PEG INF + RBV

* Treatment Naïve: **30-50%**
* Rates are lower for
  * treatment failures
  * African Americans
  * advanced fibrosis and cirrhosis
* Re-treatment with PEG-INF + RBV of prior treatment failure patients has poor SVR rates (e.g., 10% or less for prior non-responders, and 20---30% range for prior relapsers)

Ponyard, 2009; Jensen, 2009; Bacon, 2009

Telaprevir and Boceprevir

* Protease inhibitors that reversibly bind to nonstructural (NS) 3/4 site of the hepatitis C virus (HCV)
  * Proteases are involved in viral processing & replication, hence proteases inhibitors decrease viral replication
* Indicated for the <u>treatment of CHC G1 in adults when used in combination with PEG IFN + RBV</u>
* They can be used in:
  * treatment naïve patients
  * compensated liver disease, including cirrhosis
  * prior null OR partial responders, and
  * those who have relapsed after previous treatment

Telaprevir and Boceprevir

* Approved by Health Canada on:
  * BOC: July 29, 2011
  * TVR: Aug 16, 2011
* Both dosed 3 times daily
* Both have a low barrier to resistance and similar resistance patterns
  * Not likely to benefit if switching post treatment failure
* Have not been compared head-to-head in similar patient populations
* All current published trials are vs. placebo (note: both groups have baseline PEG-INF + RBV)

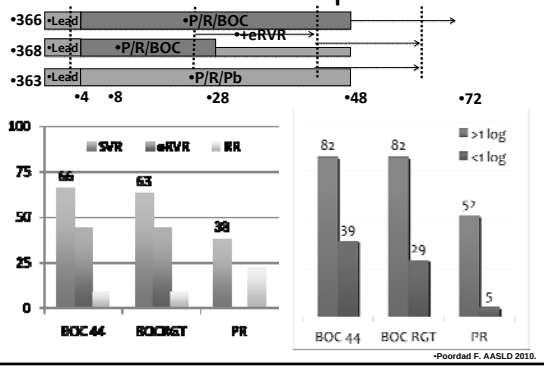
Selected Boceprevir trials

*** = statistically significant vs placebo**

Name	Design	Intervention	Primary (SVR)	SAE (%)
SPRINT-2 (treatment naïve)	DB,RCT, MC N=1099	BOC 800 mg TID x 44 wks BOC 800 mg TID x 24 wks (RGT) Placebo X 44 weeks (N=364)	66%* 63%* 38%	12% 11% 9%
RESPOND -2 (relapsers or non-responders)	DB,RCT, MC N=404	BOC 800 mg TID x 44 wks BOC 800 mg TID x 32 wks (RGT) Placebo X 44 weeks (N=364)	66%* 59%* 21%	14%* 10% 5% Note: 12%* WDAE with BOC vs 1% with PLB

EPO used to manage BOC treatment-related anemia in 35% of patients in SPRINT-2 and 40% in RESPOND-2 vs. 20% in PLB).

SPRINT-2: BOC phase 3



•Poordad F. AASLD 2010.

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Table 1. Results of Phase 2 and 3 Randomized Controlled Trials for Telaprevir

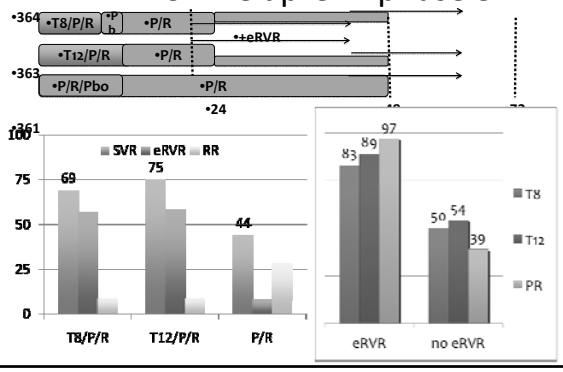
Study	Treatment Group		Sustained Virologic Response, % (p value)	Rapid Virologic Response, % (p value)	Nonresponse (viral breakthrough), %	Discontinuation Rate,* %	Relapse Rate,*
PROVE 1[40] (Phase 2), N = 263	T12PR24	TN 61-67%	61 (0.02)	81	7[b]	21[b]	2
	T12PR48		67 (0.002)	81			6
	T12PR12		35	59			33
	PR48		41 (NA)	11	11		23
PROVE 2[41] (Phase 2), N = 334	T12PR24	TN 60-69%	69 (<0.001)	69 (<0.001)	5	13	14
	T12PR12		60 (0.12)	80 (<0.001)	1	11	30
	T12P12		36 (0.20)	50 (<0.001)	24	8	48
	T12PR12 and T12P12		48 (0.89)	66 (<0.001)	1	7.0	22
	PR 48		46	13			
PROVE 3[42] (Phase 2), N = 465	T12PR24	TE 50-53%	51 (<0.001)	61	13	13	30
	T24PR48		53 (<0.001)	50	12	50	13
	T24P24		24 (0.02)	47	32	19	53
	PR48		14 (NA)	0	3	6	53
ADVANCE[34] (Phase 3), N = 1085	T12PR24 (if RVR or EVR) or T12PR48	69-75%	75 (<0.0001)	88		7	9
	T8PR24 (if RVR or EVR) or T8PR48		69 (<0.0001)	92		8	9
	PR48	TN	44	9		4	28
ILLUMINATE[35] (Phase 3), N = 540	T12PR24[c]	TN	92	100			6
	T12PR48[c]		88	100			3
	Overall[d]		72	72[e]		7	8
REALIZE[36] (Phase 3), N = 662	Either T12PR48; or PR4, then T12P12, then PR32	TE	86,[f] 57,[g] 31,[h] 64,[i] 66[j]				
	PR48		24,[g] 15,[h] 5[j]				

TN = Treatment Naïve

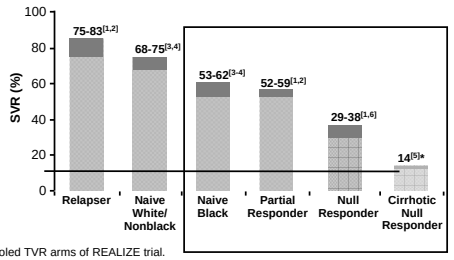
TE= Treatment Experienced

RVR = extended rapid virologic response; EVR = early virologic response; NA = not available; PR4 = 4 weeks of peginterferon and ribavirin; PR 32 weeks of peginterferon and ribavirin; PR48 = 48 weeks of peginterferon and ribavirin; RVR = rapid virologic response; T8PR24 = 8 weeks telaprevir and 24 weeks of peginterferon and ribavirin; T12P12 = 12 weeks of telaprevir and 12 weeks of peginterferon; T12PR12 = 12 weeks telaprevir and 12 weeks of peginterferon and ribavirin; T12PR24 = 12 weeks of telaprevir and 24 weeks of peginterferon and ribavirin; T12PR4

ADVANCE: Telaprevir phase 3



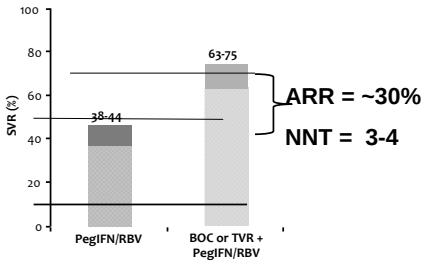
Pooled TVR or BOC SVR rates by Patient Group



*Pooled TVR arms of REALIZE trial.

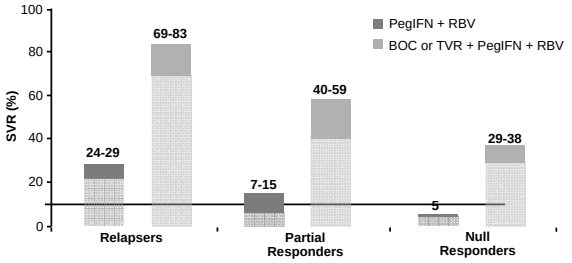
1. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428. 2. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 3. Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416. 4. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 5. Zeuzem S, et al. EASL 2011. Abstract 5. 6. Vierling JM, et al. AASLD 2011. Abstract 931.

Overall SVR Rates with BOC or TVR in Genotype 1 **Treatment-Naive** Patients



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

SVR Rates With BOC or TVR in GT1 **Treatment-Experienced** Patients



Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. Zeuzem S, et al. N Engl J Med. 2011;364:2417-2428.
Vierling JM, et al. AASLD 2011. Abstract 931.

BOC Adverse Events from Clinical Trials

- Most notable adverse events occurring more frequently with boceprevir-based therapy vs pegIFN/RBV alone
  - Anemia, neutropenia, and dysgeusia

Adverse Event, %	Boceprevir + PegIFN/ RBV	PegIFN/RBV
Treatment-naive patients	(n = 1225)	(n = 467)
▪ Anemia	50	30
▪ Neutropenia	25	19
▪ Dysgeusia	35	16
Treatment-experienced patients	(n = 323)	(n = 80)
▪ Anemia	45	20
▪ Dysgeusia	44	11

Boceprevir [package insert]. May 2011.

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TVR Adverse Events from Clinical Trials

- Most notable adverse events occurring more frequently with telaprevir-based therapy vs pegIFN/RBV alone
  - Rash, anemia, and anorectal symptoms

Adverse Event, %	Telaprevir + PegIFN/RBV (n = 1797)	PegIFN/RBV (n = 493)
Rash	56	34
Anemia	36	17
Anorectal symptoms	29	7

Telaprevir [package insert]. May 2011.

Limitations of the available data

- All trials use SVR (surrogate outcome) for primary endpoint
  - SVR is used in many current hepatitis trials (pts who achieve a SVR may have a reduced risk for developing fibrosis, cirrhosis or hepatocellular carcinoma (Cardoso, 2010; Sobesky, 1999; Ponyard, 2000) and survival (Backus 2010)
  - SVR sometimes assessed differently (24 wks post last "planned" dose vs last "administered" dose)
- TVR and BOC have **NOT** been compared head-to-head in similar patient populations
- Lots of different PI regimens tried
- QoL data tended to worsen for both groups – no different in overall QoL seen

Drug Interactions

- TVR is a CYP3A enzyme inhibitor, as well as an inhibitor of P-glycoprotein transporters.
- Therefore, drug interactions may occur with agents that are substrates for CYP3A or P- glycoproteins (e.g., midazolam, buspirone, felodipine, lovastatin, sildenafil, simvastatin, triazolam, aliskiren, colchicine, dabigatran, digoxin, everolimus, saxagliptin, sirolimus, sitagliptin.

•Kieffer T. AASLD 2010. Vierling J. AASLD 2010. Hezode C. NEJM 2009.

Drug Interactions

Drug Class	Contraindicated With BOC[1]	Contraindicated With TVR[2]
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Alfuzosin
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	N/A
Antimycobacterials	Rifampin	Rifampin
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agents	Cisapride	Cisapride
Herbal products	*Hypericum perforatum* (St John's wort)	*Hypericum perforatum*
HMG CoA reductase inhibitors	Lovastatin, simvastatin	Atorvastatin, lovastatin, simvastatin
Oral contraceptives	Drospirenone	N/A
Neuroleptic	Pimozide	Pimozide
PDE5 inhibitor	Sildenafil or tadalafil when used for tx of pulmonary arterial hypertension	Sildenafil or tadalafil when used for tx of pulmonary arterial hypertension
Sedatives/hypnotics	Triazolam; orally administered midazolam	Orally administered midazolam, triazolam

Protease Inhibitor Resistance

- Rapidly selected with monotherapy
- ≈10% during combination therapy
  - High fold change variants @ breakthrough on PI
    - 3% ADVANCE Study
  - Low fold change variants @relapse or on PEG/R
    - 5-10% ADVANCE Study
  - Impact of lead-in unclear
  - No (or low dose) RBV arms increased resistance
    - 40-45% PI resistance
  - HCV subtype matters (1a vs 1b)

•Kieffer T. AASLD 2010. Vierling J. AASLD 2010. Hezode C. NEJM 2009.

What is the prevalence of Hepatitis C Infections in Canada?

A. <0.5%

B. 0.5-1%

C. 2%

D. π (3.1415…)

E. 5%

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What percentage of those infected with Hepatitis C will spontaneously clear the virus?

A. 2-5%
B. 10%
C. 25%
D. 50%

What percentage of treatment naïve patients receiving Boceprevir or Teleprevir with Interferon and Ribavirin get a sustained virologic response ?

A. 25%
B. 40%
C. 50%
D. 70%
E. 90%

Conclusions and Key Messages

* Hepatitis C infection is self limiting for 25% of those infected, but can be a serious, life threatening disease
* Standard care with PEG-INF + RBV has a SVR = 30-50%
* TTVR or BOC to PEG INF + RBV results in an absolute increase in SVR of ~ 30 % for CHC G1; NNT = 3-4
* Adverse effects of BOC: anemia and dysgeusia
* Adverse events of TVR: rash, pruritus, anemia, & diarrhea
* A 48 week course of therapy of PEG INF + RBV costs $20,000.
* TVR or BOC treatment course is $30,000 - $35,000
* Total cost of PI + INF + RBV 48 week treatment is $50,000 - $55,000

Conclusions and Key Messages

* BOC or TVR must be used with PEG INF + RBV; not monotherapy
* Pharmacare has followed the CDR recommendation to list for those CHC G1 in non-HIV patients with fibrosis stage 2 or higher
  * No current published data for use in those with HIV – but it is coming…

Covering HPV strains – 2,4 or maybe more

Natasha Press

April 20, 2012.

Conflict of interest

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

Objectives

1. Overview of HPV
2. HPV vaccines
3. What the critics say
4. Pap tests and future diagnostics

What is HPV

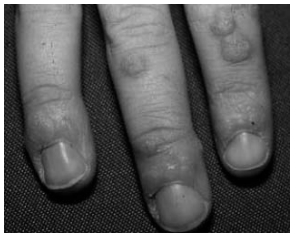
- Human Papillomaviruses
- Name of a group of viruses
- >100 different strains
- >30 of them are sexually transmitted
- Only infect humans
- Infect skin or mucosa

What is HPV

- **Warts**
- **Cancer**

HPV causes warts on hands/feet

- **Common skin warts**
- **HPV types 1,2,3,4**



University of Indiana Department of Pathology

Natasha Press

HPV in the anogenital area

- **Anogenital warts**
- **Condyloma acuminata**
- **HPV strains 6, 11 cause 90% of genital warts**

Risk factors for anogenital warts

- Sexual activity (any kind)
- Number of sexual partners
- Not toilet seats!
- (the virus can only be passed from one skin surface to another)

Overview of HPV

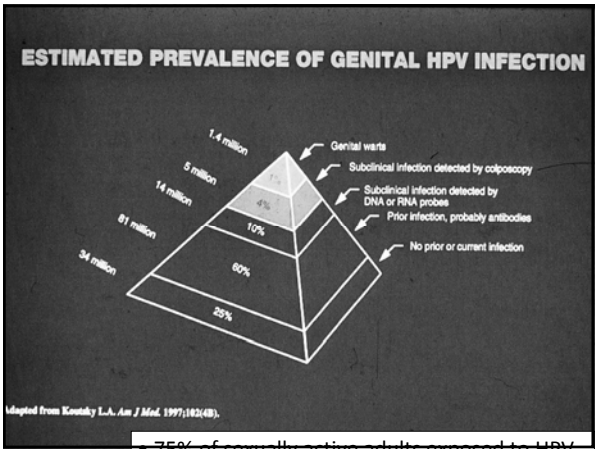
Low Risk	High Risk
• HPV types: 6, 11	• HPV types: 16, 18
• Genital warts • Respiratory papillomatosis • Low-grade cervical or anal changes	• Dysplasia (genital, anal) • Cancer (genital, anal) • Head and neck cancers

HPV types

- HR HPV: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
- LR HPV: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81

HPV-associated cancers

- Nearly all cervical cancers (70% due to HPV 16,18)
- 85% of anal cancers
- 70% of vaginal cancers
- 40% of vulvar cancers
- 40% of penile cancers
- 35% of throat cancers
- 25% of mouth cancers



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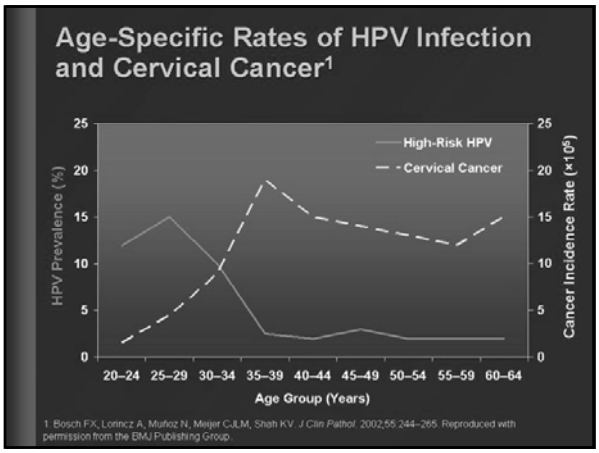
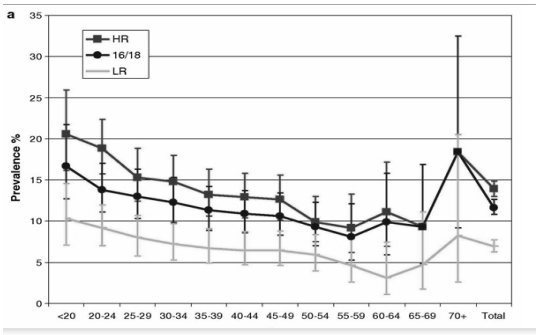
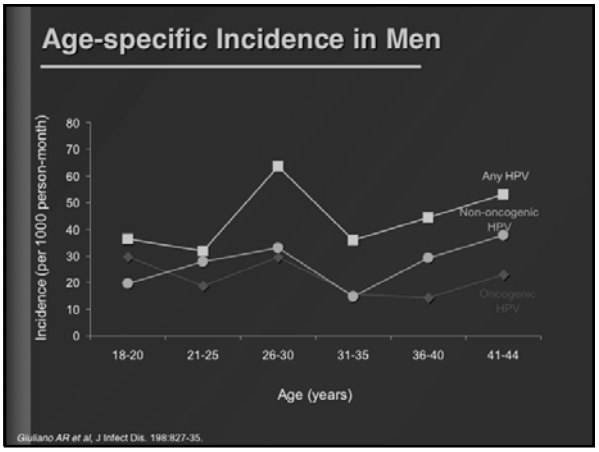


How much HPV is in BC Women



Cancer Causes & Control, Oct2009, Vol. 20 Issue 8, p1387-1396



How much HPV is in BC men

	women	**MSM**
HPV	15%	62%
HPV 16, 18	10%	23% (41% in HIV)

Sexually Transmitted Diseases. 38 (10), Oct 2011

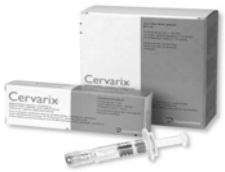
How to prevent HPV

- Refrain from any genital contact
- Monogamous relationship with an uninfected partner
- Condoms (OR 0.5)
- Vaccine

HPV Vaccines

- **HPV4**
- **16, 18**
- **6, 11**

- **HPV2**
- **16, 18**



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HPV4 status in Canada

- **Approved by Health Canada for:**
- **M aged 9-26 years old**
- **F aged 9-45 years old**
- **(NACI still hasn't put out a statement regarding M)**

HPV4 status in BC

- **Routine immunization for girls in Grade 6**
- **Available for other M and F through their dr.**

- **Uptake:**
- **65% received first dose (vs. 88% for hepatitis B)**
- **Reasons for parent refusal: vaccine safety (29%)**

PLoS Medicine 7(5):e1000270, 2010 May

HPV4 – RCT

Study	gender	age	n	endpoints	efficacy
Future 1	F	16-24	5442	CIN, VIN, VaIN, PIN, genital warts, persistent infection (naïve individuals)	Warts 99% >98%
Future 2	F	15-26	12,157		
Future 3	F	21-45	3817		85% (67, 94)
020	M	15-27	4055		Warts 90% (65,98) 80-100%
			600 MSM substudy		AIN 77% (39.6, 93.3)

HPV4 and HPV2

- Almost complete protection against new genital infection/disease
- Does not alter course of preexisting HPV 16/18 infections
- Continue to protect >4 years
- Safety profile similar to that of other vaccines

HPV4 vs. HPV2

- Gardasil
- protects against warts
- $400

- Cervarix
- higher cross-protective efficacy
- $300

Nature Medicine Volume:18,Pages:28–29Year published:(2012)

Adverse Events

- Local: injection-site reactions
- Systemic: headache and fever
- Fainting

ACIP, 2011.

Natasha Press

HPV Vaccine in HIV+

- HIV+ men
  - Safety and immunogenicity study
  - No adverse effects on CD4 or VL
  - Efficacy studies needed
- HIV+ women
  - Seroconversion (personal communication Deb Money)

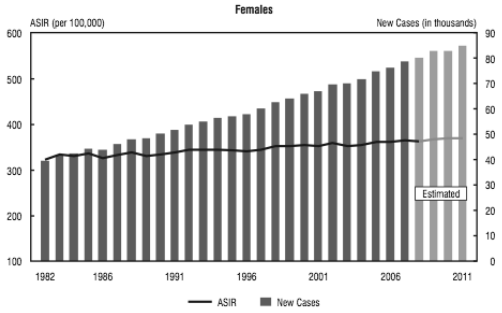
JID Oct 2010

What the critics say

Cervical Cancer in Canada

- Incidence declining by 1.4% per year
- Mortality declining by 3.4% per year
- 400 deaths/year

Canadian cancer incidence (females)



What the critics say

- Higher in Aboriginal women: reflects inequity in health care access
- Will disadvantaged women be left out? Will cervical cancer rate decline?

Lippman A. CMAJ 2007

PAPs and Future Diagnostics

- vaccinated individuals should continue to have routine PAP tests
- HPV DNA?!

Natasha Press

Conclusions

- HPV causes warts and cancer
- Vaccines prevent anogenital precancer/warts
- HPV4 approved in BC for F (aged 9-45) and M (aged 9-26)
- publically funded grade 6 program (girls only)
- schedule changed (3rd dose after 60 months)
- best efficacy ~ 100%
- lasts > 5 years
- pap tests still required to test for non-vaccine HPV

Acetaminophen in Children: Is Tylenol at #1, 2, or 3?

Roxane Carr, PharmD, BCPS, FCSHP
Children's & Women's Health Centre of BC
University of British Columbia

Conflict of Interest Statement

No conflicts of interest to declare.

Acetaminophen

- Common medication given to babies & children
- Used to treat fever & pain
- Well tolerated

Acetaminophen

- **Anti-pyretic:**
  - Inhibits hypothalamic heat-regulating centre
- **Analgesic:**
  - Inhibits synthesis of prostaglandins in CNS
  - Blocks pain impulse generation in periphery

Anti-Pyretic

- Acetaminophen 15 mg/kg/dose q4-6h
  - Max 75 mg/kg/day
- Ibuprofen 10 mg/kg/dose q6-8h
- Equally effective & tolerated
- Alternating acetaminophen & ibuprofen?
- Concerns re: ibuprofen → acute renal failure in dehydrated children

Clin Pharm 1992;11:1005-21; Curr Med Res Opin 2007;23:2205-11; Pediatrics 2011; 127 :580-7.

Acetaminophen & Vaccines

- Vaccines:
  - Injection pain
  - Post-vaccination adverse reactions:
    - Fever
    - Fussiness/malaise

Injection Pain

- Systematic review: 31 studies
  > 3500 infants & children
- 10 studies: topical anesthetics → mixed results
- 11 studies: sweet-tasting solutions → mixed results
- 4 studies: breastfeeding → decreased pain

Clin Ther 2009;31:S104-51.

Injection Pain

- Systematic review: 31 studies
  > 3500 infants & children
- 2 studies: vapo-coolants → no benefit
- 4 studies: combinations → ≥ 2 interventions better than 1
- 0 studies: acetaminophen or ibuprofen

Clin Ther 2009;31:S104-51.

Preventing Post-Vaccination Adverse Reactions

- Acetaminophen vs Ibuprofen vs Placebo
- Before vaccination and 12-24 hours post
- 5 studies
- Benefit (↓ fever, redness, pain, swelling):
  - Diphteria, **cellular pertussis** and tetanus vaccine
- No benefit:
  - DTaP vaccine
  - Other routine childhood immunizations

Ann Pharmacother 2007;41:1227-32

Post-Vaccination Fever

	Acetaminophen N= 176	Placebo N = 176	RR (95% CI)
Temp ≥ 38 ºC (N(%))	25 (14)	39 (22)	0.63 (0.4-1.01)
Fussiness (N(%))	17 (10)	42 (24)	0.42 (0.25-0.7)
Unblinded (N(%))	5 (3)	16 (9)	0.31 (0.11-0.83)

PLoS One 2011;6:e20102

Preventing Post-Vaccination Adverse Reactions

•Open label, RCT
•Prophylactic acetaminophen vs placebo X 3 doses post initial & booster

	Acetaminophen N = 226	Placebo N = 233
Temp ≥ 38 ºC (N (%))	94 (42)	154 (66)
Temp ≥ 39.5 ºC (N(%))	1 (0.4)	3 (1.3)
Antibody titres	Decreased	

Lancet 2009;374:1339-50.

Preventing Post-Vaccination Adverse Reactions

Prevention of vaccine related:

- Injection pain → Not studied
- Adverse effects:
  - Pain, injection site reaction → No benefit
  - Low grade fever → mixed results
  - High fevers → relatively rare
- Unknown impact on immunization effectiveness
- **Do not recommend routinely before or after vaccines, only if child experiences fever, pain or discomfort**

Analgesia

- Effective: mild to moderate pain
- Neonates & infants < 3 months:
  - 10 mg/kg/dose PO q4-6h PRN
  - Max 60 mg/kg/day
- Infants > 3 months & children:
  - 10-15 mg/kg/dose PO q4-6h
  - Max: 75 mg/kg/day or 4 g/day

Pediatrics 2010;126:1430-44.; Lexicomp 18th ed 2012

Safety

- Hepatotoxicity
  - If exceed recommended dosage
    - Unintentional
    - Intentional
  - Malnourished
  - Pre-existing liver disease

Pediatrics 2010;126:1430-44.

Safety

Acetaminophen & Asthma

- Observational studies
- Most retrospective
- Recall/Reporting issues
- Definitions of outcome: wheeze vs asthma

Clin Exp Allergy 2011;41:482-9; Obstet Gynecol 2009;114:1295-306; Chest 2009;136:1316-23

Safety

Acetaminophen & Asthma

Maternal use during pregnancy:
Wheeze/asthma in child

- Odds ratio: 0.59 - 1.6
  (95% CI 0.53-1.10;1.16-41)

Clin Exp Allergy 2011;41:482-9; Obstet Gynecol 2009;114:1295-306; Chest 2009;136:1316-23

Safety

Acetaminophen & Asthma

Usage in early infancy (< 6 mos) and :

- Odds ratios: 1.08 - 2.20

(95% CI: 0.91-1.29 to 1.13-4.3)

Respir Med 2012;106:329-37; Acta Pediatr 2011;100:90-6; Clin Exp Allergy 2011;41:482-9; Int J Epidemiol 2011;40:662-7; Chest 2009;136:1316-23; BMJ 2010;341:1-7.

Safety

Increased risk of Asthma:

- Upper Respiratory Tract Infections?
- Febrile illness?
- Genetic predisposition: polymorphism in glutathione pathway

Respir Med 2012;106:329-37; Acta Pediatr 2011;100:90-6; Clin Exp Allergy 2011;41:482-9; Int J Epidemiol 2011;40:662-7; Clin Exper Allerg 2009;40:32-41

Mechanism

- Acetaminophen & glutathione:
  - ↓ alveolar glutathione → ↓ respiratory antioxidant defenses
  - ↓glutathione in antigen presenting cells → ↓cytokine production →↑ atopic diseases
  - ↓COX-2 activity → ↓ prostaglandin E2 production

Int J Epidemiol 2011;40:662-7; Clin Exper Allerg 2009;40:32-41

Summary

- Use to treat fever and pain intermittently
- Avoid prophylactic use
- Ensure parents aware of correct dose and product selection

The Latest On Zoster Immunization

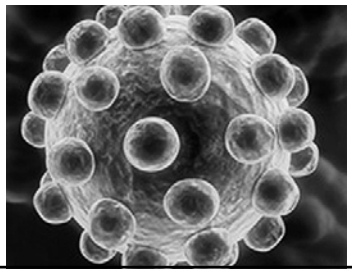
Val Montessori
Division of Infectious Diseases
St. Paul's Hospital
April 2012

Disclosure of Commercial Support

- **Advisory board meetings for:**
  - **Bristol Myers Squibb**
  - **Pfizer**
  - **Tibotec**

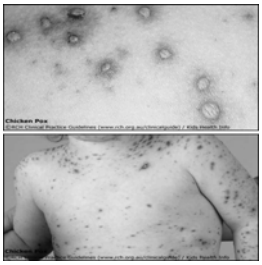
Objectives

- **Review of Varicella Zoster Virus**
- **Review of Zoster Vaccine**
- **FAQs**

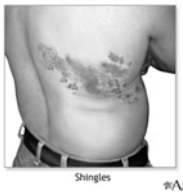


Varicella Zoster Virus (VZV)

- **1º VZV**
- **Chickenpox**



- **2º VZV**
- **Herpes Zoster**
- **Shingles**

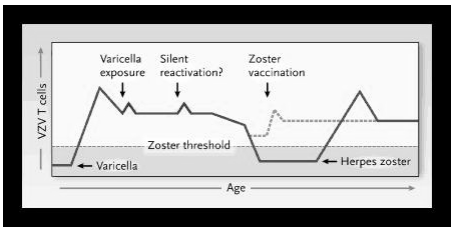


Varicella Zoster Virus (VZV)

- **1º VZV infection (chickenpox)**
  - **Lifelong immunity**
  - **Remains latent in sensory neurons**
- **2º VZV infection (zoster, shingles)**
  - **Reactivation of VZV**
  - **Dermatome corresponds to the sensory ganglion in which VZV is latent**

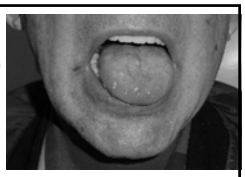
Zoster

- Age = main risk factor for zoster
- "Lifelong" immunity ↓ over time
- If immunity is below a critical level → zoster



Mayo Clin Proc 2007; 82:1341-9., NEJM 2005: 352(22):2266-7.

Zoster

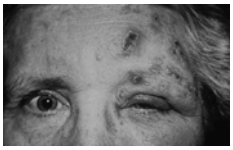


- Zoster is common
  - 50% of 85 years olds
- A second episode may occur in <5%

Mayo Clin Proc 2007; 82:1341-9.
NEJM 2005: 352(22):2266-7.

Complications

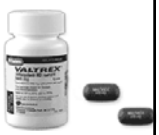
- Post-herpetic neuralgia (PHN) 10-20%
  - Age = primary risk factor
- Herpes zoster ophthalmicus (10-25%)
- Neurologic (e.g. Ramsey-Hunt)
- Dissemination (immunocompromised)



MMWR June 6, 2008/57(05);1-30.

Treatment of Zoster

- Valacyclovir 1000mg tid x7 d
- Famciclovir 500mg tid x 7 d
- Acyclovir 800mg 5x/d x7-10 d



  - Speeds healing by 1 – 2 d
  - ↓ risk for progression to PHN (NNT 6-11)

Clin Infect Dis 2007;44 (Suppl 1): S1-26.

Treatment of Zoster

- Antivirals for all, especially if:
  - >50 years old
  - mod/severe pain
  - mod/severe rash
  - nontruncal dermatomes

- Within 72 hours or as soon as possible
- Use of steroids does not prevent PHN

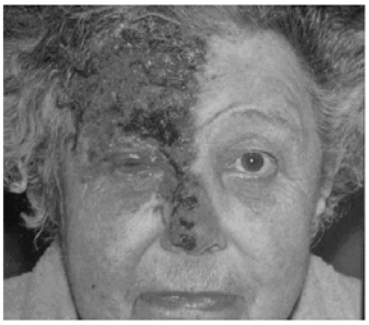
Clin Infect Dis 2007;44 (Suppl 1): S1-26.

Zoster vaccine

- Zostavax®
- Merck
- Available in Canada
- $150

www.zostavax.ca

FIGURE 2. Case of herpes zoster ophthalmicus



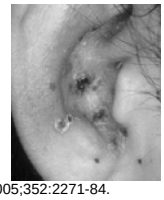
Photo/MN Oxman, University of California, San Diego

Varicella Zoster Vaccine

- randomized, double-blind, placebo-controlled trial of 38,546 adults
- 60 years of age or older
- a history of infection or had resided in the United States for 30 years; serologic testing for varicella was not performed
- 3 years follow up

Zoster vaccine

- Shingles Prevention Study
- ↓ zoster 50%
- ↓ post-herpetic neuralgia 66%
- ↓ severity of zoster by 60%



N Engl J Med 2005;352:2271-84.

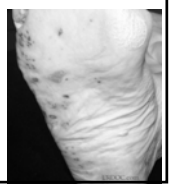
Zoster vaccine - Initial Study

- Age ≥60 years
- Boosts cell-mediated immunity
- Have already had chickenpox
- Don't ask about history of chickenpox
- Don't do serology

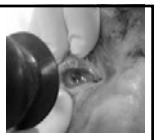
MMWR June 6, 2008/57(05);1-30.

Effectiveness

- For the average 69-year-old:
  - the risk of shingles in the 5-year period after vaccination is expected to be reduced from 5.5% to 2.5% (from 1 in 18 to 1 in 40)
  - risk of PHN from 0.7% to about 0.25% (from 1 in 140 to 1 in 400)



Zoster vaccine



- Shingles Prevention Study
- In >80 years old: ↓ zoster 18%
- More effective for severity of illness
- Safe
- So far, efficacy ongoing at 7 years

N Engl J Med 2005;352:2271-84.

Initial recommendations

- All persons ≥ 60 years
- Even if already had zoster
- OK for chronic medical conditions (diabetes, COPD, CRF, RA)
- To prevent 1 case of HZ NNT=11
- To prevent 1 case of PHN NNT=43

MMWR June 6, 2008/57(05);1-30.

Patients 50 - 59

- In March 2011, FDA expanded age indication to include persons 50 through 59 years of age
- Study of 22,000
  - 30 cases in ZV group, incidence rate 1.99 per 1000 person-years vs 99 cases in placebo group, incidence rate 6.57 per 1000 person-years
- NNT = 150 (in first 1.3 years after vaccination)
- No information regarding post-herpetic neuralgia

Schmader KE, Levin MJ, Gnann JW Jr, et al. Efficacy, immunogenicity, safety, and tolerability of zoster vaccine in subjects 50 to 59 years of age. Presented at the 48th Annual Meeting of the Infectious Diseases Society of America, Vancouver, Canada, October 21--24, 2010. Available at http://idsa.confex.com/idsa/2010/webprogram/Paper3363.html. Accessed February 1, 2012.

Recommendations for Zoster Vaccine

- ACIP and BCCDC recommend a single dose for persons 60 years of age and older
- At this point, no recommendation for routine vaccination of persons 50 through 59 years of age

FAQs

- Who cannot be given Zostavax®?
- Live vaccine, therefore, not for use in:
  - HIV+ with CD4 <200
  - Leukemia/lymphoma
  - Immunosuppressives
- Anaphylactic allergy to components
  - Gelatin, neomycin

MMWR June 6, 2008/57(05);1-30.

FAQs

- Are there any barriers to supplying Zostavax®?
- Needs to be stored at -15ºC
- To find a clinic: www.zostavax.ca

FAQs

- Can I administer Zostavax® with other vaccines?
- Yes
- E.G. can administer with flu shot or pneumovax

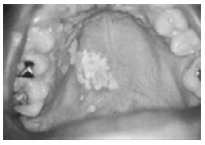
Clin Infect Dis 2010: 51(2):197-213.

FAQs

- Can I use varicella vaccine instead of Zostavax®?
- No
- Zostavax® is 14x the dose of varicella vaccine

FAQs

- **What about vaccinating patients before immunosuppression?**
- **At least 2 weeks before**
- **4 weeks better**



MMWR June 6, 2008/57(05);1-30.

FAQs

- **Can people who received varicella vaccine get Zostavax®?**
- No (but not in the age-group yet)
- Wait and see
- Recipients of varicella vaccine have lower rates of zoster
- But higher rates of “breakthrough” chickenpox

MMWR June 6, 2008/57(05);1-30.

Conclusions: Zoster Vaccine

- **≥ 60 years old (though can consider in 50-59)**
- **offered at first clinical encounter →**
  - **link to flu vaccine**
- **live vaccine**
- **less effective at preventing zoster in very elderly**
- **if patient does get zoster, may prevent severity and PHN**

BMJ

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

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*[1], G Michael Allan *associate professor*[2]

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, BC, Vancouver, Canada V6T1Z3; [2]Department of Family Medicine, University of Alberta, AB, Edmonton, Canada

Over the past 70 years, antibiotics have influenced and improved the treatment of many symptomatic infections. Unfortunately, antibiotics produce side effects and—regardless of whether they are used appropriately or inappropriately—will ultimately lead to a change in the sensitivity of organisms, which can sometimes lead to a reduction in clinical effectiveness.

Many attempts have been made to implement programmes that are designed to improve the use of antibiotics, particularly in primary care. The linked randomised controlled trial by Butler and colleagues (doi:10.1136/bmj.d8173) describes the most recent of these attempts.[1] The authors used social learning theories to develop an extensive and comprehensive educational programme (Stemming the Tide of Antibiotic Resistance; STAR) aimed at reducing antibiotic use in primary care clinics in Wales. Their multifaceted intervention incorporated many of the approaches other reviews have identified as helpful, such as education, feedback, and patient involvement.[2] Practices randomised to receive the STAR programme dispensed significantly fewer oral antibiotics (26.1 items/1000 registered patients/year)—a total reduction of 4.2% (95% confidence interval 0.6% to 7.7%). The intervention cost about £3000 (€3500; $4713) per practice. The results are similar to (although at the lower end of) reductions seen with other such programmes.[3]

Is a 4% reduction in use of antibiotics clinically important? The authors found no significant differences in hospital admissions or reconsultations for a respiratory tract infection within seven days of an index consultation. Although it was essential to examine these outcomes, the study sample size and the effect on prescribing were too small to ascertain if the decrease in antibiotic use improved or worsened patient outcomes.

The authors did not assess whether resistance patterns changed. In a country-wide programme in Finland, reducing the use of erythromycin by 50% reduced the resistance of group A streptococcal isolates from 17% to 9%.[4] Another study found that a decrease of 50 amoxicillin items per 1000 patients per year reduced resistance by 1%.[5] Others have found that a 20% reduction in the prescription of ampicillin and amoxicillin resulted in 1% fewer resistant isolates.[6] So, although reducing the use of antibiotics can affect resistance, the small reduction seen in the STAR study is unlikely to lead to a clinically important change in resistance patterns.

Most people agree that antibiotic prescribing in primary care needs to be improved. Understanding why antibiotics are prescribed is an essential first step. The ethos of antibiotic prescribing is multifactorial and somewhat unique. Fear on the part of the patient and clinician that the infection may turn into something serious plays a major role in decision making.[7]

Antibiotic prescribing can also arise from a clinician's desire to do something that might help or the perception that the patient wants an antibiotic. This is despite research showing that clinicians accurately distinguish only about half of the patients who want or don't want antibiotics.[8] Patients' satisfaction depends more on improved understanding of their illness, however, than on receiving a prescription.[9]

Most (80-90%) oral antibiotic prescriptions in primary care are for respiratory tract infections, urinary tract infections, or skin and soft tissue infections. In theory, diagnostic certainty should help improve the use of antibiotics. Reliable diagnostic criteria are available for sore throats but not for sinusitis or other upper respiratory tract infections. Decision support tools may help clinicians reduce antibiotic prescribing for upper and lower respiratory tract infections and urinary tract infections. Some tests may help to distinguish bacterial infections from viral ones. For example, the use of procalcitonin as an indicator of bacterial infection reduced antibiotic use from 97% to 25% in primary care patients with both upper and lower respiratory tract infections.[10]

When seeing a patient with a possible community acquired infection, clinicians may find it helpful to outline to their patients some of the potential benefits and harms of treatment. The STAR programme, along with many others, provides clinicians

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with useful bite sized synopses of the evidence. Rational use of antibiotics does not involve quibbling over starting antibiotics in very sick patients, but for non-serious illnesses that may or may not be bacterial a reasonable option to reduce antibiotic prescribing is to use delayed antibiotic prescriptions. This makes clinicians feel they are doing something and gives control to the patient. Delayed prescriptions can reduce the proportion of people who receive antibiotics for upper respiratory tract infections from 93% to 32%,[11] a reduction similar to that seen with the use of procalcitonin. Patients who are not given a prescription initially will still ultimately get an antibiotic 14% of the time. However, delaying antibiotics may worsen outcomes—such as fever at day three—and reduce patient satisfaction, but it may also reduce adverse events such as diarrhoea. The 61% (93% minus 32%) absolute difference in antibiotic use from choosing a delayed prescription may be a worthwhile compromise in areas of uncertainty because a strict "no prescription" approach will only "buy" another 18% (32% minus 14%) absolute difference in antibiotic use.

Most community acquired infections still respond to the same antibiotics that have been used for decades and many guidelines still support their use. Amoxicillin for respiratory tract infections and cloxacillin for soft tissue infections (unless community acquired meticillin resistant *Staphylococcus aureus* is suspected) are still solid treatment choices, with doxycycline (not in children) a reasonable alternative for patients who are allergic to or intolerant of these antibiotics. For uncomplicated urinary tract infections, nitrofurantoin, co-trimoxazole, or trimethoprim alone are still good choices. Clinicians need to question why the above agents are not their first choices, especially for patients who are not seriously ill.

Data on the development of resistance suggest that treatment with high dose shorter duration antibiotics may reduce the emergence of resistance.[12] Although several studies show that shorter courses of antibiotics for relatively self limiting infections in primary care are as effective as longer ones, it is never known how an individual patient will respond. Given that, 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. Patients also need to be advised what to do if no improvement is seen within 24-48 hours. To support this approach, patients need to know that the often used warning to finish the whole antibiotic course is not evidence based. Use of the prescription label "Finish all this medication unless otherwise directed by prescriber" should be discouraged.

Competing interests: Both authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

This is an abbreviated reference list and a full list is available from the authors.

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Cite this as: *BMJ* 2012;344:d7955

Johanna Trimble

Delirium:

What to do if it's "relative"?

23rd Annual Drug Therapy
Decision Making Course
April 20-21, 2012

Johanna Trimble
BC Patient Voices Network, Steering Committee
Patients for Patient Safety Canada (CPSI)
Community Engagement Advisory Network (Vancouver Coastal Health)

No financial support was received for this presentation

Fervid Trimble, age 86 (2003), enjoying her apartment in a senior's residence she'd chosen for herself.

Fervid's "family care team"
Johanna, Dale, Fervid and Kathie

Fervid experienced a precipitous mental decline after entering the Care Centre for "a few days" to recover from the 'flu in November 2003. We suspected new medications.

Why we decided to intervene:

- Her mental and physical decline was precipitous and didn't fit with her diagnosis on admission

- Several new drugs had been prescribed
- We suspected an interaction between a pain drug (tramadol) and an SSRI, both affecting seratonin

Johanna Trimble

The process

- Pay attention to your loved one: watch, listen, write it down
- Research: identify REPUTABLE internet and print resources to research drugs and treatments
- Compare: symptoms with the adverse effects or interactions
- Communicate: first as a family – then with the doctor
- Timing: delays can cost precious time in reversing adverse effects

"Assume that any new symptom you develop upon starting a new drug may be caused by the drug. If you have a new symptom, psychiatric or otherwise, report it to your doctor"

Public Citizen, Health Research Group
www.worstpills.org

Has a baseline for the patient been determined? This is where the family must be involved.

"(This frail elder) would have…been treated by people who didn't know him or his medical history. Everyone taking care of him would have had good intentions, but they would not have seen the big picture. This happens so often it's routine" says Dr. Diane Meier, Geriatrician."

The Treatment Trap
- by Gibson, R and Singh, JP

Much prescribing for the elderly is an "evidence-free zone".

A Bitter Pill: How the Medical System is Failing the Elderly (2009)
- by Dr. John Sloan

- Reading Dr. Sloan's book encouraged me to become active in seeking changes in the care of frail elders to address the poor quality of remaining life when over-medicated and perhaps a sooner and less dignified death.
- I realized the experience our family went through was not a rare occurrence but is almost a norm of care for frail elders.

Loss of function:

Delirium and confusion in any care setting will keep a patient in bed and result in loss of function.

Johanna Trimble

- Delirium and confusion in any care setting will keep a patient in bed and result in loss of function.
- 1 in 3 elderly admitted to acute care is discharged at a higher level of disability than when admitted.
- These seniors have a risk of further disability when they return home.
- At least 50% of that disability is preventable.
- Physical activity is critical, patients lose up to 5% of muscle strength for every day in bed.

- Dr. Janet McElhaney
Head, Division of Geriatric Medicine
Providence Health Care

Fervid's drug interaction

Symptoms of Seratonin Syndrome that we noticed:

1. Cognitive/behavioral changes: **confusion, agitation, lethargy**
2. Autonomic instability: **rapid heart rate, sweating**
3. Neuromuscular changes: **twitching a muscle or group of muscles**

*Serotonin syndrome **is often self-limited if it is recognized early**, treatment with the suspected drug or drugs is stopped, and supportive care is given. **It can be fatal left unrecognized and untreated**.*

Delirium

- Fervid's delirium was a result of a specific drug interaction
- But polypharmacy, along with age, is probably the number one factor in delirium.
- A minor change (in drugs) can precipitate a crisis among vulnerable elders.
- Delirium is a serious health threat, but also largely preventable.
- After an episode of delirium, one year mortality among frail elderly can be as high as 35 to 40%.

- Delirium Prevention Training program: IPPOD
Sunnybrook Health Sciences Centre, Toronto ON

Therapeutics Initiative's review of Aricept: a drug suggested by the facility's Psychiatrist who diagnosed Fervid with "Alzheimer's"

- The clinical significance of the small differences remains to be established; the studies were not designed to detect improvement in activities of daily living or delay in institutionalization
- Conclusion: Further trials are required to test whether Aricept offers improvement in more clinically meaningful outcomes.

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Some side effects of Aricept were side effects we were already attempting to alleviate.

The results of Fervid's "drugectomy"

- A return to normal mental status
- She began to improve physically and work with (& attempt to defy) her physiotherapist
- She was able to attend meetings and complain!
- She returned to "training" care aides she thought needed improvement
- She formed close relationships with several of the care aides
- She was again able to join us for family outings

Fervid enjoying white wine and oysters at her favourite restaurant with us after recovering from her diagnosis of "Alzheimer's"

Two other possible endings to our story:

Scenario One:

- If we had NOT intervened, Fervid would likely have been further medicated to treat the side effects of drugs she was already taking and would have likely died confused, delirious, unable to recognize her family – and much sooner (she lived for another 4 years and died at 92 years).

Scenario Two:

If we had been able to have the drug interaction recognized sooner, and corrected, Fervid would likely have recovered from her initial 'flu and returned to her home, perhaps to one of the assisted-living apartments.

Residents suffer terribly from isolation in a nursing-home environment and Fervid greatly missed her life and many friends at her former residence.

Question: Is there really an epidemic of Alzheimer's and dementia?

- The media constantly refers to the "epidemic" of Alzheimer's and dementia and how the "boomer" generation will make our health system unsustainable.
- Is our standard treatment of frail elders with multiple medications and overuse of acute care a big part of the problem?
- How do you want it to be when YOU get there?

What we learned from Fervid

Fervid's words to her family

"Well, I think I'll leave all my love to the next generation. May they realize the agenda we've set out for them with love and affection. It's too precious not to live—we've enjoyed each other so much. I think it will grow (love). That's the ticket into the next world. We will always be together, our love is always there and we will be part of the great growing field of love".

Fervid Trimble, 2008

Quality of Life, Dignity of Death

Fervid lived for 4 years after her initial over-medicated, confused & delusionary state. If she had died earlier, and delusional, our family wouldn't have received these expressions of love and wisdom as her farewell.

Families remember and take to heart their experiences with the deaths of their loved ones.

Johanna Trimble

Patient Safety

- Lack of patient [& family] involvement in care is the strongest risk factor for self-reported medical errors [twice as likely]. – *Take As Directed* by Church, R and MacKinnon, N
- Be an informed and involved partner in your own care and those you care about.
- Medical professionals may know medicine, but the family knows the patient.

"Would this be good enough for me, my family and those I care about?" - "Involving People in Healthcare Policy and Practice", Green, S

What really turns my crank:

- Public Member, Steering Committee, Optimal Prescribing Update and Support (OPUS), Practice Support Program (PSP), GPSC
- Coming soon to a Division of Family Practice near you!
- Public Member of the Polypharmacy Working Group, Shared Care, PSP, GPSC
- Pilot programs are beginning to be offered through Divisions of Family Practice

A profound difference in Fervid

Over-medicated

After the "drugectomy"

Dedicated to Fervid Trimble 1917 - 2008

A picnic in the garden with Fervid

Contact:

johanna@daletrimble.com

Peter Chan

Delirium: making the relative absolutely better

Dr. Peter Chan, MD, FRCPC
Consultation-Liaison and Geriatric Psychiatrist,
Vancouver General Hospital.
Clinical Professor,
UBC Dept. of Psychiatry.

Learning Objectives

1) describe 3 practical measures when managing delirium, and 3 pitfalls

2) discuss the advantages and disadvantages of various classes of psychotropic medications for the treatment of delirium

3) understand the role but limitations of the use of benzodiazepines in alcohol withdrawal delirium

CAM – Short Form

CAM: Confusion Assessment Method
The diagnosis of delirium requires the presence of features 1 and 2, *plus* either 3 or 4.

Feature 1: Acute onset and fluctuating course
This feature is usually confirmed by comments of a family member or health care professional and is shown by positive responses to the following questions:
- Is there evidence of an acute change in mental status from the patient's baseline?
- Does the (abnormal) behavior fluctuate during the day, tending to come and go, or increase and decrease in severity?

Feature 2: Inattention
This feature is shown by a positive response to the following question:
- Does the patient have difficulty focusing attention? For example, is the patient easily distracted or having difficulty keeping track of what is being said?

Feature 3: Disorganized thinking
This feature is demonstrated by a positive response to the following question:
- Is the patient's thinking disorganized or incoherent, as evidenced by rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

Feature 4: Altered level of consciousness
This feature is shown by one answer other than "alert" to the following question:
- Overall, how would you rate the patients level of consciousness?
  - Alert (normal)
  - Vigilant (hyperalert)
  - Lethargic (drowsy, easily aroused)
  - Stuperous (drowsy, difficult to arouse)
  - Comatose (unarousable)

Delirium: The Myths

1) Delirium is a bedside diagnosis
   - Requires 24 hour observation
2) Delirium means agitation and behaviour problems
   - Watch for "Apathetic" (hypoactive) Delirium
3) Delirium always has an identifiable cause
   - May not find a single cause; multiple factors with geriatric delirium
4) Delirium is a transient phenomenon
   - May persist or lead to permanent cognitive and/or functional sequelae in elderly

Differential Dx: DIMS-R

DIMS-R (Drugs, Infection, Metabolic, Structural, Retention): Common precipitating factors for delirium

Drugs
- Prescribed (narcotics, steroids, anticholinergic, NSAIDs)
- Over-the-counter (dimenhydrinate, diphenhydramine)
- Drug intoxication or withdrawal (alcohol, sedative-hypnotics, narcotics

Infection (urinary tract, lungs, skin, blood)

Metabolic disturbances
- Fluid (dehydration, hypovolemia)
- Electrolyte (sodium, potassium, magnesium)
- Nutrition (malnutrition, thiamine deficiency, anemia)

Structural insults
- Cardiovascular (angina, infarction, congestive heart failure)
- Central nervous system (stroke or ischemia, concussion)
- Pulmonary (hypoxia [e.g., COPD exacerbation])
- Gastrointestinal (bleeding with anemia, *C. difficile*, colitis)

Retention problems (urinary retention, constipation)

- Practical Tip #1:
  Check for urinary retention with a bladder scanner!

Medications which may cause or worsen delirium in the elderly patient

Analgesics	Antihistamines	Anti-Nauseants	Anti-Parkinsons	Anti-Seizure	Cardiovascular
Narcotics: •Codeine •Meperidine •Oxycodone •Morphine	• Chlorpheniramine • Diphenhydramine (Benadryl®) • Hydroxyzine	• Scopolamine • Dimenhydrinate (Gravol®)	• Amantadine • Benztropine • Trihexyphenidyl • Procyclidine • Levo-dopa • Bromocriptine	• Phenobarbital • Phenytoin	• Captopril • Furosemide • Nifedipine • Digoxin • Dipyridamole • Isosorbide Dinitrate

Gastrointestinal	Genitourinary	Psychiatric	Pulmonary	Sedatives	Other
• Cimetidine • Ranitidine	• Dicyclomine • Hyoscyamine • Oxybutynin • Tolterodine	**Some Tricyclic anti-depressants (TCA)** •Amitryptiline •Doxepin •Clomipramine •Imipramine **Older anti-psychotics** •Chlorpromazine •Thioridazine **Other:** •Lithium	• Theophylline	• Barbituates • Chloral Hydrate **Benzodiazepines** • Diazepam • Lorazepam • Oxazepam • Triazolam • Alprazolam • Clonazepam	• Alcohol • Meclizine • Prednisone • Prednisolone • Warfarin • B-lactam and quinolone antibiotics

Peter Chan

Reducing the Medication Load

- Discontinuing/substituting anticholinergic medications
  - Benadryl
  - Gravol
  - Atarax
  - Cogentin, etc.
- Discontinuing Benzodiazepines (monotherapy)
- Do not use Cimetidine!
- Monitoring the effects of High Dose Steroids, Quinolones
- Switching Narcotics to:
  - Dilaudid
  - Oxycodone
  - Fentanyl (chronic pain)

Physical Restraints in the Medically Ill Elderly

Pitfall #1: Restraints are necessary to prevent morbidity such as falls, and help with delirious pts.

- Physical restraints increase risk of *developing* delirium by 4.4x Precipitating Factors in Hospital-Acquired Delirium, Inouye and Charpentier, JAMA 1996; 275: 852-57
  - Additional morbidities (eg: pneumonia, DVT, stasis ulcers) and mortality risk

In 2001, the Ontario government passed Bill 85, the *Patient Restraints Minimization Act*

Avoid limb or posey restraints in the frail elderly!

Predisposing Factors

Inouye, SK et al. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 1993; 119:474-481

- cognitive impairment
- sleep deprivation
- immobility
- visual impairment
- hearing impairment
- Dehydration

Practical tip #2: Ask about use of visual and hearing aids! Carry a voice amplifier

General considerations: Diagnosing Geriatric Delirium

- 24 hr. observation, including sleep-wake cycle
- anxiety
- new incontinence
- unsteady gait, falls
- dysarthria/incoherence
- mood/affect lability
- subtle paranoia and hypervigilance

Practical tip #3: Ask specifically about vivid dreams or nightmares!

Pharmacological Management

Pharmacological Management of Delirium

- "Haloperidol as treatment of choice"
  - APA Guidelines 1999
- Other conventional antipsychotics
  - Loxapine (Loxapac)
  - Chlorpromazine
  - Methotrimeprazine (Nozinan)
  - Perphenazine
- Atypical antipsychotics
  - Risperidone, Olanzapine, Quetiapine

Peter Chan

Haloperidol in Delirium Management

- Comparator to atypicals (3 RCT's in Cochrane)
- Prolonged QTc, especially I.V.– baseline ECG
- Risk of Extrapyramidal Symptoms, esp. elderly
  - >4.5 mg/day in Cochrane Review
- "Evidence" based on 1 RCT (Breitbart 1996)
  - AIDS Dementia population; CPZ, Haldol, Lorazepam

  Pitfall #2: Haloperidol is best treatment as best evidence

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Pharmacologic Management of Geriatric Delirium

We recommend…

- Antipsychotics are the treatment of choice to manage the symptoms of delirium (with the exception of alcohol or benzodiazepine withdrawal delirium). (B)
- Haloperidol is suggested as the antipsychotic of choice based on the best available evidence to date. (B) Initial dosages are in the range of 0.25 mg- 0.5 mg. Od-bid (D)
- Atypical antipsychotics may be considered as alternative agents as they have lower rates of extra-pyramidal signs. (B)
- Benztropine should not be used prophylactically with haloperidol in the treatment of delirium. (D)

Pharmacologic Management

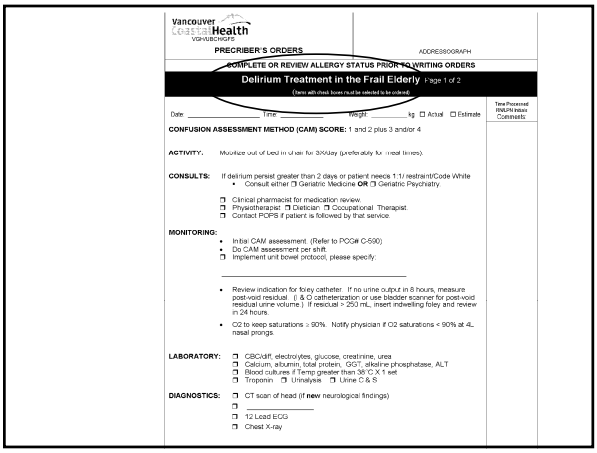
We recommend…

- In older persons with delirium who also have Parkinson's Disease or Lewy Body Dementia, atypical antipsychotics are preferred over typical antipsychotics. (D)
- Sedative-hypnotic agents are recommended as the primary agents for managing alcohol withdrawal delirium (B). Their use in other forms of delirium should be avoided (D).

Antipsychotics for Geriatric Delirium

From: Chan, BC Med J. Oct 2011

Medication	Trade Name	Category	Starting Dose (mg)	Usual Dose Range (mg)	Routes of Administration
Loxapine	Loxapac	Conventional	5-15	5-100	IV, IM, SC, PO
Methotrimeprazine	Nozinan	Conventional	2.5-10	2.5-100	IV, IM, SC, PO
Chlorpromazine	Largactil	Conventional	6.25-12.5	2.5-100	IM, SC, PO
Perphenazine	Trilafon	Conventional	1-2	2-16	IV, IM, PO
Haloperidol	Haldol	Conventional	0.5-1.0	0.5-5	IV, IM, SC, PO
Risperidone	Risperdal	Atypical	0.5-1.0	0.25-3	PO liq/tabs, SL
Olanzapine	Zyprexa	Atypical	1.25-5	2.5-15	PO, SL, IM
Quetiapine	Seroquel	Atypical	12.5-50	12.5-200	PO (IR, XR)



Vancouver Coastal Health

PRECRIBER'S ORDERS — ADDRESSOGRAPH

COMPLETE OR REVIEW ALLERGY STATUS PRIOR TO WRITING ORDERS

Delirium Treatment in the Frail Elderly Page 1 of 2

(Items with check boxes must be selected to be ordered)

Date _____ Time _____ Weight _____ kg ☐ Actual ☐ Estimate

Time Processed (RN/LPN Initials Comments)

CONFUSION ASSESSMENT METHOD (CAM) SCORE: 1 and 2 plus 3 and/or 4

AGTIVITY: Mobilize out of bed in chair for 3/4/day (preferably for meal times)

CONSULTS: If delirium persist greater than 2 days or patient needs 1:1/ restraint/Code White
- Consult either ❒ Geriatric Medicine **OR** ❒ Geriatric Psychiatry.

❒ Clinical pharmacist for medication review.
❒ Physiotherapist ❒ Dietician ❒ Occupational Therapist
❒ Contact PCPS if patient is followed by that service.

MONITORING:
- Initial CAM assessment. (Refer to PCG# C-590)
- Do CAM assessment per shift.
- ❒ Implement unit bowel protocol, please specify.

_____

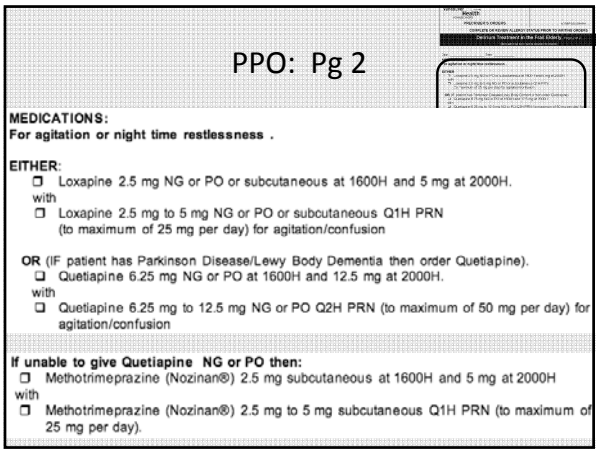
- Review indication for foley catheter. If no urine output in 8 hours, measure post-void residual. (I & O catheterization or use bladder scanner for post-void residual urine volume.) If residual > 250 mL, insert indwelling foley and review in 24 hours.
- O2 to keep saturations ≥ 90%. Notify physician if O2 saturations < 90% at 4L nasal prongs.

LABORATORY: ❒ CBC/diff, electrolytes, glucose, creatinine, urea
❒ Calcium, albumin, total protein, GGT, alkaline phosphatase, ALT
❒ Blood cultures if Temp greater than 38 C X 1 set
❒ Troponin ❒ Urinalysis ❒ Urine C & S

DIAGNOSTICS: ❒ CT scan of head (if **new** neurological findings)
❒ _____
❒ 12 Lead ECG
❒ Chest X-ray

Peter Chan

PPO: Pg 2



MEDICATIONS:
For agitation or night time restlessness .

EITHER:
- ❒ Loxapine 2.5 mg NG or PO or subcutaneous at 1600H and 5 mg at 2000H.

with
- ❒ Loxapine 2.5 mg to 5 mg NG or PO or subcutaneous Q1H PRN (to maximum of 25 mg per day) for agitation/confusion

OR (IF patient has Parkinson Disease/Lewy Body Dementia then order Quetiapine).
- ❒ Quetiapine 6.25 mg NG or PO at 1600H and 12.5 mg at 2000H.

with
- ❒ Quetiapine 6.25 mg to 12.5 mg NG or PO Q2H PRN (to maximum of 50 mg per day) for agitation/confusion

If unable to give Quetiapine NG or PO then:
- ❒ Methotrimeprazine (Nozinan®) 2.5 mg subcutaneous at 1600H and 5 mg at 2000H

with
- ❒ Methotrimeprazine (Nozinan®) 2.5 mg to 5 mg subcutaneous Q1H PRN (to maximum of 25 mg per day).

Alcohol Withdrawal and Delirium

Inappropriate use of Symptom-Triggered Therapy for Alcohol Withdrawal in the General Hospital Hecksel et al. Mayo Clin. Proc. 2008;83(3)

- 124 OF 495 PATIENTS RX WITH CIWA PROTOCOL IN TWO MAYO CLINIC AFFILIATED HOSPTIALS
- 52 % - 64/124 OF PATIENTS RX DID NOT MEET INCLUSION CRITERIA
- 14 % - 9 PTS UNABLE TO COMMUNICATE
- 55 % - 35 PTS HAD NO RECENT ALCOHOL HX
- 31 % - 20 PTS MET NEITHER CRITERIA

CIWA Protocol at VGH

- Protocol differs for:
  - Age 69 and under vs. Age 70 and over
  - In "older":
    - no diazepam
    - lower lorazepam doses
    - use of CAM to screen for concurrent delirium

Pitfall #3: Ask about alcohol and hypnotic use. Frail, medically ill seniors usually don't drink as much as estimated, but take more hypnotics than estimated.

CIWA in Older Adults

- **Physician to reassess for regular dosing on a daily basis**
  - **Nurse to screen for delirium using Confusion Assessment Method (CAM) and to call physician if CAM screen is positive.**
  - Nurse to call if CIWA≥20 or Lorzapam≥10mg/24hrs or seizure or HR>120 or SBP>180 or DBP>120
  - If CIWA-Ar score 0 to 9, call MD to have regular benzodiazepine dose tapered.
- **PRN:**
  - **Lorazepam 0.5 to 1 mg PO or SL or IM or SUBCUT Q1H PRN**
- **CIWA-Ar Score and dosing of lorazepam PRN:**
  - 0 to 9 No Medication Q1H x 3, then Q6H x 24 hours, then Q24H x 72 hours
  - 10 to 19 0.5 or 1 mg Q1H PRN Q1H until score below 10
  - 20 or greater Call Physician Q30 to 45 MIN until score below 20
- **Stop CIWA-Ar and call physician if patient confused, agitated, or drowsy.**

Pearls and Pitfalls

Practical tips	Pitfalls
• Check for urinary retention with a bladder scanner!	• Restraints are necessary to prevent morbidity such as falls, and help with delirious pts.
• Ask about use of visual and hearing aids! Carry a voice amplifier.	• Haloperidol is best treatment as best evidence
• Ask specifically about vivid dreams or nightmares!	• Ask about alcohol and hypnotic use. Frail, medically ill seniors usually don't drink as much as estimated, but take more hypnotics than estimated.

Peter Chan

Web Resources

- Care for Elders Interactive Delirium Module
  - UBC Division of Geriatric Psychiatry
  - www.careforelders.ca
- VIHA Delirium information
  - www.viha.ca/mhas/resources/delirium
- Canadian Coalition of Seniors Mental Health
  - Clinical practice guidelines (2006)
  - www.ccsmh.ca
- BCMJ Oct 2011: Chan, "Clarifying the Confusion about Confusion: Current Practices in Managing Geriatric Delirium"

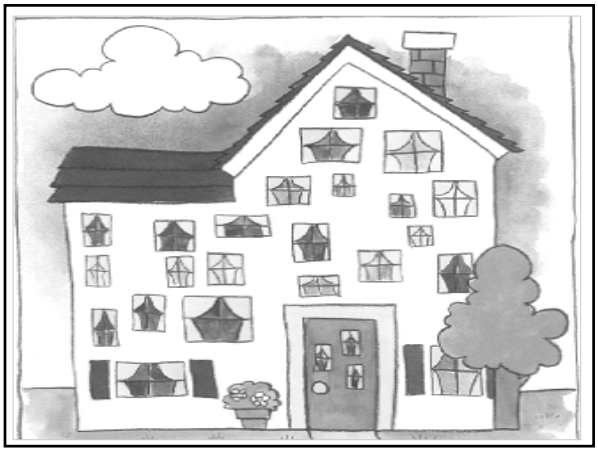
Drugectomy – Count on a 90% Success Rate

(aka 90% De-prescribing Success)

Stephen M. Setter, PharmD, DVM
De-Pharmacist
Associate Professor of Pharmacotherapy
Washington State University
Elder Services
Spokane, WA

Disclosure

- Steve has no disclosures to disclose or conflict with a COI to report or reveal: however he wakes daily and sometimes nightly with recurring thoughts of:
  - Prescribing cascade
  - Iatrogenic error
  - SE amplification
  - Therapeutic debridement
  - Drugectomy
  - Polypharmacy….is a disease?
  - Polyprescribers
  - Marinated in drugs
  - Minimally disruptive medicine
  - Burden of chronic disease
  - Pill Burden - ILL burden
  - Prescription multiplication
  - Evidence Free Zone - EFZ
  - De-prescribing – Getting the ILL out of pILLS
  - Pill a cat
  - Phlebotomizing a cat – giving Tylenol to a cat!!!



Can You HELP!!!

- My mother fell and broke her hip and I believe her medications made her weak and fatigued and caused her fall. Can you help?
- My husband died 3 months ago and for the last few months of his life he was prescribed so many drugs I think he died because of them. Can you help?
- I feel sick and tired all the time and my health care providers have me on 27 medications. Can you help?

Can You HELP!!!

- My father had a pacemaker placed last week and I was reading up on the drugs he takes and one of them says it can lead to premature pacemaker placement. Can you help?
- My father is starting to shake and he was told he has Parkinson's. But something doesn't seem right. Can you help?
- My mother was having a bad day and she started crying in the doctor's office and she got prescribed the antidepressant sertraline. Both of us don't think she is depressed but her doctor is adamant that she take sertraline. Can you help?

Objective

- State clinical situations where a discontinuation of therapy may increase patient ***well being***

BMJ 2011;343:d5184 doi: 10.1136/bmj.d5184

OBSERVATIONS

REALITY CHECK

Is your mum on drugs?

When "de-prescribing" may be the best medicine

Ray Moynihan *author, journalist, and conjoint lecturer, University of Newcastle, Australia*

Soon after she went into a small hospital a few years back, Johanna Trimble's mother in law seemed to enter a rapid physical and cognitive decline.

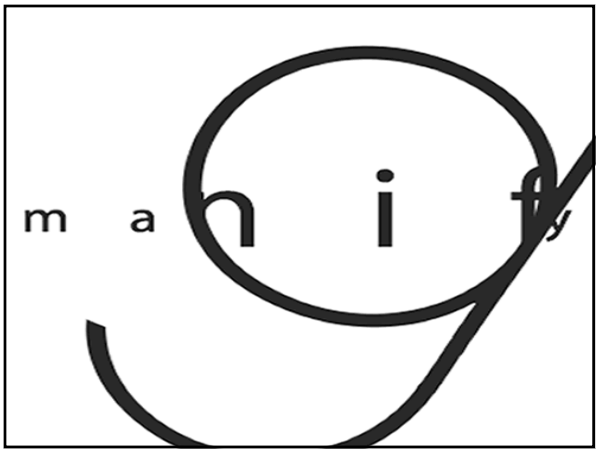
Fervid Trimble was at the time a woman in her late 80s, living

In this case, though, hearing what happened to Fervid Trimble helps tell the wider story of the dangerous overdrugging of our elders and the fact that families and loved ones can do something to stop it.

Why STOP Drug Therapy?

Causing SE
Not currently being used
No current indication
Used irregularly: non-life threatening
Treating SE of another drug
Iatrogenesis

Feeling better
Spending less $$$
Less complicated drug regimen



Stephen Setter

RD: 73 yo male

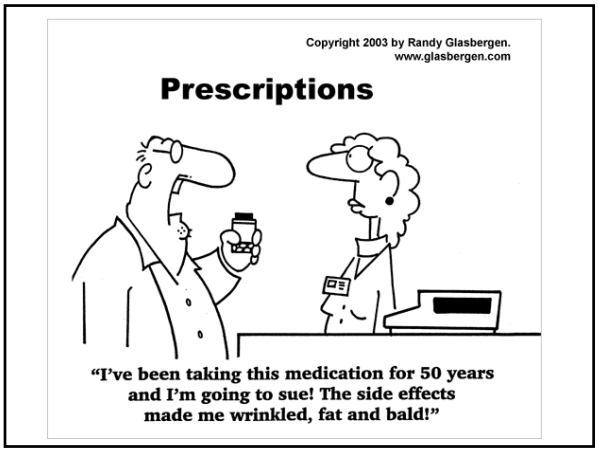
- **Phenytoin (Dilantin-ER) 300 mg QD**
- **Alprazolam (Xanax): 0.5 – 1.0 mg up to TID**

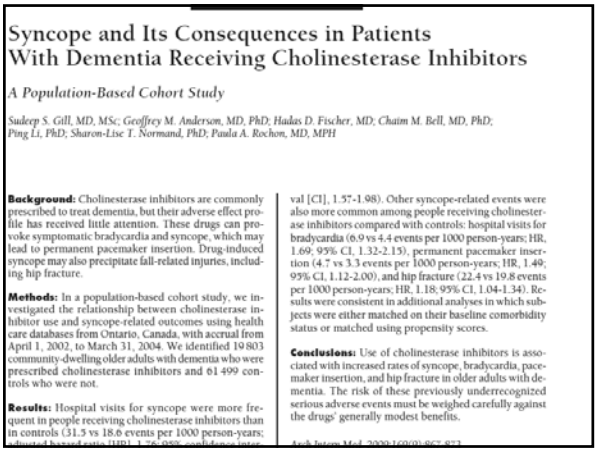
RD's Twin Brother: 73 yo male

- **Phenytoin (Dilantin) 100 mg QD**

OSDT

Stephen Setter





Syncope and Its Consequences in Patients With Dementia Receiving Cholinesterase Inhibitors

A Population-Based Cohort Study

Sudeep S. Gill, MD, MSc; Geoffrey M. Anderson, MD, PhD; Hadas D. Fischer, MD; Chaim M. Bell, MD, PhD; Ping Li, PhD; Sharon-Lise T. Normand, PhD; Paula A. Rochon, MD, MPH

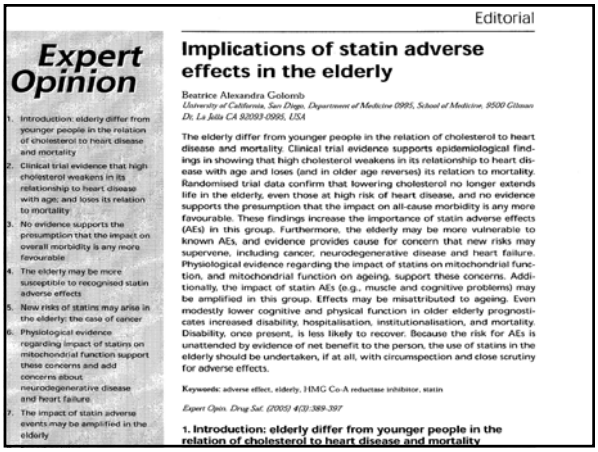
Background: Cholinesterase inhibitors are commonly prescribed to treat dementia, but their adverse effect profile has received little attention. These drugs can provoke symptomatic bradycardia and syncope, which may lead to permanent pacemaker insertion. Drug-induced syncope may also precipitate fall-related injuries, including hip fracture.

Methods: In a population-based cohort study, we investigated the relationship between cholinesterase inhibitor use and syncope-related outcomes using health care databases from Ontario, Canada, with accrual from April 1, 2002, to March 31, 2004. We identified 19 803 community-dwelling older adults with dementia who were prescribed cholinesterase inhibitors and 61 499 controls who were not.

Results: Hospital visits for syncope were more frequent in people receiving cholinesterase inhibitors than in controls (31.5 vs 18.6 events per 1000 person-years; adjusted hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.57-1.98). Other syncope-related events were also more common among people receiving cholinesterase inhibitors compared with controls: hospital visits for bradycardia (6.9 vs 4.4 events per 1000 person-years; HR, 1.69; 95% CI, 1.32-2.15), permanent pacemaker insertion (4.7 vs 3.3 events per 1000 person-years; HR, 1.49; 95% CI, 1.12-2.00), and hip fracture (22.4 vs 19.8 events per 1000 person-years; HR, 1.18; 95% CI, 1.04-1.34). Results were consistent in additional analyses in which subjects were either matched on their baseline comorbidity status or matched using propensity scores.

Conclusions: Use of cholinesterase inhibitors is associated with increased rates of syncope, bradycardia, pacemaker insertion, and hip fracture in older adults with dementia. The risk of these previously underrecognized serious adverse events must be weighed carefully against the drugs' generally modest benefits.

Arch Intern Med. 2009;169(9):867-873



Editorial

Expert Opinion

1. Introduction: elderly differ from younger people in the relation of cholesterol to heart disease and mortality
2. Clinical trial evidence that high cholesterol weakens in its relationship to heart disease with age, and loses its relation to mortality
3. No evidence supports the presumption that the impact on overall morbidity is any more favourable
4. The elderly may be more susceptible to recognised statin adverse effects
5. New risks of statins may arise in the elderly: the case of cancer
6. Physiological evidence regarding impact of statins on mitochondrial function support these concerns and add concerns about neurodegenerative disease and heart failure
7. The impact of statin adverse events may be amplified in the elderly

Implications of statin adverse effects in the elderly

Beatrice Alexandra Golomb
University of California, San Diego, Department of Medicine 0995, School of Medicine, 9500 Gilman Dr, La Jolla CA 92093-0995, USA

The elderly differ from younger people in the relation of cholesterol to heart disease and mortality. Clinical trial evidence supports epidemiological findings in showing that high cholesterol weakens in its relationship to heart disease with age and loses (and in older age reverses) its relation to mortality. Randomised trial data confirm that lowering cholesterol no longer extends life in the elderly, even those at high risk of heart disease, and no evidence supports the presumption that the impact on all-cause morbidity is any more favourable. These findings increase the importance of statin adverse effects (AEs) in this group. Furthermore, the elderly may be more vulnerable to known AEs, and evidence provides cause for concern that new risks may supervene, including cancer, neurodegenerative disease and heart failure. Physiological evidence regarding the impact of statins on mitochondrial function, and mitochondrial function on ageing, support these concerns. Additionally, the impact of statin AEs (e.g., muscle and cognitive problems) may be amplified in this group. Effects may be misattributed to ageing. Even modestly lower cognitive and physical function in older elderly prognosticates increased disability, hospitalisation, institutionalisation, and mortality. Disability, once present, is less likely to recover. Because the risk for AEs is unattended by evidence of net benefit to the person, the use of statins in the elderly should be undertaken, if at all, with circumspection and close scrutiny for adverse effects.

Keywords: adverse effect, elderly, HMG Co-A reductase inhibitor, statin

Expert Opin. Drug Saf. (2005) 4(3):389-397

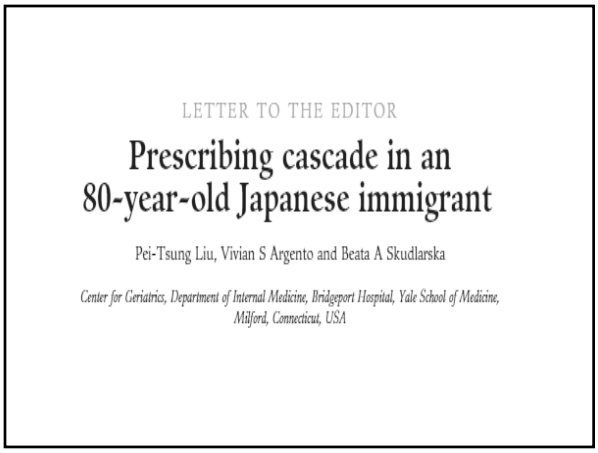
1. Introduction: elderly differ from younger people in the relation of cholesterol to heart disease and mortality

TR: 13 yo female w/ behavior issues and anxiety

- **Carbamazepine (Tegretol) 400 mg BID**
- **Buspirone (Buspar): 30 mg BID**

Tapered off of Tegretol

New onset v/d, malaise, headaches, lethargy

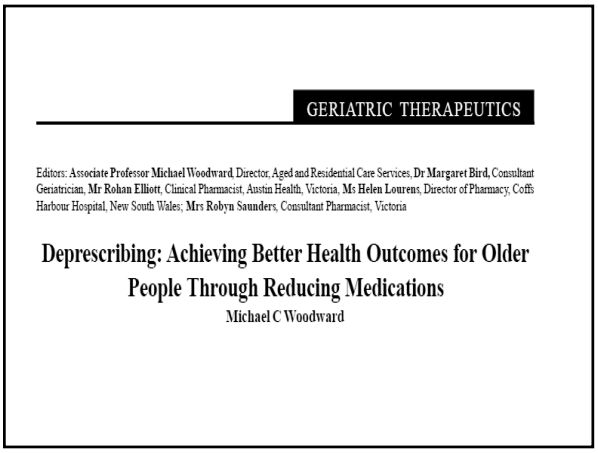


LETTER TO THE EDITOR

Prescribing cascade in an 80-year-old Japanese immigrant

Pei-Tsung Liu, Vivian S Argento and Beata A Skudlarska

Center for Geriatrics, Department of Internal Medicine, Bridgeport Hospital, Yale School of Medicine, Milford, Connecticut, USA



GERIATRIC THERAPEUTICS

Deprescribing: Achieving Better Health Outcomes for Older People Through Reducing Medications

Michael C Woodward

KEY POINTS

1. Older people are frequently prescribed unnecessary or dangerous medications.

2. It is possible and indeed an obligation to deprescribe; reduce, substitute or cease inappropriate medications.

3. Deprescribing should be planned and generally not overly hasty.

4. Deprescribing should be performed as a partnership between the patient and the prescribing team.

5. Regular patient review and support is required for successful deprescribing.

Which Meds or Category of Meds Can be Considered to be Typically "Deprescribed?"

Diuretics
Antihypertensives
Antipsychotics
Antidepressants
NSAIDs
Lipid lowering drugs
Cholinesterase inhibitors
Antiparkinson's drugs
Digoxin
Amiodarone

Call for Papers

Less Is More

The *Archives of Internal Medicine* is excited to launch Less Is More—a new feature identifying articles that provide evidence about situations in which less health care results in better health. For more details, please see the editorial in the April 12, 2010, issue, page 584.

LESS IS MORE

Feasibility Study of a Systematic Approach for Discontinuation of Multiple Medications in Older Adults

Addressing Polypharmacy

Doron Garfinkel, MD; Derelie Mangin, MBChB

Background: Polypharmacy and inappropriate medication use is a problem in elderly patients, who are more likely to experience adverse effects from multiple treatments and less likely to obtain the same therapeutic benefit as younger populations. The Good Palliative–Geriatric Practice algorithm for drug discontinuation has been shown to be effective in reducing polypharmacy and improving mortality and morbidity in nursing home inpatients. This study reports the feasibility of this approach in community-dwelling older patients.

Methods: The Good Palliative-Geriatric Practice algorithm was applied to a cohort of 70 community-dwelling older patients to recommend drug discontinuations. Success rates of discontinuation, morbidity, mortality, and changes in health status were recorded.

Results: The mean (SD) age of the 70 patients was 82.8 (6.9) years. Forty-three patients (61%) had 3 or more and 26% had 5 or more comorbidities. The mean follow-up was 19 months. Participants used a mean (SD) of 7.7 (3.7) medications. Protocol indicated that discontinuation was recommended for 311 medications in 64 patients (58% of drugs; mean [SD], 4.4 [2.5] drugs per patient overall, 4.9 per patient who had discontinuation). Of the discontinued drug therapies, 2% were restarted because of recurrence of the original indication. Taking nonconsent and failures together, successful discontinuation was achieved in 81%. Ten elderly patients (14%) died after a mean follow-up of 13 months, with the mean age at death of 89 years. No significant adverse events or deaths were attributable to discontinuation, and 88% of patients reported global improvement in health.

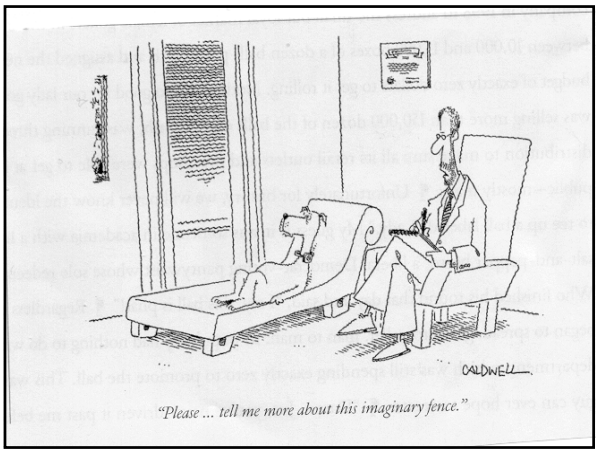
Conclusions: It is feasible to decrease medication burden in community-dwelling elderly patients. This tool would be suitable for larger randomized controlled trials in different clinical settings.

Arch Intern Med. 2010;170(18):1648-1654

EG

- **84 year old white male, Parkinson's Disease (no obvious tremor), T2DM, recurrent edema**
- **Lives at home with his wife who is also his primary care taker**
- **He is having frequent episodes of hypoglycemia with three ED visits - hospitalizations within 4 months [A1C = 5.8%]**
- **Wife is a very diligent caregiver, keeping a detailed journal and medical history**
- **EG has "dementia" and has been experiencing hallucinations of George Bush in the ceiling fan**
- **Stalevo was recently increased**
- **EG smoked cigars previously and likes to drink Italian liquor~2 shots per day (morning / eve)**

Stephen Setter



"Please ... tell me more about this imaginary fence."

Doctors:
PCP, Neurologist, Cardiologist, Dermatologist, Urologist, Ophthalmologist, Pulmonologist, Podiatrist, Psychiatrist

PMH:
Parkinson's Disease, Dementia, Depression, Type 2 Diabetes, Congestive Heart Failure

Concerns:
Patient's wife reports dramatic decline in function (won't be more specific), urinary incontinence, and is keeping a detailed journal to show us his status hourly

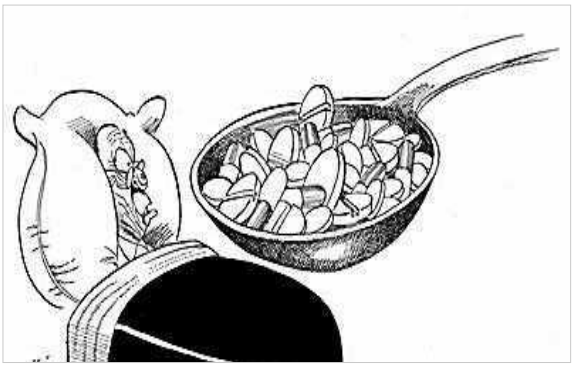
Drug Allergies: unknown

Current Medications

Hytrin® (terazosin) 10mg	**1 Q HS**
Lanoxin® (digoxin) 0.25mg	**1 Q AM**
Prinivil® (lisinopril) 20mg	**1 Q AM**
Coreg® (carvedilol) 12.5mg	**1 BID**
Imdur® (isosorbide mononitrate) 60mg	**1 BID**
Lasix® (furosemide) 80 mg	**Q AM**
Micro-K® (potassium) 10mEq/5mL	**7.5 ml BID**
Plavix® (clopidogrel) 75mg	**1 QD**
Mevacor® (lovastatin) 80mg	**1 Q PM**

Current Medications

Aspirin 325mg	**1 Q AM**
Nitrostat® (nitroglycerin) 0.4mg	**PRN**
Stalevo® (carbidopa/levodopa/entacapone) 150mg	**1 TID**
Requip® (ropinirole) 3mg	**1 AM, ½ noon, 1PM**
Lantus® (insulin glargine)	**12 U Q AM**
Humalog (lispro)	**3-4 Units ac**
Klonopin® (clonazepam) 1-2mg	**Q HS PRN**
Lexapro® (escitalopram) 20 mg	**1 QD**
Mucinex® (guaifenesin) 200mg	**1 QD**
SlowFe® (Iron SO4) 160mg	**3 TID**




"I feel a lot better since I ran out of those pills you gave me."

Can you count on the new oral anticoagulants?

Peter Loewen
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www.peterloewen.com

COI Disclosure

dabigatran
rivaroxaban

apixaban
edoxaban
betrixaban
YM150

VTE px post hip/knee surgery

stroke prevention in AF

VTE acute tx / secondary prevention

ACS

	THR/TKR, GenMed VTE Px	VTE Tx	AF	ACS
dabigatran	**RENOVATE, REMOBILIZE, REMODEL**	**RE-COVER**	**PETRO RE-LY**	
rivaroxaban	**RECORD 1,2,3,4**	**EINSTEIN EINSTEIN-PE**	**ROCKET AF**	**ATLAS-2**
apixaban edoxaban	**ADVANCE 1, 2, 3 ADOPT**		**AVERROES ARISTOTLE** **(ENGAGE-AF)**	**APPRAISE-2**

VTE px post hip/knee surgery

stroke prevention in AF

VTE acute tx / secondary prevention

ACS

www.peterloewen.com

SPARC - Stroke Prevention in Atrial Fibrillation Risk Calculator
for estimating risk of stroke and benefits & risks of antithrombotic therapy in patients with chronic atrial fibrillation

version 5.0, February 2011
Developed by Peter Loewen, ACPR, Pharm.D., FCSHP [ploewen@interchange.ubc.ca]

In your patient with atrial fibrillation, which of the following stroke or bleeding risk factors are present? (click check boxes)

? **CHADS2 CRITERIA**

- CHF/LV dysfunction (diagnosed at any time in the past)
- Hypertension (controlled or uncontrolled)
- Age > 75
- Diabetes (Type I or II) controlled or uncontrolled
- TIA or stroke at any time in the past

CHADS2 SCORE (0-6): 0

? **CHA2DS2-VASc CRITERIA***

- Prior MI, peripheral artery disease, or aortic plaque
- Age 65-75
- Female

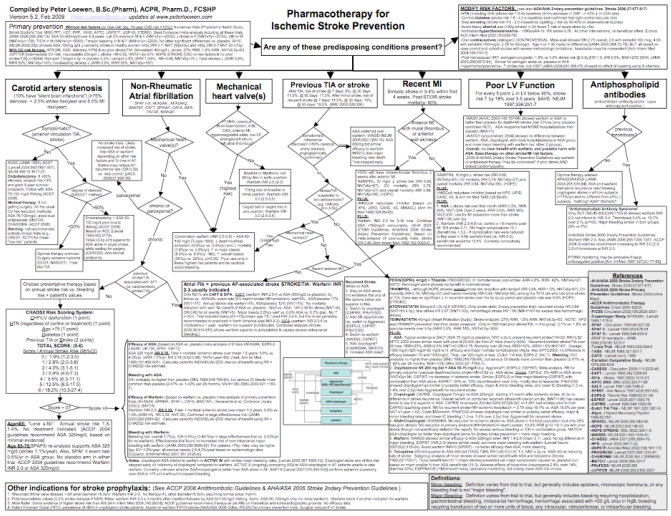
CHA2DS2-VASc SCORE (0-9): 0

*CHA2DS2-VASc has similar or possibly slightly better predictive performance than CHADS2. [BMJ 2011;342:d124 doi:10.1136/bmj.d124]

? **HAS-BLED CRITERIA****

- Abnormal renal function
- Abnormal liver function
- History of major bleeding (any cause)
- History of labile INR (time in therapeutic range <60%)
- Current "excess" use of alcohol
- Currently taking antiplatelet drug(s) or NSAID(s)

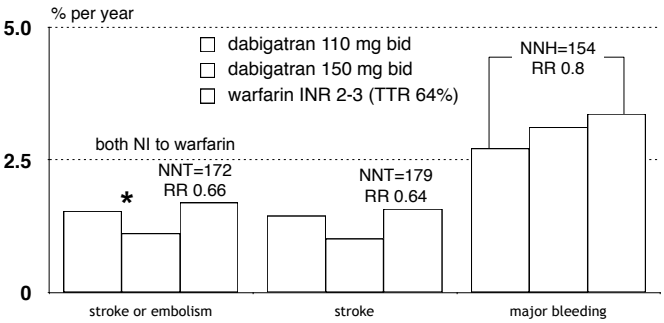
HAS-BLED SCORE (0-9): 0**



www.peterloewen.com

RE-LY: dabigatran vs. warfarin in AF

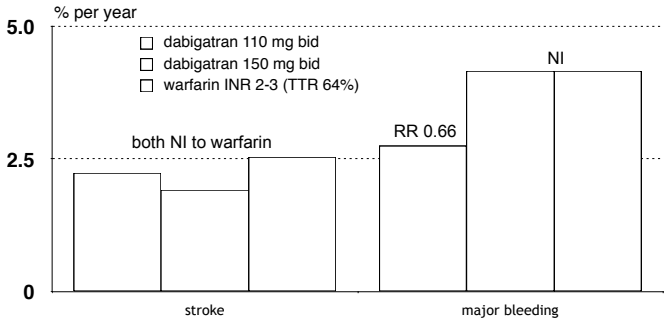
N= 18,113 AF patients with 1+ risk factors for stroke (mean CHADS2 score 2.1). Median 2y followup. Non-inferiority trial.



RE-LY. NEJM 2009;361

RE-LY: dabigatran vs. warfarin in AF - SECONDARY prevention

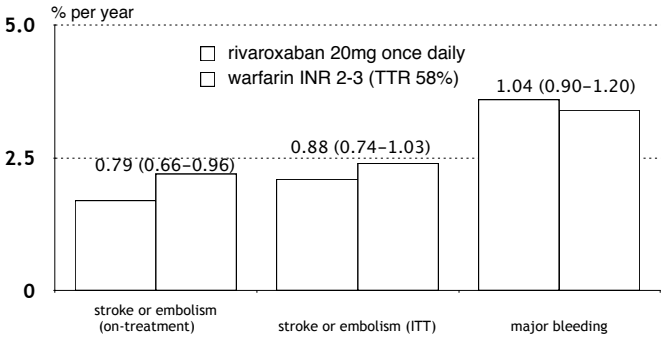
N= 3,623 AF patients with prior stroke/TIA. Median 2y followup.
Pre-specified secondary analysis



RE-LY. Lancet Neurol 2010; 9: 1157–63.

Rivaroxaban: ROCKET-AF

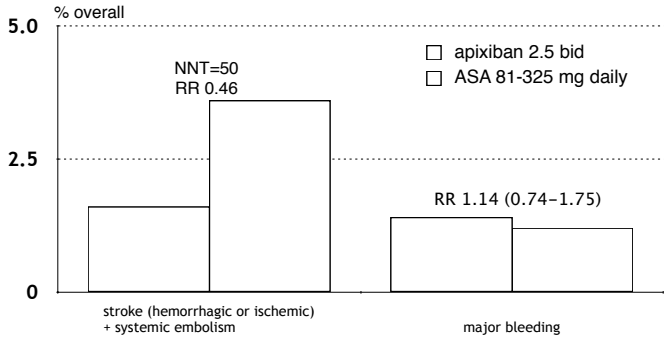
N= 14,264 AF patients, 90% with CHADS2 >2.
Median 40 months followup. DB, Non-inferiority trial.



ROCKET-AF. NEJM 2011;10.1056/NEJMoa1009638 (10AUG11)

Apixaban: AVERROES

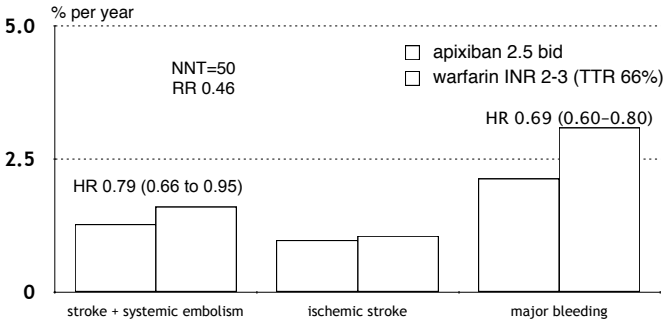
N= 5,599 AF patients with AF + intolerant or "unsuitable" for warfarin. Max 3y followup (stopped early). Superiority trial.



AVERROES. N Engl J Med 2011 (10.1056/NEJMoa1007432)

Apixaban: ARISTOTLE

N= 18,201 AF patients with AF. ~70 had CHADS2 score >1. Median 1.8y followup. DB non-inferiority trial.



ARISTOTLE. N Engl J Med 2011. (10.1056/NEJMoa1107039) 28AUG11

CCS AF Guidelines

2010

"We suggest that when OAC therapy is indicated, most patients should receive dabigatran in preference to warfarin." (Conditional recommendation, High Quality Evidence)"

Canadian Journal of Cardiology 27 (2011) 74 –90

2012

"When oral anticoagulant therapy is indicated, most patients should receive dabigatran, rivaroxaban, or apixaban (once approved by Health Canada), in preference to warfarin (conditional recommendation, high-quality evidence)."

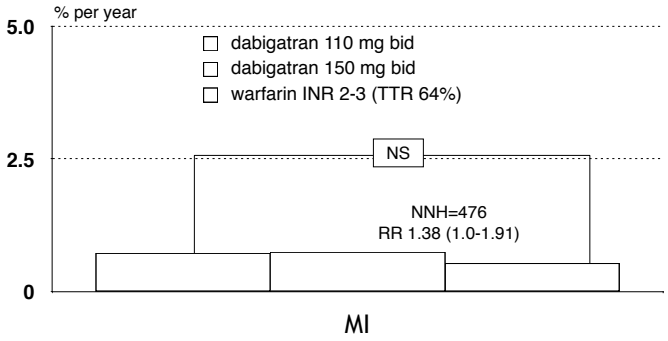
Canadian Journal of Cardiology 28 (2012) 125–136

Dabigatran & Rivaroxaban **ISSUES** in AF

- choice of dabigatran dose
- patient selection
  - candidate for anticoagulation? (stroke risk vs. bleeding risk)
  - warfarin suitable?
  - renal function?
- dabigatran MI risk
- Special bleeding issues
  - ICH risk
  - managing major bleeding events
- cost / cost-effectiveness

MI: The RE-LY side of the story

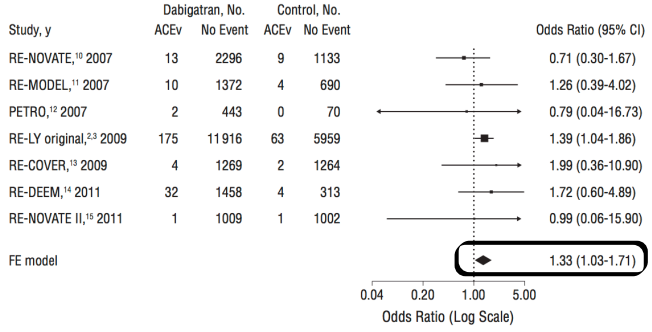
N= 18,113 AF patients with 1+ risk factors for stroke (mean CHADS2 score 2.1). Median 2y followup. Non-inferiority trial.



RE-LY. NEJM 2009;361

MI: another side

Meta-analysis of 7 RCTs, N=30,514.



Arch Intern Med. 2012;172(5):397-402

MI: More RE-LY side of the story

vs. warfarin	110 bid	150 bid
MI	1.29 (95%CI 0.96–1.75)	1.27 (95% CI 0.94–1.71)
MI, unstable angina, cardiac arrest, cardiac death	0.93 (95% CI 0.80 –1.06)	0.98 (95% CI 0.85–1.12)
Net Clinical Benefit (strokes, systemic embolism, MI, pulmonary embolism, major bleeding, and all-cause death)	0.92 (95%CI 0.84–1.01)	0.90 (95% CI 0.82–0.99)

Circulation. 2012;125:669-676

dabigatran
bleeding shenanigans

Table 4. National Estimates of Medications Commonly Implicated in Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.*

Medication	Annual National Estimate of Hospitalizations (N=99,628)		Proportion of Emergency Department Visits Resulting in Hospitalization
	no.	*% (95% CI)*	%
Most commonly implicated medications†			
Warfarin	33,171	33.3 (28.0–38.5)	46.2
Insulins	13,854	13.9 (9.8–18.0)	40.6
Oral antiplatelet agents	13,263‡	13.3 (7.5–19.1)	41.5
Oral hypoglycemic agents	10,656	10.7 (8.1–13.3)	51.8
Opioid analgesics	4,778	4.8 (3.5–6.1)	32.4
Antibiotics	4,205	4.2 (2.9–5.5)	18.3
Digoxin	3,465	3.5 (1.9–5.0)	80.5
Antineoplastic agents	3,329‡	3.3 (0.9–5.8)‡	51.5
Antiadrenergic agents	2,899	2.9 (2.1–3.7)	35.7
Renin–angiotensin inhibitors	2,870	2.9 (1.7–4.1)	32.6
Sedative or hypnotic agents	2,469	2.5 (1.6–3.3)	35.2
Anticonvulsants	1,653	1.7 (0.9–2.4)	40.0
Diuretics	1,071‡	1.1 (0.4–1.8)‡	42.4
High-risk or potentially inappropriate medications§			
HEDIS high-risk medications	1,207	1.2 (0.7–1.7)	20.7
Beers-criteria potentially inappropriate medications	6,607	6.6 (4.4–8.9)	42.0
Beers-criteria potentially inappropriate medications, excluding digoxin	3,170	3.2 (2.3–4.1)	27.6

N Engl J Med 2011;365:2002-12.

Cost-Effectiveness in AF

Net Clinical Benefit?

Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: A modelling analysis based on a nationwide cohort study

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Summary
The concept of net clinical benefit has been used to quantify the balance between risk of ischaemic stroke (IS) and risk of intracranial haemorrhage (ICH) with the use oral anticoagulant therapy (OAC) in the setting of non-valvular atrial fibrillation (AF), and has shown that patients at highest risk of stroke and thromboembolism gain the greatest benefit from OAC with warfarin. There are no data for the new OACs, that is, dabigatran, rivaroxaban and apixaban, as yet. We calculated the net clinical benefit balancing IS against ICH using data from the Danish National Patient Registry on patients with non-valvular AF between 1997–2008, for dabigatran, rivaroxaban and apixaban on the basis of recent clinical trial outcome data for these new OACs. In patients with $CHADS_2$=0 but at high bleeding risk, apixaban and dabigatran 110 mg bid had a positive net clinical benefit. At CHA_2DS_2-VASc=1, apixaban and both doses of dabigatran (110 mg and 150 mg bid) had a positive net clinical benefit. In patients with $CHADS_2$ score≥1 or CHA_2DS_2-VASc≥2, the three new OACs (dabigatran, rivaroxaban and apixaban) appear superior to warfarin for net clinical benefit, regardless of risk of bleeding. When risk of bleeding and stroke are both high, all three new drugs appear to have a greater net clinical benefit than warfarin. In the absence of head-to-head trials for these new OACs, our analysis may help inform decision making processes when all these new OACs become available to clinicians for stroke prevention in AF. Using 'real world' data, our modelling analysis has shown that when the risk of bleeding and stroke are both high, all three new drugs appear to have a greater net clinical benefit compared to warfarin.

Keywords
Dabigatran, rivaroxaban, apixaban, atrial fibrillation, stroke prevention

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VTE px post hip/knee surgery

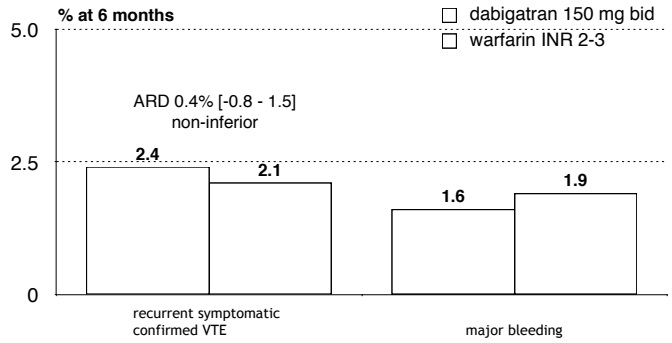
stroke prevention in AF

VTE acute tx / secondary prevention

ACS

RE-COVER: dabigatran vs. warfarin in acute VTE

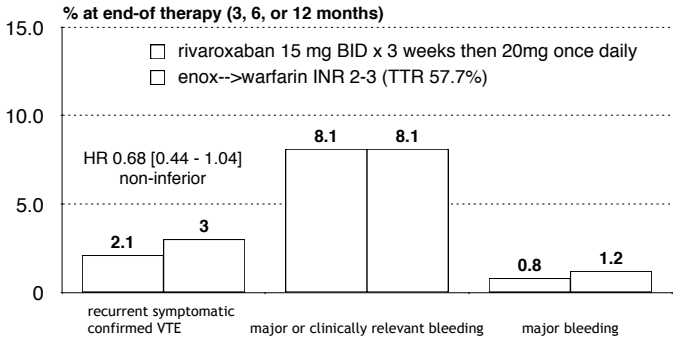
N= 2,539 with VTE and median 9 days of LMWH. 6 months followup.
Non-inferiority margin: ARD 3.6%, HR 2.75.
30% PE. 60% time in-range for warfarin.



RE-COVER. NEJM 2009;361

EINSTEIN: rivaroxaban vs. warfarin in acute VTE

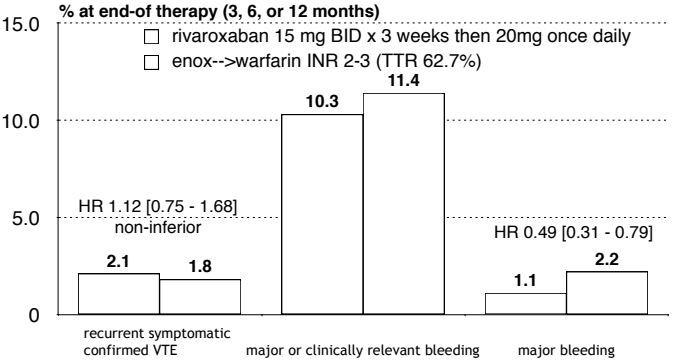
N= 3,449 with acute proximal DVT without PE. 6 months followup. Non-inferiority margin: HR 2.0.



EINSTEIN. NEJM 2010;10.1056/NEJMoa1007903

EINSTEIN-PE: rivaroxaban vs. warfarin in acute PE

N= 4,832 with acute symptomatic PE (89% hospitalized). 6 months followup. Non-inferiority margin: HR 2.0.



EINSTEIN-PE. N Engl J Med 2012;366:1287-97 (5APR12)

Who?

- warfarin fear/loathing
- warfarin labile INR (compliance? dietary variation? mysterious forces?)
- elective cardioversion?
- coverage
- post-op rivaroxaban
- switching

dabigatran Cheat Sheet

- indications: post total hip/knee replacement, AF stroke prevention
- dosage:
  - post-op: 220mg once daily (half-dose if CrCl 30-50 mL/min)
  - AFib: 150mg bid or 110mg bid
- drug-drug interactions: bleeders, rifampin, ketoconazole, verapamil, amiodarone, quinidine
- unique ADRs: bleeding, diarrhea (~2%), dyspepsia (~1%)
- lab monitoring:
- cost: ~$1.60 per capsule (all strengths) ~$3.20 / day

rivaroxaban Cheat Sheet

- indications: post total hip/knee replacement, AF stroke prevention, acute DVT (without PE) treatment
- dosage: 10 mg once daily (TKR/THR), 20 mg once daily (AF), 15 mg BID x 3 weeks then 20mg once daily (DVT) ("caution" if CrCl 30-50 mL/min)
- drug-drug interactions: bleeders, P3A4 *and* P-gp inhibitors (eg. azoles, ritonavir, PHT/CBZ/PHB)
- unique ADRs: bleeding, dyspepsia
- lab monitoring:
- cost:

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Thanks for your questions and discussion.

Thanks for completing your course evaluations.

HAVE A SAFE TRIP HOME

We hope to see you next year!