26TH ANNUAL
BEST SCIENCE MEDICINE COURSE

April 17th and 18th, 2015

Fairmont Waterfront Hotel
Vancouver, B.C.

SATURDAY SYLLABUS

Sponsored by

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

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

"It is an art of no little importance to administer medicines properly; but it is an art of much greater and more difficult acquisition to know when to suspend or altogether omit them."

Philippe Pinel 1745-1826

The New Therapeutic Commandments

Thou shalt

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

Written by R Lehman, J McCormack, T Perry, A Tejani, J Yudkin

Best Science Medicine Course 2015

FACULTY

Course Committee

Co-Chairs:
Bob Rangno, Emeritus Prof., Medicine, Pharmacology, UBC & PHC
James McCormack, Prof., Pharmaceutical Sciences, UBC
G. Michael Allan, Prof., Family Medicine, University of Alberta
& Director, Evidence and CPD Program, Alberta College of Family Physicians

Committee:

Rita McCracken, Clin. Assist. Prof., Medicine and Associate Head, Family Medicine, PHC
Tracy Monk, Clin. Assist. Prof., Medicine, UBC

Guest Faculty

G. Michael Allan, Prof., Family Medicine, University of Alberta
& Director, Evidence and CPD Program, Alberta College of Family Physicians
Scott Garrison, Assoc. Prof., Family Medicine, University of Alberta
Mike Kolber, Assoc. Prof., Family Medicine, University of Alberta
Tina Korownyk, Assoc. Prof., Family Medicine, University of Alberta
Janet Nuth, Physician Risk Manager, CMPA, Ottawa, Ontario

Local Faculty

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

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

BSMC
BEST SCIENCE MEDICINE COURSE

26th Annual Best Science Medicine Course

Formerly The Drug Therapy Decision Making Course – 25 years

Saturday, April 18, 2015

07:30 Registration (Muffins & Coffee)

"Who knows what evil lurks in the hearts of men?"

08:30	Cardiac and Risk – super important concepts and also two lesser known superheroes	Mike Allan and James McCormack
08:50	Risk assessment tools – where does he get those wonderful toys?	James McCormack
09:10	Nutrition – are there really any Superfoods?	James McCormack
09:30	Questions	
09:50	Refreshment Break	

"My spider sense is tingling"

10:10	Restless legs – slowing down The Flash	Scott Garrison
10:30	Be a Medico-Legal Survivor – High risk meds	Janet Nuth
10:50	Questions	
11:10	Immune Modulators for RA – can we thaw Mr. Freeze?	Kam Shojania
11:30	Questions	
11:50	Lunch	

"Here I come to save the day"

12:50	Prenatal care – impacting your future Superboy/Supergirl	Tina Korownyk
13:10	Dementia – I don't do can't	Rita McCracken
13:30	Tricks and tips so you can be a Superhero health care provider	The Gang plus the Audience
15:00	With Great Power Comes Great Responsibility	The End

Have a safe journey home!

James McCormack and G. Michael Allan

Cardiac and Risk

Super Important Concepts

and also two lesser known superheroes

James and Mike

Faculty/Presenter Disclosure

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

26th Annual Best Science Medicine Course

Learning Outcome Objective Slide

Provide at least one learning objective.

"Super Important Concepts and also two lesser known superheroes" Talk

1) To be able to make an estimate of CVD risk given risk factors for a particular patient

2) Using that risk make an estimate of the absolute benefit of treating these risk factors

Evidence-based risk communication

"There is likely no single best method of communicating probabilities to patients but rather several good options with some better suited to certain risk scenarios."

Ann Intern Med 2014;161:270-80

Recommended approaches

GENERAL SUGGESTIONS - these are relative
use percentages or natural frequencies(numerator/denominator)
use absolute terms
add bar graphs or icon arrays
use incremental risk format with icon arrays in the same array
avoid use of NNTs
if use relative risks add baseline risks

Ann Intern Med 2014;161:270-80

T2DM - Lifetime Treatment Benefits - absolute risk reduction

	Age	ESRD	Vision Loss	Amputation	First MI
Metformin at diagnosis	45	6.5	2.1	2.7	2.6
	55	4.2	1.6	2.2	4.0
	65	2.1	1.0	1.5	3.7
	75	0.7	0.5	0.8	2.7
Switch to Insulin after 10 years	45	1.3	0.4	0.4	1.0
	55	0.7	0.2	0.3	0.8
	65	0.3	0.1	0.2	0.6
	75	0.1	0	0.1	0.3

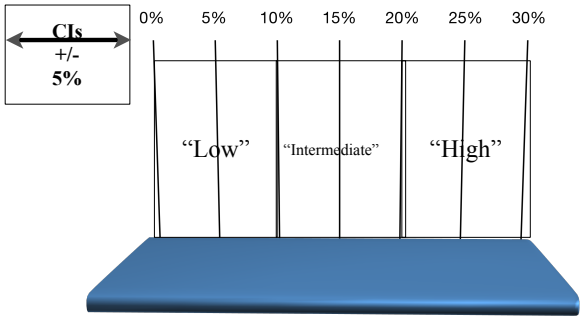
UKPDS - most optimistic

JAMA Intern Med. doi:10.1001/jamainternmed.2014.2894

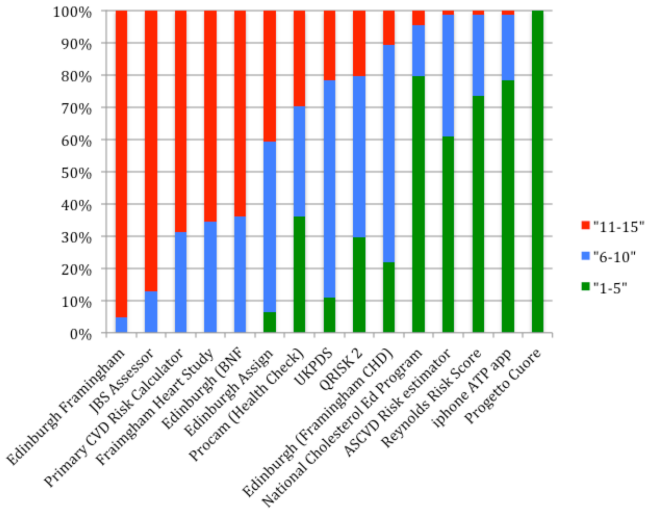
James McCormack and G. Michael Allan

How accurately can we predict risk?

Cardiovascular Endpoints



J Cardiovasc Risk 2002;9:183-90



How much do risk calculators vary in how they weight specific risk factors for the same person

Gender Female vs Male
Edinburgh ASSIGN 35% vs iPhone ATPII 225%

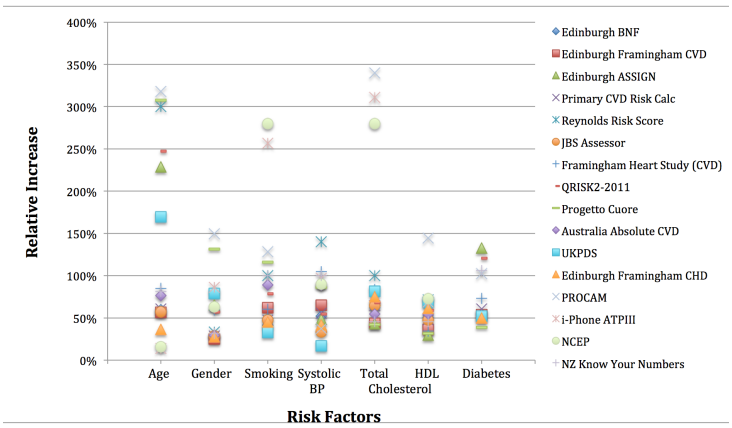
Smoking vs Not
UKPDS 31% vs PROCAM Health Check 118%

Systolic BP 120 to 160
UKPDS 16% vs Reynolds Risk Score 124%

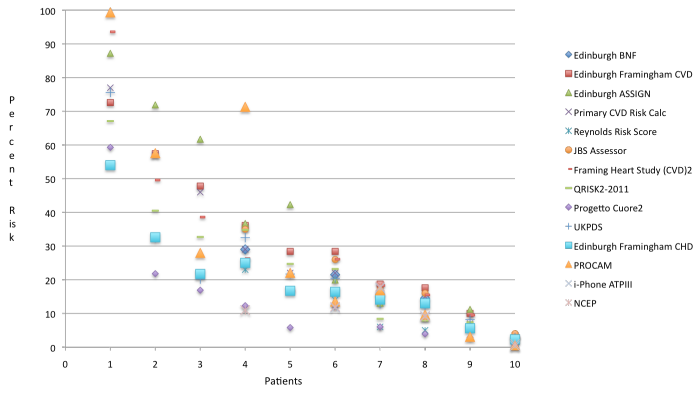
Total Cholesterol 4 – 7 mmol/L
QRISK-2 51% vs PROCAM Health Check 302%

How Relative Risk Weighting of the same Risk factors varies by Calculator

(50-year-old, Female, Smoker, 160 Systolic BP, 7 Total Chol, 0.8 HDL, Non-Diabetic)



Agreement in Risk Calculators



Circulation 2013; 127: 1948-1956

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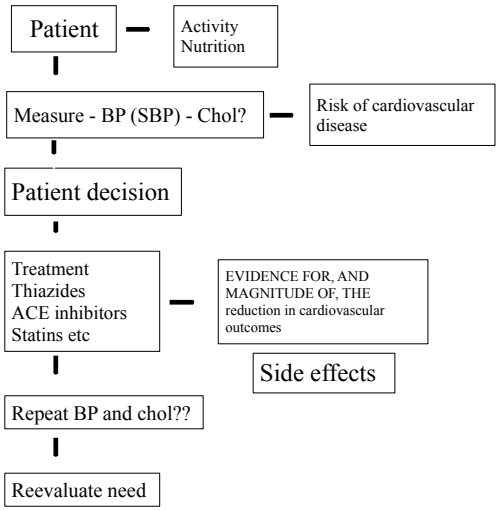
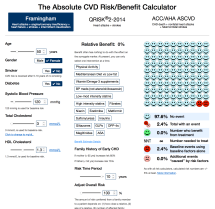
Variability in Calculating Risk

95% Confidence Intervals (CI) around 10-year predictions of CHD

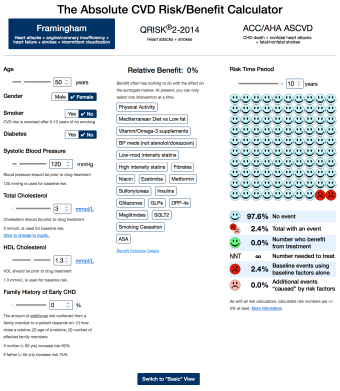
Framingham[1]	Baseline	<10%	10-20%		30-40%
	CI (+/-)	1.5%	3%		15%
Reynolds[2]	Baseline	10%	15%	20%	30%
	CI (+/-)	4%	5%	6%	7%

1. Am Heart J 1991; 121: 293-98. 2. J Cardiovasc Risk 2002; 9: 183-190.

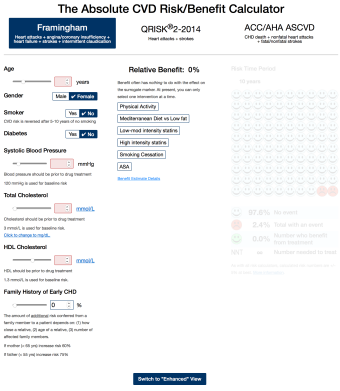




Enhanced



Basic

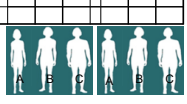


cvdcalculator.org

Intervention	Relative CVD Benefits	Evidence used for estimating the relative benefits
Physical Activity	**~25%**	Eur J Cardiovasc Prev Rehabil 2008;15:239-46, Int J Environ Res Public Health 2012;9:391-407
Mediterranean Diet vs Low Fat	**~30%**	N Engl J Med 2013 DOI:10.1056/NEJMoa1200303
Vitamins/Omega 3 supplements	**~0%**	Lancet 1996;347:781-6, JAMA 2007;297:842-57, ACP Journal Club 2007;147(1):4 http://www.acfp.ca/Portals/0/docs/TFP/20120703_015221.pdf
Blood pressure (only if SBP 140 or higher)	**~30% (~50% if diabetic)**	J Htn 1993;11(suppl4):S61-73, (Atenolol no effect on CVD) Lancet 2004;364:1684–9, Ann Intern Med 2003;138:587-92, CD004349
Low-Moderate Intensity Statins	**~25%**	Lancet 2008;371:117-25; Women-J Am Coll Cardiol 2012;59:572–82; Over age 65-J Am Coll Cardiol 2013 Aug 14 pii:S0735-1097(13)03880-1
High-Intensity Statins (atorvastatin 40-80mg; rosuvastatin 20-40mg)	**~35%**	Most of the data for this comes from secondary prevention trials - Eur Heart J 2011;32:1409-15, Int J Cardiol 2013;166:431-9
Fibrates	**~0%**	NEJM 2010;362:1563-74, Amer J Med 2009;122:962.e1-962.e8, Int J Cardiol 2009 doi:10.1016/j.ijcard.2008.11.211
Niacin	**No studies**	
Ezetimibe	**~0%**	NEJM 2008;358:1431-43
Sulfonylureas	**~0%**	Diabet Med 2013;30:1160–71
Insulin	**~0%**	N Engl J Med 2012; 367:319-328
Metformin	**~35%**	UKPDS 34
Glitazones	**~0%**	CD006063,CD006060
Dipeptidyl peptidase-4 inhibitors (DPP-4)	**~0%**	SAVOR-TIMI 53, EXAMINE
Glucagon-like peptide (GLP) agonists	**No studies**	
ASA	**~15%M ~10%F**	Arch Intern Med 2012;172:209-16
Combinations of the above interventions		Nobody really knows but hopefully there is some sort of additive benefit. If you have data on this or a way this can be shown or calculated please let me know.

AGE	SBP	WOMEN			MEN		
65-74	171-80						
	161-70						
	151-160						
	141-150						
	131-140						
	121-130						
55-64	171-80						
	161-70						
	151-160						
	141-150						
	131-140						
	121-130						
45-54	171-80						
	161-70						
	151-160						
	141-150						
	131-140						
	121-130						
35-44	171-80						
	161-70						
	151-160						
	141-150						
	131-140						
	121-130						

A) "normal" BMI - 20-25
B) "overweight" BMI 25-30
C) "obese" BMI - >30



≃ 5-year CVD[1] risk (%)[2]
>30
20-30
10-20
5-10
<5%

Smoking or diabetes approx. doubles the risk

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

Lancet 2008;371:923–31

5 main "Intensive" Statin Studies

		Mortality	"Hard" endpoints	All CVD endpoints
2004				**All cause mortality, MI, unstable angina requiring hospitalization, revascularization, stroke**
PROVE-IT 24 months	P 40 mg	3.2	NA	26.3
	A 80mg	2.2	NA	22.4
2010			Major vascular event	
SEARCH 7 years	S 20 mg	16.1	25.7	NA
	S 80 mg	16.0	24.5	NA
2005			Major CVD	Any CVD
TNT 5 years	A 10 mg	5.6	10.9	33.5
	A 80mg	5.7	8.7	28.1
2004			CVD mortality, MI. ACS, stroke	
A-Z 24 months	S 20mg	5.8	15.4	NA
	S 80 mg	4.6	13.6	NA
2005			Major coronary event/stroke	Overall CVD
IDEAL 5 years	S 20mg	8.4	13.7	30.8
	A 80mg	8.2	12.0	26.5

Orange = stat sig diff, NA = not available

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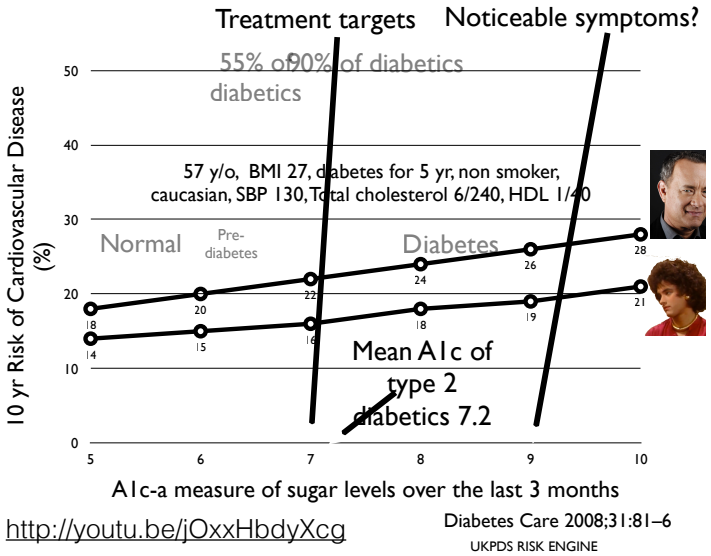
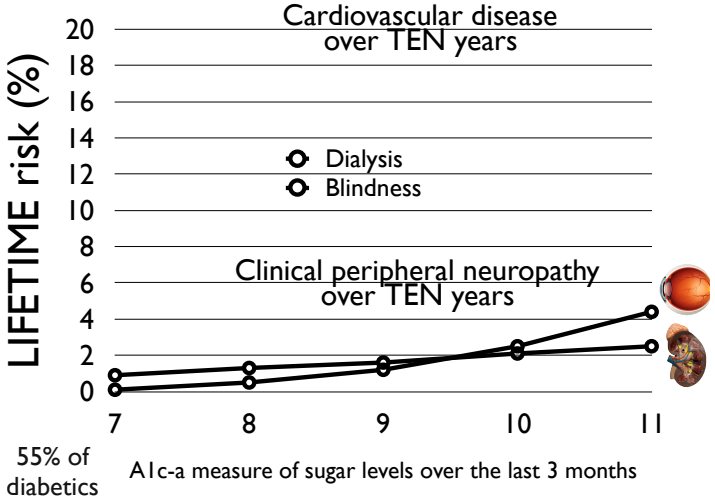


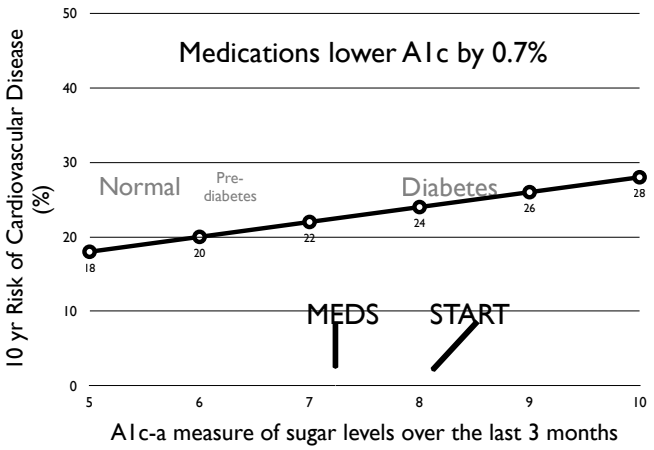
http://youtu.be/jOxxHbdyXcg

Diabetes Care 2008;31:81–6

UKPDS RISK ENGINE



Ann Intern Med 1997:127:788-95



ALL LOWER GLUCOSE							
RED - no effect on clinical outcomes	Key RCTs (patients/years)		MA (# of studies)				
METFORMIN - Glucophage, Glumetza, generic	700/11	7%	13				
SULFONLYUREAS - Gliclazide (Diamicron, generic), Glimepiride (Amaryl), Glyburide (Diabeta, Euglucon, generic)	4,000/10	UKPDS COMBO	4-11		3%		
INSULIN	12,000/6 4,000/10	UKPDS COMBO	None done				
DPP4s - Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Trajenta), Alogliptin (Nesina)	5,000/1.5 16,000/2 1,500/2	vs glimiperide	None done				
GLITAZONES - Pioglitazone (Actos), Rosiglitazone (Avandia)	4,400/4 5,200/3	?	42	?CHF harm	?	?	?
GLPs - Exenatide (Byetta) Liraglutide (Victoza), Dulaglutide (Trulicity	? - not studied		?		?	?	?
MEGLITINIDES - Nateglinide (Starlix), Repaglinide (GlucoNorm)	? - not studied		?		?	?	?
SGLT2 - Canagliflozin (Invokana) Dapagliflozin (Farxiga)	Ongoing ?CV issue		?		?	?	?
Tight control	10,000/3.5 1,800/5.5 11,000/5	?Mortality harm	3		2%	2%	2%

ALL LOWER GLUCOSE	Adverse effects
METFORMIN - Glucophage, Glumetza, generic	Indigestion, nausea, diarrhea
SULFONLYUREAS - Gliclazide (Diamicron, generic), Glimepiride (Amaryl), Glyburide (Diabeta, Euglucon, generic)	Severe low blood sugar (yearly) NNH 175 Weight gain - average 2 kg Rash, diarrhea
INSULIN	Severe low blood sugar (yearly) NNH 85 Weight gain - average 2 kg
DPP4s - Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Trajenta)	Hives, rash
GLITAZONES - Pioglitazone (Actos), Rosiglitazone (Avandia)	Fluid retention/heart failure NNH 25 Fractures (three years) NNH 85 Weight gain - average 2 kg
GLPs - Exenatide (Byetta) Liraglutide (Victoza)	Nausea, vomiting, diarrhea NNH 10-20 Weight loss - average 2 kg
MEGLITINIDES - Nateglinide (Starlix), Repaglinide (GlucoNorm)	Hypoglycemia
SGLT2 - Canagliflozin (Invokana) dapagliflozin (Farxiga)	Genital infections NNH 15

Relative risk reductions with different interventions in DM2

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

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

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Fracture Endpoints

10 year CHD risk (%) - UKPDS risk engine

A1c	50f, diabetes 3 years (1%Δ)	50m, diabetes 3 years (2%Δ)	65f, diabetes 10 years (3%Δ)	65m, diabetes 10 years (4%Δ)
7	9	16	21	36
8	10	18	24	40
9	11	20	27	44

BP 140, chol 6, hdl 1, non smoker

A simple tool for assessing the chance of your patient having osteoporosis

Does your patient have osteoporosis?

(Osteoporosis Self-assessment Tool)

Age – weight (kg) = ????

CHANCE OF OSTEOPOROSIS

> 20 – approx 50-60%

0-20 – approx 15-20%

<0 – less than 5%

An example
60 years old
130 lbs = 60 kg
Score = 0

Valid in men as well

Mayo Clin Proc 2003;78:723-7

Mayo Clin Proc. 2002;77:629-637
The Singapore Family Physician Jul-Sep 2003;29:12
MOH Osteoporosis clinical practice guidelines - Singapore Mar 2002

A simple tool for estimating chance of fractures without a BMD

Simple is better

"Simple models based on age and BMD alone or age and fracture history alone predicted 10-year risk of hip, major osteoporotic, and clinical fracture as well as more complex FRAX models"

Arch Intern Med 2009;169:2087-94

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10 year fracture risk %

Major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)/Hip

RISK FACTORS	Zero				One				Two			
BMI	35	30	25	20	35	30	25	20	35	30	25	20
Female												
50	2	3	3	3	4	4	5	5	6	6	7	8/1
60	5	6	6	7/2	7	9	10/1	10/4	11/1	13/2	14/2	16/6
70	8/1	9/2	10/2	11/4	11/2	13/3	15/4	17/7	16/4	18/6	21/7	25/12
80	14/4	16/5	19/7	21/11	20/8	23/10	27/13	31/20	28/14	33/18	38/22	43/32
Male												
50	2	2	2	2	3	3	4	4	4	5	6	6
60	3	4	4	4	5	6	6	7/1	7	8	10/1	10/2
70	4	5/1	6/1	6/2	6	7	8/2	9/4	8	10	12/4	13/6
80	6/2	7/3	9/4	9/5	9/4	11/5	13/7	14/10	13/7	16/9	19/12	21/16

Risk factors - Previous fracture "atraumatic", Parent hip fracture, Smoker, Rheumatoid arthritis, Glucocorticoids - now or more than 3 months, >3 drinks a day

FRAX® WHO Fracture Risk Assessment Tool

A simple tool for estimating chance of fractures with a BMD

10 year fracture risk %

Major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)/Hip

RISK FACTORS	Zero			One			Two		
t-score	-1.5	-2.5	-3.5	-1.5	-2.5	-3.5	-1.5	-2.5	-3.5
Female									
50	4	5/1	9/4	6	8/2	14/7	8	12/3	21/11
60	7	10/2	16/6	10/1	14/3	23/9	14/1	20/5	32/14
70	9/1	13/3	21/7	12/1	18/4	30/11	16/2	25/6	41/16
80	13/3	18/6	29/14	17/6	26/12	40/24	24/10	35/20	52/37
Male									
50	4	5/2	11/6	5	8/3	16/10	8/1	12/5	24/16
60	6/1	9/3	15/8	8/1	12/4	21/11	12/2	18/6	29/17
70	6/2	10/4	16/8	9/3	14/6	22/13	12/4	19/10	31/20
80	7/3	11/5	16/9	11/5	16/9	23/16	15/9	22/15	32/25

Risk factors - Previous fracture "atraumatic", Parent hip fracture, Smoker, Rheumatoid arthritis, Glucocorticoids - now or more than 3 months, >3 drinks a day

FRAX® WHO Fracture Risk Assessment Tool

• Osteoporosis Drugs Benefit - 2-3 years •

RELATIVE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~ 50%	~ 20%	~40%
Raloxifene	~ 40%	NS	NS
Teriparatide	~ 70%	~ 40%	NS
Vitamin D usually with calcium	~15-25%	~15-25%	~15-30%
Denosumab	~ 70%	~ 20%	~40%
Strontium	~40%	~ 15%	NS
ALL DRUGS	~50%	~20%	~25%

ABSOLUTE BENEFITS	FRACTURE RISK REDUCTION*		
	Vertebral	Non-vertebral	Hip
Bisphosphonates**	~4-8%	~2%	~0.5-1%
Raloxifene	~4%	NS	NS
Teriparatide	~10%	~4%	NS
Vitamin D usually with calcium	1-2%	1-2%	~1%
Denosumab	~5%	~2%	~0.5%
Strontium	~8%	~2%	NS
ALL DRUGS	~5%	~2%	~0.5%

*~ 90% of the studies enrolled patients with a history of fractures with the exception of the VitaminD/calcium studies where this was ~ 50%
** etidronate has only been shown to reduce vertebral fractures in secondary prevention

Bisphosphonates and atrial fib

Meta-analysis of all Merck-conducted placebo controlled trials of alendronate - 32 studies - 9,518 alendronate, 7,773 placebo - all AF events RR - 1.16 CI = 0.87-1.55

Osteoporos Int 2010 DOI 10.1007/s00198-011-1546-9

Six observational studies (n=149,856) and six RCTs (n=41,375) were included for analysis - RCTs revealed increased risk of serious AF - OR - 1.40 CI =1.02-1.93 - no increases in risk of stroke

Chest 2013;144:1311–22

Nine studies (5 RCTs and 4 observational studies) - pooled data from both - risk of new-onset AF with intravenous RR-1.40 CI 1.32-1.49 and oral RR-1.22 CI 1.14 to 1.31 - ABS RISK 0.4% ORAL

Am J Cardiol 2014;113:1815-21

SPARC - Stroke Prevention in Atrial Fibrillation Risk Tool
for estimating risk of stroke and benefits & risks of antithrombotic therapy in patients with chronic atrial fibrillation
references/notes
version 6.21, March 2013
Developed by Peter Loewen, ACPR, Pharm.D., FCSHP
peter.loewen@ubc.ca

In your patient with atrial fibrillation, which of the following stroke or bleeding risk factors are present?

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

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

*no studies have observed major bleeding in patients with score>5, so these must be interpreted as "risk probably >10%".

PERCENT PER YEAR

THERAPY	Stroke / Embolism CHADS2	CHA2DS2-VASc	Major Bleeding Pop.Avg.	HAS-BLED
NO THERAPY	1.2%	0.7%	0.6%	
ASPIRIN	0.9%	0.5%	1.1%	
ASPIRIN+CLOP	0.7%	0.4%	3.8%	
WARFARIN	0.4%	0.2%	3.8%	1.2%
DABIGATRAN 110	0.4%	0.2%	3.0%	1.0%
DABIGATRAN 150	0.3%	0.2%	3.8%	1.2%
RIVAROXABAN	0.4%	0.2%	3.8%	1.2%
APIXABAN	0.3%	0.2%	2.6%	0.8%

http://www.sparctool.com

James McCormack and G. Michael Allan

Bisphosphonates and Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women

A population-based, nested case-control study to explore the association between bisphosphonate use and fractures in a cohort of women aged 68 years or older from Ontario

52,595 women with at least 5 years of bisphosphonate therapy

subtrochanteric or femoral shaft fracture 0.13% during the subsequent year - 0.22% within 2 years

JAMA 2011;305:783-9

Risk of atypical fracture among women - annual absolute risk of 11 fractures (95% CI, 7 to 14) per 10,000 person-years of use

N Engl J Med 2014; 371:974-976

Jaw osteonecrosis from bisphosphonates

More often occurs after dental procedures

A minimum and maximum frequency of ONJ in patients receiving oral BPs as one in 2,030 and one in 950, respectively, and a minimum and maximum frequency of patients receiving oral BPs who have undergone extractions as one in 270 and one in 125, respectively

J Oral Maxillofac Surg 2007;65:415-23

Osteonecrosis of the jaw - 0.03%–4.30%

Ann Intern Med 2014 doi:10.7326/M14-0317

Afib Stroke Endpoints

An easy A fib table

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

http://www.sparctool.com

An even easier A fib table

	Patient's ~ ANNUAL risk (%) of ischemic stroke			Difference in benefit between ASA and OAC
$CHADS_2$ Score	No therapy	ASA	OAC	
0	2	1.5	0.5	~1
1	3	2.5	1	~1.5
2	4	3	1	~2
3	6	5	2	~3
4	9	7	3	~4
5	18	14	6	~8

Heart Failure

In systolic heart failure, 3 drugs do Big things

- Aldosterone antagonists[1,2] ~25%
- β-blockers[3] ~29%
- ACE inhibitors[4,5] ~23%

Assuming mortality= 25%/yr (after 1st hospitalization),[6]

Number needed to Treat are

- Aldosterone antagonists = NNT 16
  - 25% of 25% = 6.25% ➜ 100/6.25 = 16
- β-blockers = NNT 14
  - 29% of 25% = 7.25% ➜ 100/7.25 = 14
- ACE inhibitors = NNT 18
  - 23% of 25% = 5.8% ➜ 100/5.8 = 18

1. NEJM. 1999; 341:709–17. 2. NEJM. 2011; 364:11–21. 3. Arch Intern Med. 2000; 160:621–7. 4. JAMA. 1995; 273(18):1450–6. 5. Lancet. 2000; 355:1575–81. 6. NEJM. 2006;355(3):260-9.

James McCormack and G. Michael Allan

Crunching the Numbers

N Engl J Med 2012;366:321-9	≥ 2 major risk factors		≥ 1major risk factors	
	Men	Women	Men	Women
Baseline lifetime risk of cardiovascular disease (%)	50	35	35	25
Risk % if treat 3 factors and each one provides a 25% (1 risk factor)	21 (38)	15 (26)	15 (26)	11 (19)
% who benefit = baseline risk minus treated risk	29 (12)	20 (9)	20 (9)	14 (6)
% who will **NEVER** benefit from a lifetime of treatment	71 (88)	80 (91)	80 (91)	86 (94)

Major risk factors include being a current smoker or having diabetes, having treated hypercholesterolemia, having an untreated total cholesterol level of at least 240/6.2, or having treated hypertension, untreated systolic blood pressure of at least 160 mm Hg, or untreated diastolic blood pressure of at least 100 mm Hg.

James McCormack

Faculty/Presenter Disclosure

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

26th Annual Best Science Medicine Course

Learning Outcome Objective Slide

Provide at least one learning objective.

"Nutrition - are there really any Super Foods" Talk

1) List three reasons why it may be impossible to study the impact of individual food items

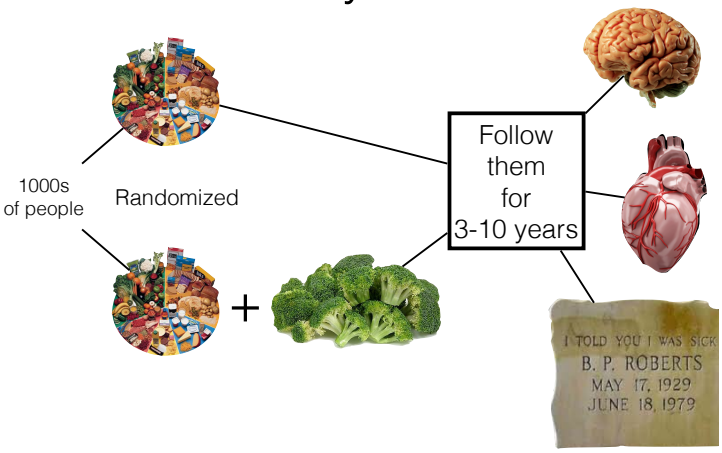
2)Briefly discuss the best available evidence around salt, eggs, fiber, coffee, daily servings of fruits and vegetables, and alcohol

When do we have debate about health issues?

the answer may be impossible to know
the best available evidence is tenuous
the potential difference in outcome is "small"
there is a belief about "a mechanism"
the stakes are high - pharmaceutical and nutrition beliefs are very "marketable"

FOOD, especially with individual nutrients, HAS ALL OF THESE

The Best Way - RCTs -10s



The OK way - Cohort Studies -100s

Prospective or retrospective

Quantiles
Tertiles
Quartiles
Quintiles
Can help prevent misclassification

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The Process

Present the best available evidence I could find - MA or SR

Not doing a detailed critical appraisal - all RCTs and cohorts have design and implementation issues

If these "studies" I present have serious limitations then we are basically stuck with opinion that is not informed by evidence

Single Nutrients

and some little behaviours

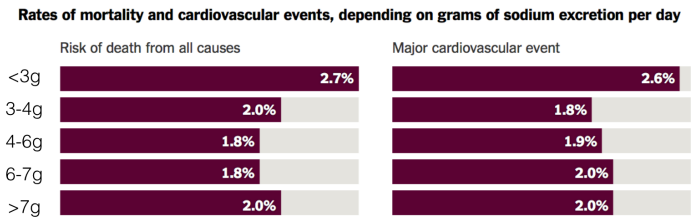
Salt, eggs, fiber,
coffee, daily servings, alcohol

Does salt increase blood pressure and increase risk of cardiovascular disease?

The problem of the surrogate marker

PURE study

Cohort - 101,945 people in 17 countries - 3.7 years
Association between CVD and sodium **excretion**



ABSOLUTE RISKS

N Engl J Med 2014;371:612-23

"These provocative findings beg for a randomized, controlled outcome trial to compare reduced sodium intake with usual diet. In the absence of such a trial, the results argue against reduction of dietary sodium as an isolated public health recommendation"

N Engl J Med 2014;371:677-9

Do eggs increase the risk of coronary heart disease?

The problem of mechanisms and surrogate markers

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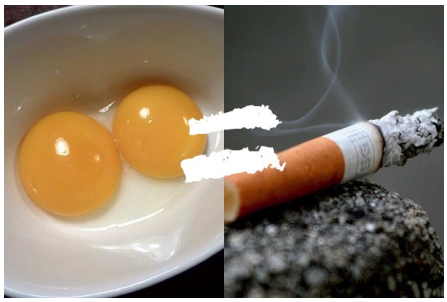
2012



"Eggs almost as bad as smoking"
"Your breakfast is trying to murder you"
"What do egg yolks and smoking have in common"

Atherosclerosis 2012;224:469-73

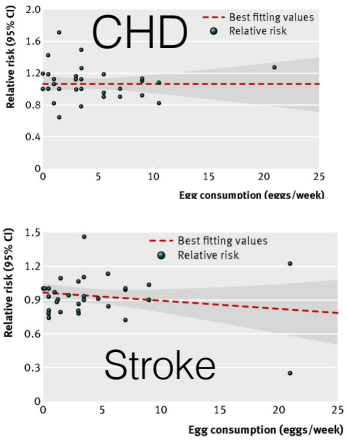
Egg consumption and risk of coronary heart disease and stroke: dose-response meta-analysis of prospective cohort studies

8 articles - 17 reports - 9 for CHD, 8 for stroke

3,081,269 person years and 5847 incident cases for CHD; 4,148,095 person years and 7579 incident cases for stroke

Risk for every additional egg eaten/day
CHD 0.99 (0.85-1.15), Stroke 0.91 (0.81-1.02)

BMJ 2013;346:e8539 doi: 10.1136/bmj.e8539



Another systematic review and meta-analysis supports these data
overall CVD 0.97 (0.86, 1.09)
Am J Clin Nutr doi: 10.3945/ajcn.112.051318

BMJ 2013;346:e8539 doi: 10.1136/bmj.e8539

Does increasing fiber decrease the risk of cardiovascular disease?

The problem of the size of the difference

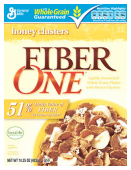
ORIGINAL INVESTIGATION

Dietary Fiber and Risk of Coronary Heart Disease

A Pooled Analysis of Cohort Studies

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

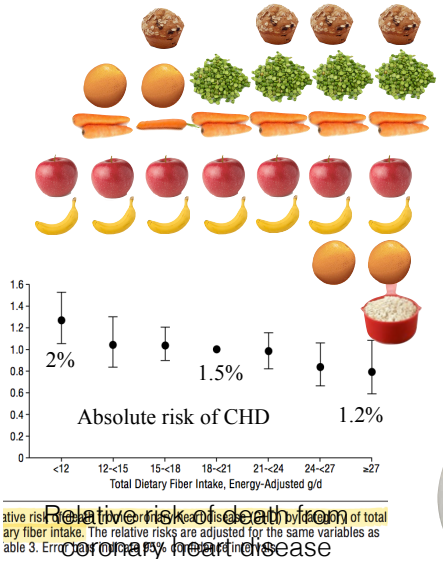
Arch Intern Med 2004;164:370-6



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

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

55 y/o increase fiber from none to a lot for 5-10 years 1 in 125 would not die from CHD



Relative risk of death from coronary heart disease

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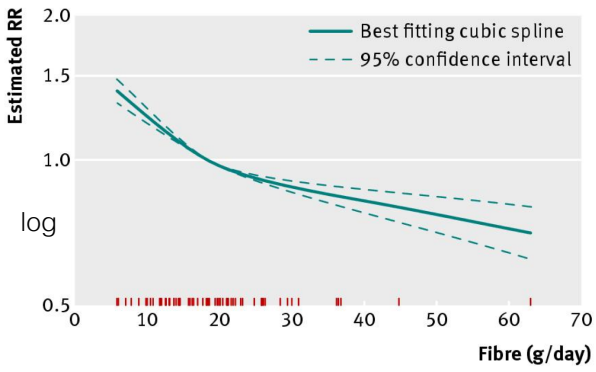
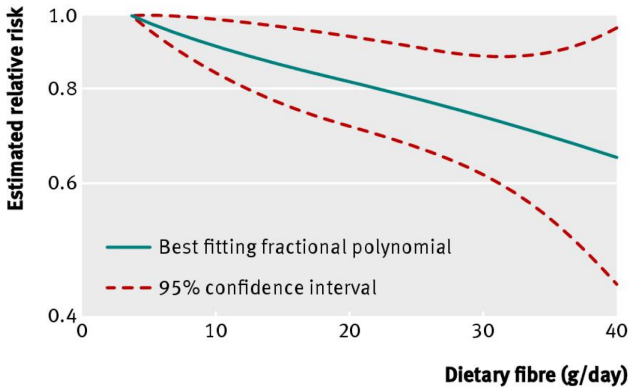
Fibre and risk of cardiovascular disease



get relative risks

BMJ 2013;347:f6879

Fibre and risk of colorectal cancer

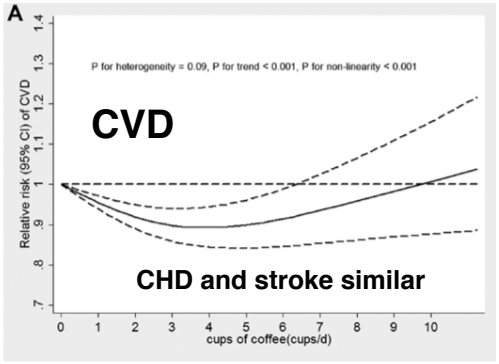


BMJ 2011;343:d6617 doi: 10.1136/bmj.d6617

Does coffee increase cardiovascular risk?

The problem of "I like coffee"

Thirty-six prospective cohort studies
1,279,804 participants, 36,352 CVD cases



"the lowest CVD risk at 3 to 5 cups per day of coffee consumption, and heavy coffee consumption was not associated with CVD risk"

Circulation 2014;129:643–59

"coffee intake is inversely related to all cause and, probably, CVD mortality"

Eur J Epidemiol 2013;28:527–39

How many daily servings of fruits and vegetables a day do we need?

The problem of inappropriate conclusions and reporting


theguardian

News | Sport | Comment | Culture | Business | Money | Life & style

News › Society › Health

Five a day will do, larger study of fruit and veg intake suggests

Chinese and American researchers settle on lower number than seven-a-day recommendation of English study


EXPRESS

Forget the five-a-day servings of fruit and veg... now you need seven to be healthy

5 a day

7+ a day


The Telegraph

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A five a day diet of fruit and vegetables is best – more is pointless study finds

Five five portions of fruit and vegetables per day and no more cuts your risk of dying early, a study has found, contradicting recent findings suggesting optimum number may be seven servings.


BBC NEWS HEALTH

Seven-a-day fruit and veg 'saves lives'

James McCormack

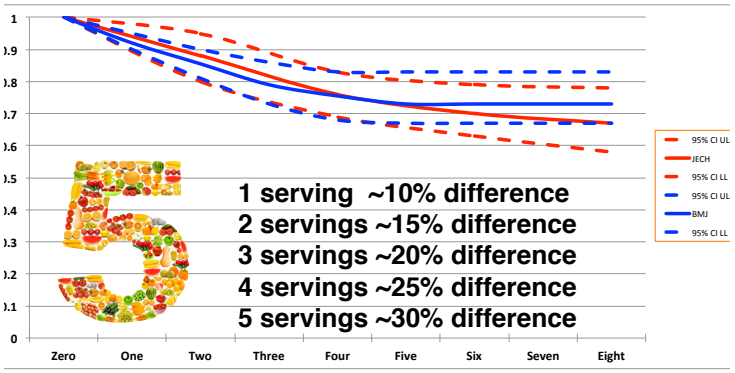
Fruit and vegetable consumption and all-cause, cancer and CVD mortality: analysis of Health Survey for England data

J Epidemiol Community Health - March 2014

Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies

BMJ - June 2014

Numbers of servings a day vs total mortality



Cancer mortality - no difference observed

Does alcohol or red wine decrease the risk of cardiovascular disease

The problem of "I like wine"

The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis

44 observational studies
38,627 IHD events (mortality or morbidity) among 957,684 participants

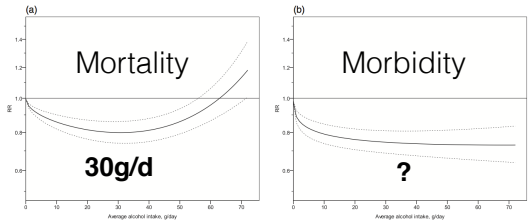
20 grams
~ Pint (550 mL) of beer/cider
~1/4 (200 mL) bottle of wine
~ Double (70 mL) spirits (vodka, whisky, rum, gin)

Addiction 2012;107:1246–60

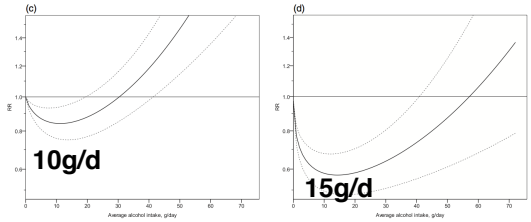
Ischemic heart disease

20 grams
~ Pint (550 mL) of beer/cider
~1/4 (200 mL) bottle of wine
~ Double (70 mL) spirits

Men



Women



Multiple Nutrients and Behaviours

Weight loss is another topic

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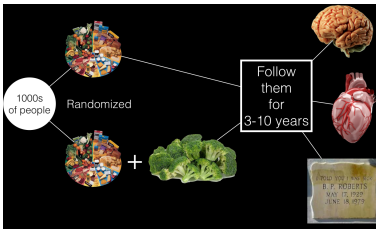
Are there differences in cardiovascular outcomes in people randomized to different diets?



Mediterranean diet in secondary prevention of coronary heart disease - Lyon Diet Heart Study

27 months - 605 patients <age 60 with a previous MI in the last 6 months - 90% male

one group advised in a one-hour session (with a couple of follow ups) to adopt a diet of more bread, more root vegetables, more fish, less beef, lamb and pork (replaced with poultry), no day without fruit; and butter and cream replaced with margarine - also used rapeseed, and olive oils in salad

Results

Weight, cholesterol, lipoproteins and blood pressure were not statistically different between groups

Lancet 1994;343:1454-9

Mediterranean diet in secondary prevention of coronary heart disease

	Total mortality (%)	Cardiovascular deaths (%)	Non-fatal MI's (%)	Total primary endpoints (%)
Dietary intervention	3.5	1.0	1.7	2.6
No dietary intervention	6.6	5.3	5.6	10.9
Relative risk reduction	47	81	NSS	76
Absolute risk reduction	3.1	4.3		8.3
Number needed to treat	32	23		12

Lancet 1994;343:1454-9

Women's Health Initiative Randomized Controlled Dietary Modification Trial - "low fat"

48,835 postmenopausal women (62 y/o) - 4% pref CVD - 8.1 years

1) lower fat intake to 20% of their total calories, and to eat five or more fruit/vegetable servings and six or more grain servings a day

2) asked not to make any dietary changes

led to ~10% reduction in energy from fat and one more serving a day of vegetables/fruit

no statistical difference in CHD, CVD, stroke, breast cancer, colorectal cancer

JAMA 2006;295:629-642, 643-54, 655-66

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet PREDIMED - 4 years, 67 y/o, 58% male, 48% T2DM

	Total mortality (%)	Myocardial infarction, stroke, and death from cardiovascular causes (%)	MI (%)	Stroke (%)
Control "Low fat"	4.7	4.4	1.6	2.4
Mediterranean diet - EVOO - 1 liter/week**	4.6	3.8*	1.5	1.9*
Mediterranean diet - NUTS (30 gm of mixed nuts per day)**	4.7	3.4*	1.3	1.3*

**increased weekly servings of fish (by 0.3 servings) and legumes (by 0.4 servings)

* statistical different from control

N Engl J Med 2013; 368:1279-90

Reduced or modified dietary fat for preventing cardiovascular disease (Review)

36 hard (non-surrogate) outcomes were reported

1 outcome showed a statistically significant difference in combined cardiovascular events 0.86 (0.77-0.96)

If true - 1% absolute reduction in risk

CD002137

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Do saturated fats increase the risk of cardiovascular disease

The problem of a theory gone completely haywire

Association of Dietary, Circulating, and Supplement Fatty Acids With Coronary Risk

Systematic Review and Meta-analysis

32 observational studies (512,420 participants) of fatty acids from dietary intake
17 observational studies (25,721 participants) of fatty acid biomarkers
27 randomized controlled trials (105,085 participants) of fatty acid supplementation

Compared tertiles

Ann Intern Med 2014;160:398-406

Monounsaturated fat	Polyunsaturated fat
Olive oil Canola oil Sunflower oil Peanut oil Sesame oil Avocados Olives Nuts (almonds, peanuts, macadamia nuts, hazelnuts, pecans, cashews) Peanut butter COHORT 9 studies - CHD 1.00 (0.91-1.10)	Soybean oil ω-6 FA Corn oil ω-6 FA Safflower oil ω-6 FA Walnuts ω-3 FA Sunflower, sesame, and pumpkin seeds ω-6 FA Flaxseed ω-3 FA Fatty fish (salmon, tuna, mackerel, herring, trout, sardines) ω-3 FA Soymilk ω-6 FA Tofu ω-3 FA COHORT ω-6 8 studies - CHD 0.98 (0.90-1.06) COHORT ω-3 short chain Plant oils 7 studies - CHD 0.99 (0.86-1.14) COHORT ω-3 long chain Marine Oils 16 studies - CHD 0.87 (0.78-0.97)
Saturated fat	**Trans fat**
High-fat cuts of meat (beef, lamb, pork) Chicken with the skin Whole-fat dairy products (milk and cream) Butter Cheese Ice cream Palm and coconut oil Lard COHORT 20 studies - CHD 1.03 (0.98-1.07)	Commercially-baked pastries, cookies, doughnuts, muffins, cakes, pizza dough Packaged snack foods (crackers, microwave popcorn, chips) Stick margarine Vegetable shortening Fried foods (French fries, fried chicken, chicken nuggets, breaded fish) Candy bars COHORT 5 studies - CHD 1.16 (1.06-1.27)

"Current evidence does not clearly support cardiovascular guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of total saturated fats"

Ann Intern Med 2014;160:398-406

"The present systematic review [secondary prevention] provides no evidence (moderate quality evidence) for the beneficial effects of reduced/modified fat diets in the secondary prevention of coronary heart disease"

BMJ Open 2014;4:e004487 doi:10.1136/bmjopen-2013-004487

Does added sugar consumption increase the risk of obesity or cardiovascular disease?

The potential problem of a new theory and the size of the differences

Original Investigation

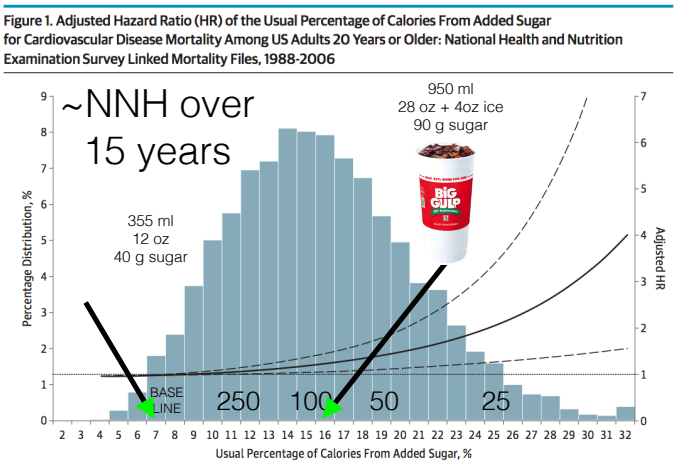
Added Sugar Intake and Cardiovascular Diseases Mortality Among US Adults

DEFINITION OF ADDED SUGARS
all sugars used in processed or prepared foods, such as sugar-sweetened beverages, grain-based desserts, fruit drinks, dairy desserts, candy, ready-to-eat cereals, and yeast breads, BUT NOT naturally occurring sugar, such as in fruits and fruit juices

FREE SUGARS = ADDED SUGARS + honey, syrups, or fruit juice

JAMA Intern Med 2014;174:516-24

James McCormack



JAMA Intern Med 2014;174:516-24

Can We Say What Diet Is Best for Health?

"There have been no rigorous, long-term studies comparing contenders for best diet laurels using methodology that precludes bias and confounding, and for many reasons such studies are unlikely"

Annu Rev Public Health 2014; 35:83–103

What is the answer?

Teasing out the benefits and harms of things we eat is EXTREMELY complicated

SINGLE NUTRIENTS

Not enough robust data to ascribe causality

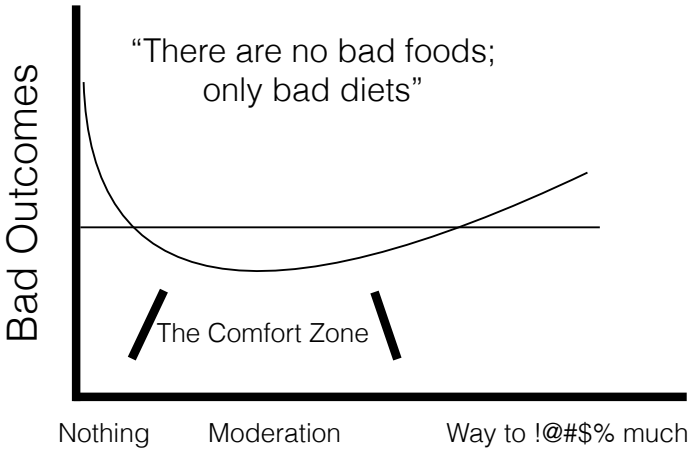
Some interesting associations - eggs, salt, coffee, alcohol

MULTIPLE NUTRIENTS AND BEHAVIOURS

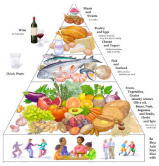
Issues of RCTs and Cohorts - bias and confounding - answer may be unknowable

How to best lose weight is very individual - low carb/higher fat/protein maybe somewhat better? - is the difference important?

Overall nutrition is hugely personal and emotional



1. ENJOY EATING



If you don't tolerate a food, DON'T EAT IT
Differences in outcomes are typically found from "extremes" and are "small"
The Mediterranean diet (whatever it is) seems reasonable - also CFG/USDA ~DASH
Eat in moderation/moderation/moderation
Avoid "highly" processed food - within reason
You can easily justify some red meat, butter etc
Eggs, coffee, salt, and alcohol in moderation seem fine if not even healthy

9. Saturated fats - OK - trans-fat?
Added sugars at the high end seem to increase risk
"Big Gulps"- really what is the point of them?
It is VERY unlikely a single "nutrient" would have an important effect
Animal rights/environmental issues are a whole other topic

The M&M's Diet

Mediterranean

Moderation

"The secret of life is to eat what you like and let the food fight it out inside"
Mark Twain

Scott Garrison

Restless Leg Syndrome

Faculty/Presenter Disclosure

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

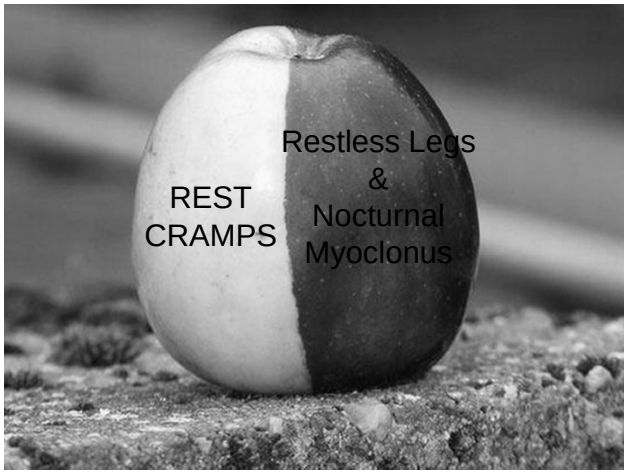
Disclosure of Commercial Support

- **This program has received no financial support**
- **This program has received no in-kind support**
- **Potential for conflict(s) of interest:**
  - None

Learning Outcome Objective Slide

- To differentiate restless leg syndrome from other disorders of the lower limbs which disrupt sleep
- To understand the wide variety of treatment options available to lessen the symptom burden in this condition

"Leggy things that keep you up at night"



Scott Garrison

Restless Leg Syndrome[1]

Restless Leg Syndrome
Coming soon to a leg near you!

Nocturnal Myoclonus - aka
Periodic Leg Movements of Sleep

Nocturnal Myoclonus - aka
Periodic Leg Movements of Sleep

Treatment?

First…a little perspective

Scott Garrison

Pooling 24 RCTs (N = 1527)[2]

Placebo Arm
- 40% respond

Active Arm
- 70% respond

Respond = "much improved" or "very much improved" on CGI change of condition scale; IRLS score indicative of no or mild symptoms; no RLS "attacks" for 1 wk; wish to continue the treatment

Non-Prescription Therapies
- Iron
- Exercise
- Medication Changes

Prescription Therapies
- Dopamine Agonists
- Opioids
- Benzodiazepines
- Gabapentin / Pregabalin
- Carbamazepine

Iron

(30-40% of RLS sufferers are Fe deficient)

2012 Cochrane review[3]; 6 studies; N = 192

Dialysis X1; Ferritin <45; Ferritin < 75

IVX4; Ferrous sulfate 325mg BIDX2studies

Primary Outcome: Chg IRLS severity scale
- 4 studies (-3.79, -7.68 to 0.10, p=0.06)
- 5th study (different scale -3/10, p=0.01)
- Iron status not different in responders
- IV not obviously better

Vitamin C?[4] (single RCT with benefit)

Exercise

3 studies[5-7]; N = 99
- Dialysis X2; Ad responders X1
- 30 min Treadmill + leg resistance 3/wk x 12wks
- 30 min Stationary bike 3/wk x 16wks
- Recumbent stationary bike 3/wk x 6 months
- Comparator = no intervention X2; DA or placebo

Primary Outcome: Chg IRLS severity scale
- All show benefit but studies with no intervention as comparator show only placebo like responses.
- 6 mo placebo study DOES show DA like benefit

Medication Changes

Several medications implicated[8,9]
- Antidepressants (SSRI + TCA)
  - especially citalopram, paroxetine, fluoxetine, amitriptyline, mirtazapine
  - exception is bupropion
- Antipsychotics
- Antihistamines
- Metoclopramide

Also "caffeine, alcohol, nicotine"

Prescription Therapies

- Several to choose from
- Start with as needed (intermittent) use

Dopamine Agonists

Pramipexole, Ropinarole, Rotigotine

- 17 RCTs[10], >2700 pts
- All clearly work (70% pts respond)
- Pramipexole 0.125mg once daily to start
  - 0.25mg, 0.50mg, 0.75mg/day equally effective

Adverse Effects:

- Mild nausea, lightheadedness, fatigue < 14 days
- *Augmentation* = worsening of RLS (eg symptoms more intense, earlier in day, involve upper limbs). Occurs in 6% pramipexole pts @ 1yr, *30% @ 2yr*
- Impulse Control: eating/gambling/hypersexuality

Gabapentin / Pregabalin

Pregabalin

- 2 RCTs[11,12], 777 pts, both show benefit and 1 shows 300mg *non-inferior to pramipexole* 0.5mg

Gabapentin Enacarbil (Prodrug)/Gabapentin

- Several studies suggest benefit[13-15](≤1800mg)

Adverse Effects:

- Somnolence, fatigue, gait unsteadiness

Opioids

2 DB Placebo Control RCTs[16,17] – with benefit

- N = 11 crossover oxycodone alone 2.5 – 25mg
  - Mean dose 11.39mg
- N = 276 treatment resistant pts; 1-8 tabs BID of oxycodone 5mg / naloxone 2.5mg
  - Mean 21.9mg oxycodone / 11.0mg naloxone

Adverse Effects:

Constipation, fatigue, nausea

In practice all opioids used

Benzodiazepines

Only 1 tiny (N=6) crossover RCT[18] of clonazepam 1mg vs placebo (showing benefit)

Open label studies (eg 14 of 15 pts responding to clonazepam) and clinical experience drive benzo use

Adverse Effects:

Drowsiness, cognitive impairment, nocturnal unsteadiness

Carbamazepine

1 study; N = 174 X 5 wks; mean 257mg of carbamazepine vs placebo found benefit[19]

Adverse Effects: Dizziness (44%), Drowsiness (32%), nausea (29%), headache (22%), ataxia (15%)

Putting it together

Scott Garrison

Putting it together

- 40% of patients respond well to placebo & 70% will respond to an active agent
- Check iron status
- Consider iron supp / exercise / Rx changes
- If needed try intermittent minimal doses of drugs such as dopamine agonists (eg pramipexole 0.125 - 0.25mg), pregabalin (75mg-300mg), opioids (eg oxycodone 5-15mg), benzodiazepines & carbamazepine

THE END

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Janet Nuth

CMPA

Be a Medico-Legal Survivor: High risk medications

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Physician Risk Manager, CMPA
Associate Professor
Dept of Emergency Medicine
University of Ottawa

26th Annual Best Science Medicine Course
Vancouver, April 18, 2015

This slide set does not follow the same order as the presentation and CMPA cases and some CMPA data will not be included in this handout.

Faculty / Presenter Disclosure

Faculty: Dr Nuth_____
Employee of: CMPA

Relationships with commercial interests: None

- Grants / Research Support: __No_____
- Speakers Bureau / Honoraria: __No_____
- Consulting Fees: _No_____
- Other: __No_____

Conflict of Interest - I have no financial or professional affiliation with any organization that can be perceived as a conflict of interest in the context of this presentation.

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Objectives

1. Name 3 high risk medications seen in CMPA cases
2. Identify 2 strategies for reducing your medico-legal risk with cases involving medication

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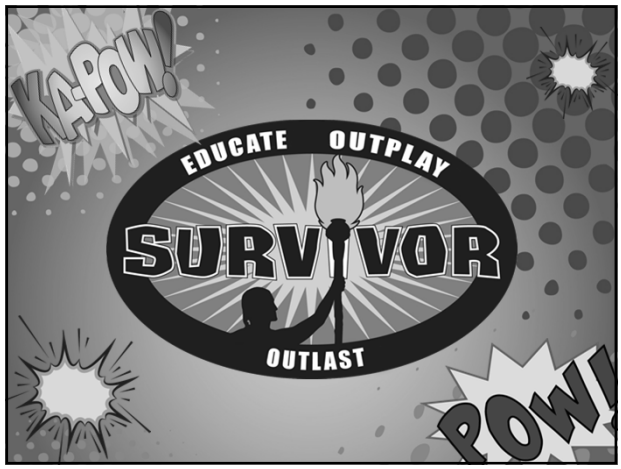
Score sheet

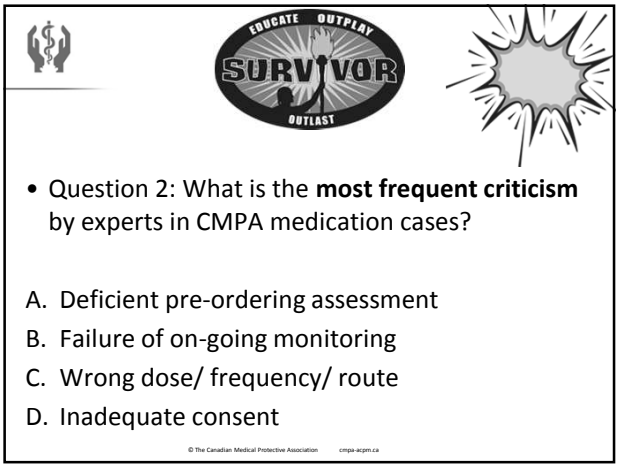
- 1._____
- 2._____
- 3_____
- 4. _____
- 5._____ _____ _____ _____
- _____(pts)

Final score_____



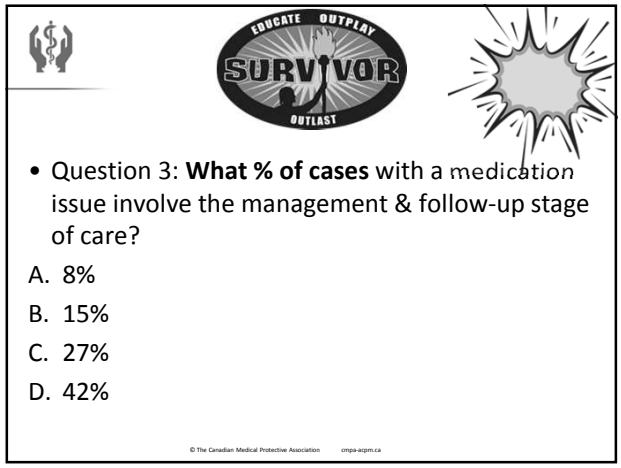
- Question 1: Which is true regarding medico-legal cases involving medication in FM?

A. Most cases were legal actions vs College complaints
B. 50% of legal actions were settled
C. 85 % of cases had unfavourable outcomes
D. Most College complaints had favourable outcomes



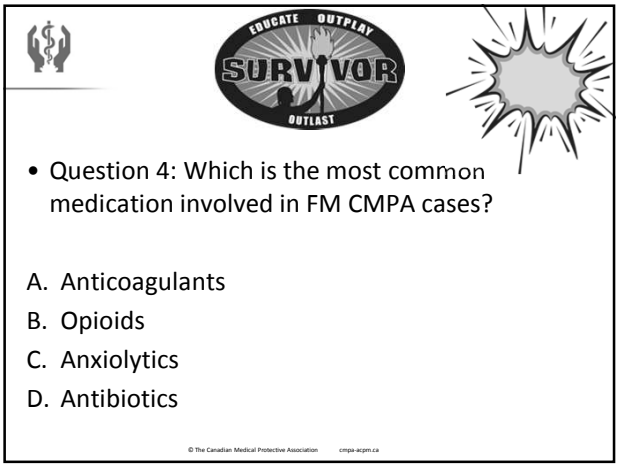
- Question 2: What is the **most frequent criticism** by experts in CMPA medication cases?

A. Deficient pre-ordering assessment
B. Failure of on-going monitoring
C. Wrong dose/ frequency/ route
D. Inadequate consent



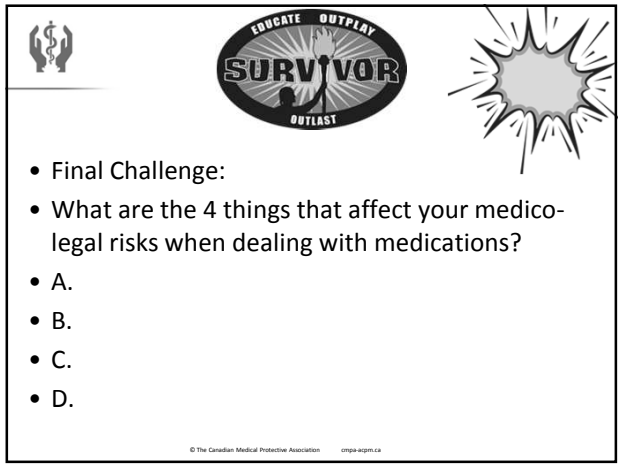
- Question 3: **What % of cases** with a medication issue involve the management & follow-up stage of care?

A. 8%
B. 15%
C. 27%
D. 42%



- Question 4: Which is the most common medication involved in FM CMPA cases?

A. Anticoagulants
B. Opioids
C. Anxiolytics
D. Antibiotics



- Final Challenge:
- What are the 4 things that affect your medico-legal risks when dealing with medications?
- A.
- B.
- C.
- D.

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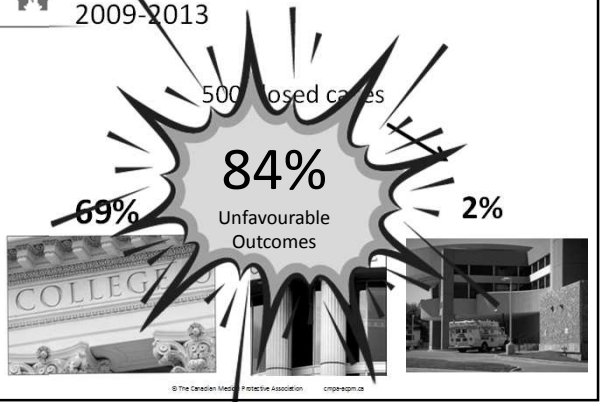
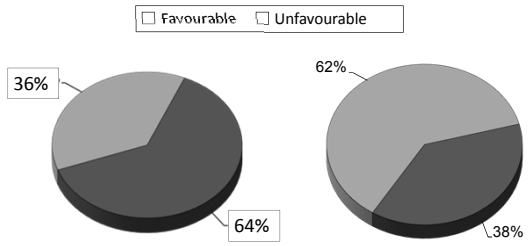
Cases with medication issue in FM 2009-2013



Legal Outcome – Comparison
Legal Actions Closed 2009 - 2013



Medication issues

CMPA all legal actions

Deficient documentation was the most frequent contributing factor in cases with unfavourable outcomes

Documentation saved the day !

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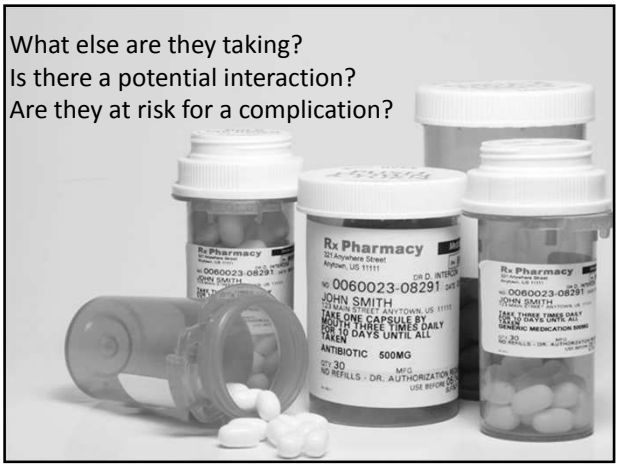
47% involved deficient pre-ordering assessments & investigations


10% cases: medication was contraindicated


What else are they taking?
Is there a potential interaction?
Are they at risk for a complication?
Rx Pharmacy
JOHN SMITH
ANTIBIOTIC 500MG


Have you documented your consent discussion regarding potential risks?

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Medication Reconciliation

Eliminate undocumented intentional discrepancies
Identify unintentional discrepancies

« Best Possible Medication Discharge »

Best Possible Medication Discharge Plan (BPMDP)
Discharge Date: _____
Allergies: _____
Primary Diagnosis: _____
Community Pharmacy: _____ Phone Number: _____

Patient Addressograph

To be completed by RPh , RN or MD Name: _____ Date _____								To be completed by MD			
Current Medications	Dose	Route and Directions	Source (BPMH / MAR)	Same as prior to admission	Adjusted in hospital	Discontinued in hospital	New in hospital	Do Not Continue	Quantity	Repeats	Comments / Codes

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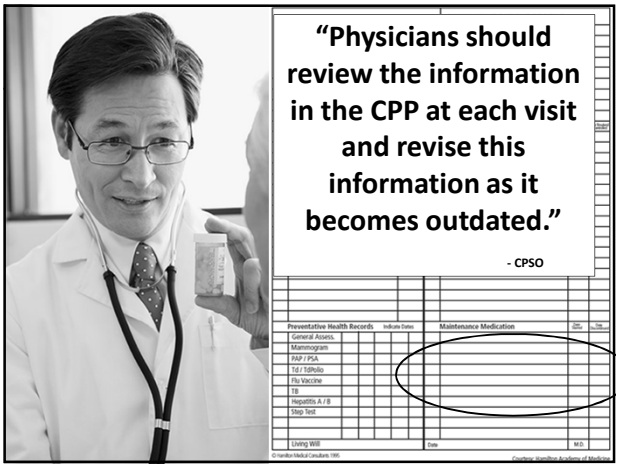

"Physicians should review the information in the CPP at each visit and revise this information as it becomes outdated."

- CPSO

Follow up
- Efficacy
- Side effects

Lab monitoring
- INRs
- Drug levels
- Electrolytes
- Creatinine/LFTs/CBC

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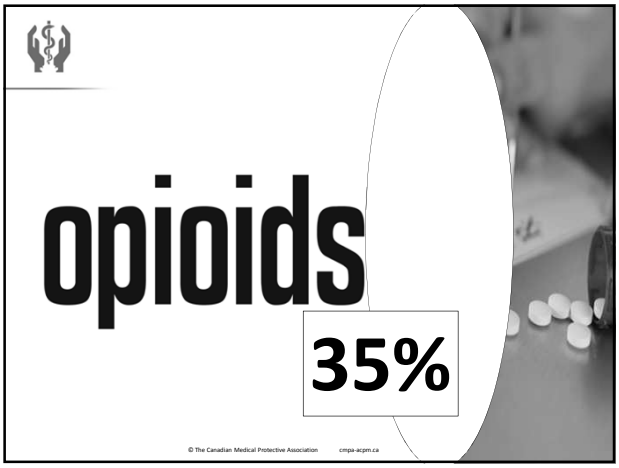
Renal failure
Statin myopathy
Neutropenia
Drug toxicity
Bleeds
Death


« I thought you were doing it! »
« No – I thought *you* were doing it!»


opioids
35%
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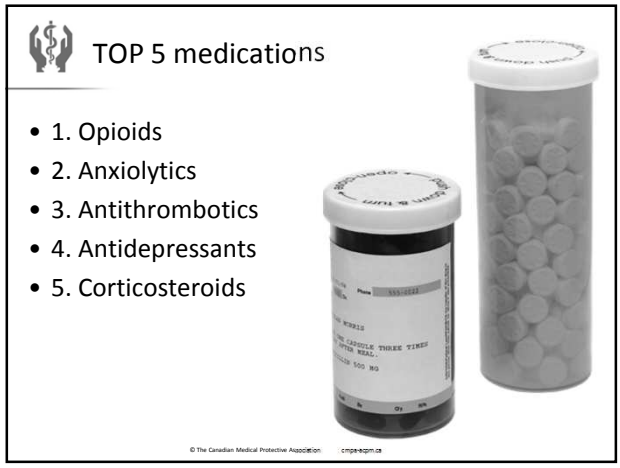
TOP 5 medications
• 1. Opioids
• 2. Anxiolytics
• 3. Antithrombotics
• 4. Antidepressants
• 5. Corticosteroids
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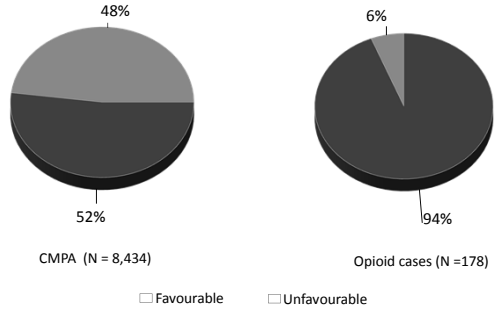
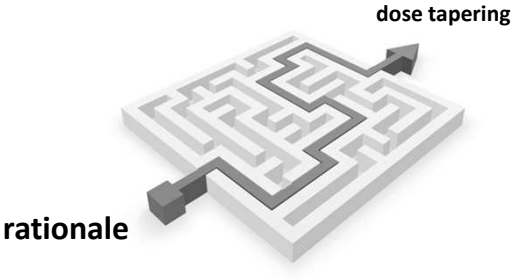
Closed college cases 2010 – 2014



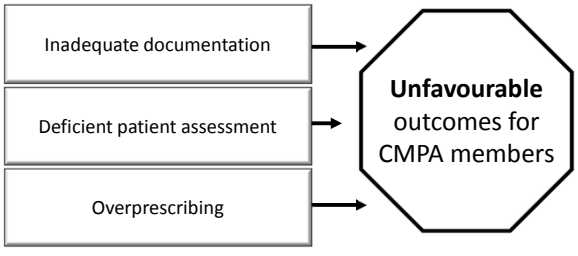
The physician's prescribing trap

1. Initiation without adequate evaluation
2. Renewals without assessment
3. Dose increases without assessment

What's your exit strategy?



Deficient Assessment / Overprescribing



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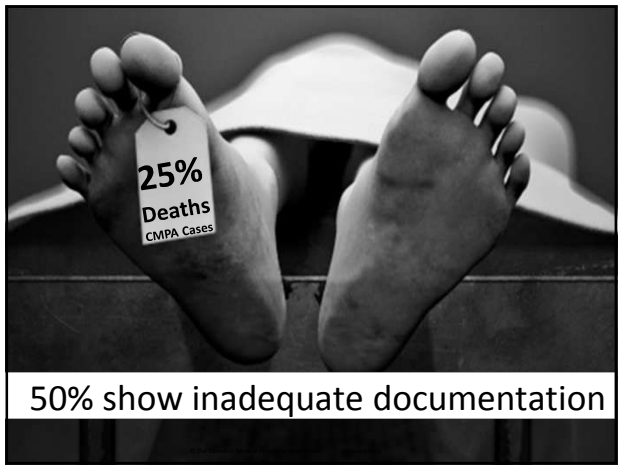
High potency opioids

- Children
- Elderly
- Opioid-naïve patients



CPSBC
Provides Link to Guidelines for MDs

http://nationalpaincentre.mcmaster.ca/opioid/

CMPA does not endorse any specific guidelines. Reference purposes only

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Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain

http://nationalpaincentre.mcmaster.ca/opioid/

DME

Maintenance & Monitoring Chart

		D / M / Y	D / M / Y	D / M / Y
Date				
Opioid prescribed				
Daily dose				
Daily morphine equivalent				
	More than 200 (Watchful Dose > than 200)			
	Less than 200			
Goals achieved →	Yes, No, Partially			
Pain interest				
Functional status →	Improved, No Change, Worsened			
Adverse effects	Nausea			
	Constipation			
0 = None	Drowsiness			
1 = Limits ADLs	Dizziness/Vertigo			
2 = Prevents ADLs	Dry skin/Pruritis			
	Vomiting			
	Other?			
Complications?	(Reviewed: Y/N)			
Aberrant Behaviour	(Reviewed: Y/N)			
Urine Drug Screening	(Y/N)			

The CMPA supports the use of guidelines to optimize patient care.

CPSBC

Provides Link to Guidelines for MDs

http://nationalpaincentre.mcmaster.ca/opioid/

Opioid Risk Tool

By Lynn R. Webster MD

Item (circle all that apply)	Item score if female	Item score if male
1. Family History of Substance Abuse:		
Alcohol	1	3
Illegal Drugs	2	3
Prescription Drugs	4	4
2. Personal History of Substance Abuse:		
Alcohol	3	3
Illegal Drugs	4	4
Prescription Drugs	5	5
3. Age (mark box if 16-45)	1	1
4. History of Preadolescent Sexual Abuse	3	0
5. Psychological Disease Attention Deficit Disorder, Obsessive-Compulsive Disorder, or Bipolar, Schizophrenia	2	2
Depression	1	1
Total		

Total Score Risk Category:
Low Risk: 0 to 3, Moderate Risk: 4 to 7, High Risk: 8 and above

Neurology 2014;83(14):1277-84

1. Monitor pain and function
2. Monitor the Daily Morphine Equivalent
   a) Seek help above 80-120 mg/d
3. Be aware of other opioid prescribers
4. Screen for
   a) PTSD, anxiety, depression
   b) Past/current substance abuse
5. Random urine screening
6. Treatment contracts

4 areas of medicolegal risk

A dequate assessments

B e viligent: side effects/ monitoring

C onsent discussions

D ocumentation

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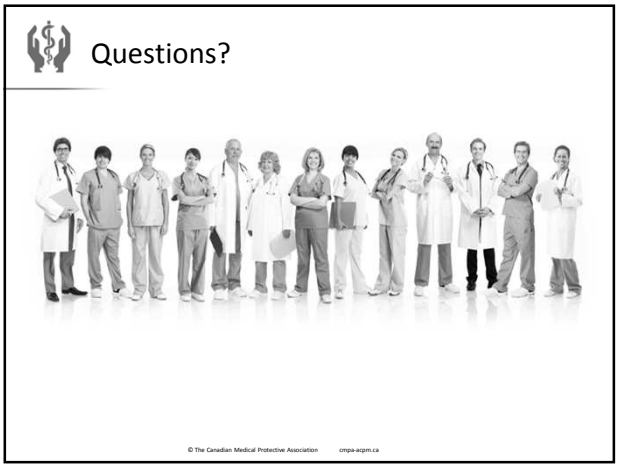
You have survived!
Did anyone get 10 points?


Questions?
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Kam Shojania

Immune Modulators in Rheumatoid Arthritis

Kam Shojania
Rheumatologist
Clinical Professor and Head,
UBC Division of Rheumatology

Faculty/Presenter Disclosure

- **Faculty:** Kam Shojania
- Title: Immune Modulators in Rheumatoid Arthritis

- **Relationships with commercial interests:**
  - **Grants/Research Support: Indirectly, via collaborators:** Janssen, BMS, Abbvie, Pfizer, Roche, UCB, Amgen.
  - **Speakers Bureau/Honoraria:** Three industry talks last year.
  - **Consulting Fees:** Four times in the past year
  - **Other:** UBC salary, Ministry of Health contract for IVIG management. Arthritis Research Centre, CHEOS, Arthritis Society
  - Investments relevant to this talk: Augurex – biotech company for laboratory testing. I have stock options in this company (what the hell are 'stock options' anyway?)

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

- **This program has received financial support from** Nobody **in the form of** Nothing.
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- **Potential for conflict(s) of interest:**
  - Kam Shojania has received grant support from No companies whose products are being discussed in this talk.
  - No drug companies other that some generic MTX makers or other companies that make generic hydroxychloroquine or generic sulfasalazine a product that will be discussed in this program: MTX, Sulfasalazine, Hydroxychloroquine, Prednisone.
  - Anti-inflammatories will be mentioned only to disparage them.

CFPC CoI Templates: Slide 3

Mitigating Potential Bias

- I will not be discussing biologics in this presentation so don't even ask me about them.
- Biologics aren't really the point here – immune modulators such as methotrexate, sulfasalazine and hydroxychloroquine when used early and in combination, can reduce the need for costly biologic therapies.

26th Annual Best Science Medicine Course: Slide 4

Learning Outcome Objective Slide

Because treating new inflammatory arthritis early is a medical urgency, participants will quickly refer early inflammatory arthritis for diagnosis and initial treatment with appropriate DMARDs or start the DMARD themselves within 4 weeks of symptoms.

Participants will NOT presribe prednisone without making a diagnosis first because steroids mask the diagnosis and thus prevents appropriate treatment. Less steroids is better.

Participants will NOT use NSAIDs as sole therapy for rheumatoid arthritis or other inflammatory arthritis because NSAIDs do not reduce damage or improve long term outcomes.

Kam Shojania

Objectives

1. Diagnosing RA early makes it much easier to treat
2. Smoking increases the chance of developing rheumatoid arthritis and makes it more severe
3. All patients with RA should be on a DMARD
4. Steroids increase morbidity and mortality in RA
5. Methotrexate increases quality AND quantity of life in RA

This changed my practice

- This Changed My Practice (UBC CPD)
- **Five clinical points on Rheumatoid Arthritis in Family Practice**
- By Dr. Kam Shojania and Dr. Neda Amiri on January 21, 2014
- http://thischangedmypractice.com/rheumatoid-arthritis/

RESOURCES

- arthritisIDPro (free app to diagnose polyarthritis)
- www.rheuminfo.com (Great site for medication and disease information

Ms. S. P.

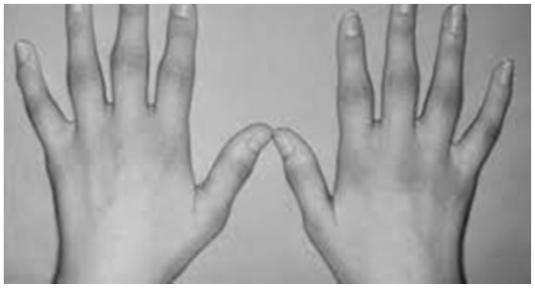
- 32 yo caucasian woman with a 8 week history of joint pain at her wrists, MCPs, PIPs, MTPs. AM stiffness. Previously had a swollen knee 3 months ago. Post partum 4 months. Breastfeeding.
- Went to a walk-in clinic. Started on prednisone 50mg daily. Referred to rheumatology 'Arthritis, please see'.

We saw her

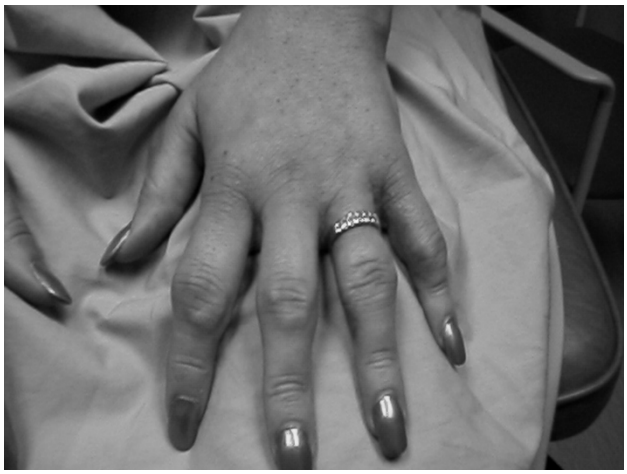
- Doing well. Doing GREAT!
- No symptoms.
- No findings.

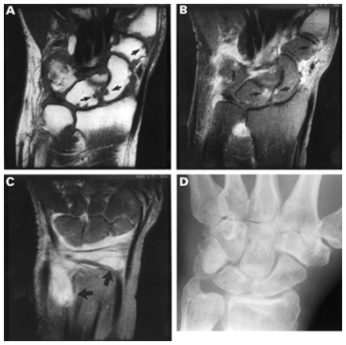
- DDx?
- Investigations?
- Suggestions?

Early Rheumatoid Arthritis



Kam Shojania





(A) MRI scan of the right wrist of one of the patients. T1 weighted coronal sequence showing erosions in the lunate, scaphoid, and trapezium (black arrows). (B) T1 weighted fat suppressed, post-gadolinium, coronal sequence. Erosions containing enhancing synovium are present in the lunate, scaphoid, trapezium, and triquetrum (black arrows). (C) T1 weighted post-gadolinium coronal sequence. Synovial hypertrophy and enhancement in the distal radioulnar and radiocarpal joints (wide arrows). (D) Plain radiograph of right wrist. No profiled cortical erosions but focal lucencies present in the capitate and scaphoid.

1. Diagnosing RA early makes it much easier to treat

Patient-reported joint swelling and morning stiffness lasting more than 30min

- Joint pain in wrists, MCPs and MTPs is common in RA and other types of inflammatory arthritis.
- Stress-tenderness is a good screen.
- ArthritisIDPro – free app to diagnose inflammatory arthritis

Patient with new RA – Window of Opportunity for remission

- Any age, but typically 40-50 year old female
- AM stiffness for more than 30min
- Three or more joints (often wrist, MCP, MTP)
- Elevated acute phase reactants
- RF or anti-CCP positivity

Fin-RAco

- Delay to institution of therapy and induction of remission using single drug or combination DMARD in early RA
- 4 month delay reduced remission when using single DMARD regimens

Mottonen et al. Fin-RACo. A+R 2002
Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. A+R 2003

What do I do to achieve remission?

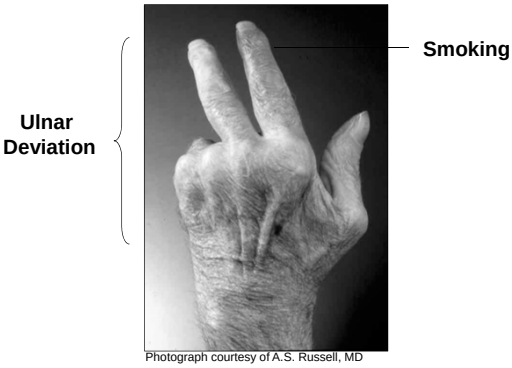
- Triple therapy: MTX + HCQ + SS
- Short course of prednisone 20mg to 0 in 6 weeks
- Why? This has the best chance of achieving remission.

O'Dell et al. Treatment of RA with MTX alone, SS and HCQ or a combination of all three medications. NEJM 1995

Kam Shojania

Smoking

2. Smoking increases the chance of developing rheumatoid arthritis



Photograph courtesy of A.S. Russell, MD

Smoking and RA

- Smoking is the best-studied environmental factor in RA.
- Increased risk of RF or anti-CCP positivity
- Possibly smoking increases citrullination of peptides (anti-CCP)
- Smoking may increase periodontal disease (also a risk factor for RA).

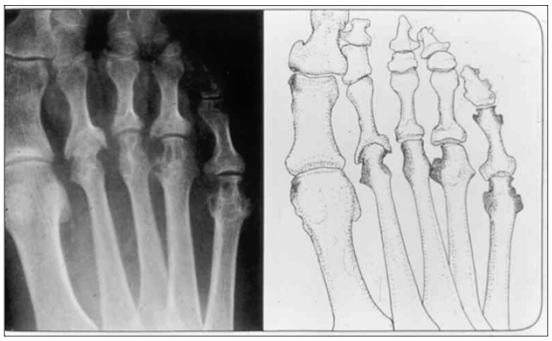
F

Smoking and First Nations

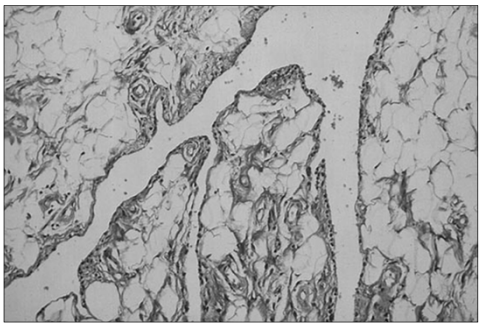
Late RA?

- Is it ever too late?
- If we miss the boat and we do not aggressively treat in the first year, we have resigned ourselves to persistent, smoldering disease, progression and damage, and need for biologics.
- But we can still treat and slow the RA progression

X-Ray of Foot

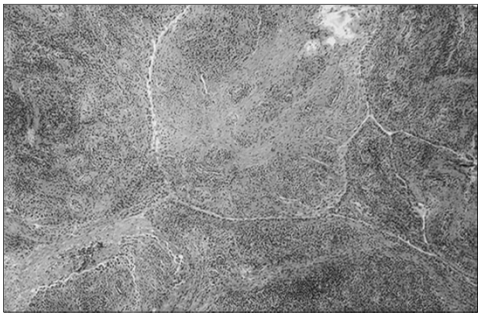


Normal Synovial Lining



Photograph courtesy of A.S. Russell, MD

Synovial Tissue



Photograph courtesy of A.S. Russell, MD

Extra-articular manifestations

- Rheumatoid nodules
- Eye inflammation
  - episcleritis, scleritis
  - corneal melt
- Interstitial lung disease
- Sicca Symptoms
- Vasculitis
  - small vessel
- Pleuritis
- Pericarditis
- Neuropathy
  - mononeuritis
  - symmetrical peripheral

3. All patients with RA should be on a DMARD

- DMARDs (MTX, Lef) slow down progression of RA, reduce disability, morbidity and mortality in RA
- NSAIDs and Steroids have NO beneficial long term effect

Sing JA, Furst DE et al. 2008 ACR recommentations for the use of DMARDs in the treatment of RA. Arthritis Care Res. 2012
Smolen JS, Landewe et al. EULAR recommendations for the management of RA with DMARDs

Disease modifying anti-rheumatic drugs (DMARDs)

- Miscellaneous group of drugs
- Reduce or prevent joint damage, preserve joint integrity and function.
- Maintain functional level of the patient
- Reduce overall health costs

Disease modifying anti-rheumatic drugs (DMARDs)

- Antimalarials
- Sulfasalazine
- Methotrexate
- Leflunomide
- Biologics:
  - Anti-TNF
  - Anti-CD20
  - CTLA4-Ig
  - IL-6 inhibition
  - SEBs

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4. Steroids increase morbidity and mortality in RA

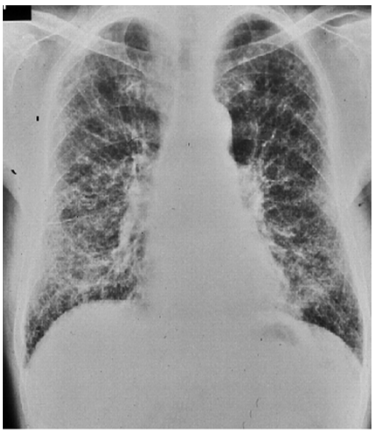
- Used to suppress inflammation. Very powerful agents and fast acting
- No analgesic effect however patients usually feel less pain due to reduction of inflammation.
- Systemic effect of RA reduced.
- Ideal for rapid treatment of life-threatening complications of RA

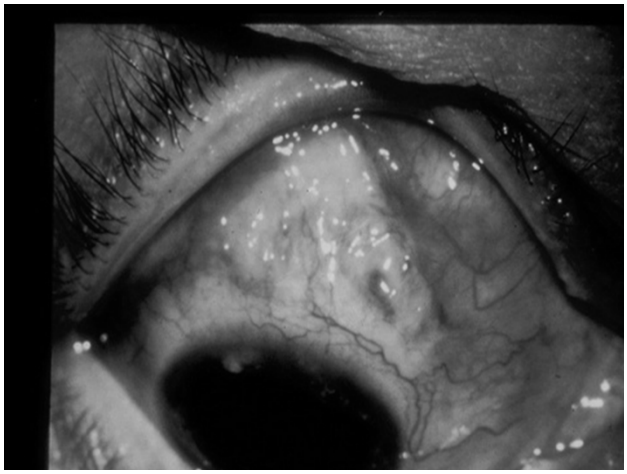
Prednisone 50mg daily

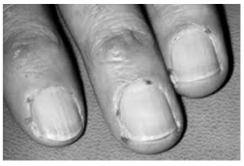
- Reserve for life or organ threatening disease.
- Don't do this for symptom relief

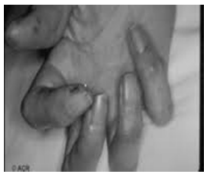
Ms. S. P.

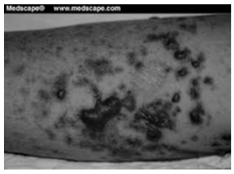
- 32 yo caucasian woman with a 8 week history of joint pain at her wrists, MCPs, PIPs, MTPs. Previously had a swollen knee 3 months ago. Post partum 4 months. Breastfeeding.
- Went to a walk-in clinic. Started on prednisone 50mg daily. Referred to rheumatology 'Arthritis, please see'.

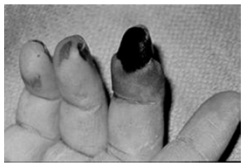












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Glucocorticoids - any route

- Oral - bridging therapy while waiting for DMARD effect
- Intravenous - high dose therapy for life-threatening or organ-threatening disease. Very fast onset of action
- Intra-articular - useful for one or two inflamed joints. Less systemic effect

Glucocorticoids - Major side effects

- Early
  - Mood disturbance
  - Hyperglycemia
  - Blurred vision
  - Hypokalemia
  - Osteonecrosis
- Late
  - Osteoporosis
  - Cushingoid features
  - Hypertension
  - Increased cardiovascular risks
  - Osteonecrosis
  - Cataracts

Glucocorticoids - Final Message

- Major side effects are inevitable with chronic, higher doses
- Use smallest dose possible and taper
- Frequent cause of patient morbidity, physician distress, medical malpractice cases - Informed Consent
- Steroids increase long term cardiovascular complications (MI, CVA)

Aviña-Zubieta JA, Abrahamowicz M, De Vera MA, et al. Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study. Rheumatology. 2013;52(1):68-75.

5. Methotrexate increases quality AND quantity of life in RA

- Choi showed that the hazard ratio for MTX in RA for CV death was 0.3 (0.2-0.7) compared to non-CV death at 0.6 (0.2-1.2)
- Multiple studies show reduced work disability, reduced damage and improved QoL with MTX.

Choi et al. Methotrexate and mortality in patients with RA: A prospective study. Lancet 2002

Non-steroidal anti-inflammatory drugs (NSAIDs) do not alter the course of RA

- Both analgesic and anti-inflammatory properties.
- Fast acting (days - 2 weeks)
- Do not alter disease outcomes
- May increase CV morbidity and mortality.

Limitations of NSAIDs

- Ineffective as sole therapy for RA
- Do not prevent joint damage
- Side effects, e.g., dyspepsia (common), gastric bleeding or perforation, renal insufficiency, hypertension.
- Drug interactions

ACR Ad Hoc Committee on Clinical Guidelines. *Arthritis Rheum* 1996;**39**:723-731

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Pharmacological Therapy

- **Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**
- **Glucocorticoids**
- Disease-Modifying Anti-Rheumatic Drugs (DMARDs)

While waiting for DMARD effect:

- NSAID
- Low dose, oral prednisone (<=7.5mg/d), intra-articular steroids
- Physical measures
- Analgesic agents

RA therapy with DMARDs

- Mild RA (elderly onset, RF neg, few swollen jts)
  - Hydroxychloroquine
- Early RA (with poor prognostic signs)
- Late RA
  - Triple therapy
  - MTX with move to combination Tx.
  - Biologics with MTX
- Resistant RA

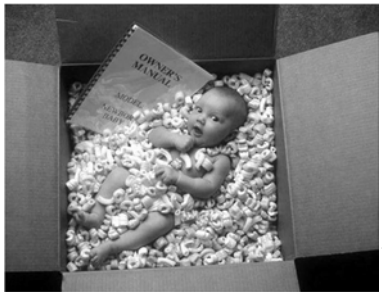
Treat Severe RA

- DMARD - methotrexate initially. Rapidly maximize dose over 12 weeks. I usually start with Triple therapy.
- If MTX not tolerated, switch to 2nd agent (Treat life-threatening extra-articular disease with high dose oral or IV steroids while awaiting DMARD benefit
- Biologic agents usually added to MTX in patient who have not responded.
- In BC, must try 3 traditional DMARDs and a combination before starting biologics

1. Diagnosing RA early makes it much easier to treat
2. Smoking increases the chance of developing rheumatoid arthritis and makes it more severe
3. All patients with RA should be on a DMARD
4. Steroids increase morbidity and mortality in RA
5. Methotrexate increases quality AND quantity of life in RA

Tina Korownyk

Prenatal Care - Impacting your future Super boy/Super girl



Tina Korownyk

Faculty/Presenter Disclosure

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

CFPC CoI Templates: Slide 3

Disclosure of Commercial Support

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

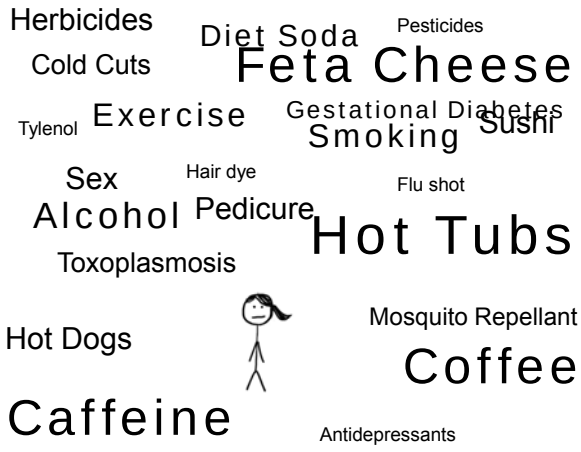
Mitigating Potential Bias

N/A

Objectives

To become familiar with the evidence regarding medications and or interventions that may commonly be used in pregnancy.

i.e. SSRIs, ASA, Folic Acid, Caffeine, Medical therapy for smoking cessation



Tina Korownyk

MOTHERISK ROUNDS

The Fetal Safety of Fluoxetine: A Systematic Review and Meta-Analysis

Lauren Riggin, MSc, Zipora Frankel, MD, Myla Moretti, MSc, Anna Pupco, MD, Gideon Koren, MD
The Motherisk Program, Department of Paediatrics, The Hospital for Sick Children, University of Toronto, Toronto ON

ACP Journal Club | 15 December 2009

SSRIs in early pregnancy were associated with increased risk for septal heart defects but not major congenital malformations overall

Ann Intern Med. 2009;151(12):JC6-15. doi:10.7326/0003-4819-151-12-200912150-02015

Text Size: A A A

Systematic review and meta-analysis

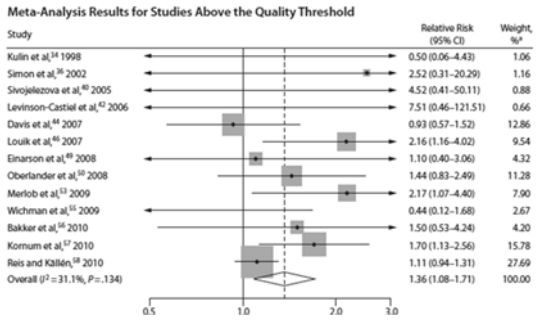
Antidepressant exposure in utero is associated with an increased risk of cardiovascular malformation

10.1136/eb-2013-101489

Serious Shortage of Reliable Info & Cardiac Malformations

Systematic Review	Estimate
J Clin Psychiatry 2013;74(4):e293-e308.	1.36 (1.08-1.71)
Aust N Z J Psychiatry 2013 47:1002	1.15 (0.999–1.32)
Daru. 2012 Nov 1;20(1):75.	1.19 (0.39-3.64)

2013 Sys Rev all SSRIs



J Clin Psychiatry 2013;74(4):e293-e308.

Serious Shortage of Reliable Info & Cardiac Malformations

Systematic Review	Estimate	Risk with Paroxetine	
J Clin Psychiatry 2013;74(4):e293-e308.	1.36 (1.08-1.71)	1.43 (1.08-1.88)	
Aust N Z J Psychiatry 2013 47:1002	1.15 (0.999–1.32)	1.44 (1.12-1.86)	
Daru. 2012 Nov 1;20(1):75.	1.19 (0.39-3.64)	-	
Birth Defects Res A Clin Mol Teratol. 2010 Mar;88(3):159-70	-	1.46 (1.17-1.82)	
J Obstet Gynaecol Can. 2008 Aug;30(8):696-701	-	1.18 (0.88-1.59)* case control	
Clin Ther. 2007 May;29(5):918-26	-	1.72 (1.22-2.42)	

Serious Shortage of Reliable Info & Cardiac Malformations

Systematic Review	Estimate	Risk with Paroxetine	Conclusion
J Clin Psychiatry 2013;74(4):e293-e308.	1.36 (1.08-1.71)	1.43 (1.08-1.88)	Not important
Aust N Z J Psychiatry 2013 47:1002	1.15 (0.999–1.32)	1.44 (1.12-1.86)	Important
Daru. 2012 Nov 1;20(1):75.	1.19 (0.39-3.64)	-	Important
Birth Defects Res A Clin Mol Teratol. 2010 Mar;88(3):159-70		1.46 (1.17-1.82)	Important
J Obstet Gynaecol Can. 2008 Aug;30(8):696-701		1.18 (0.88-1.59)* case control	Not important
Clin Ther. 2007 May;29(5):918-26		1.72 (1.22-2.42)	Not important

Cohorts, Causality & Confounders

Why harm might be overstated	Why harm might be understated
Detection bias[1] Women on paroxetine>anxiety than other SSRIs (OR 4.11) 30% ↑ use of Ultrasound 2x ↑ echos 1st year VSD detected in 5% of infants screened–most resolve by 1 yr	Many studies excluded women who miscarried
Confounders (ie smoking, etoh, depression itself)	Confounders

1) Clin Ther. 2007 May;29(5):918-26.

Tina Korownyk

NEJM 2014
Depression as a confounder

- Cohort 949,504 women, 6.8% antidepressants 1st trimester. Association with cardiac defects attenuated with increasing adjustment for confounding:

- Unadjusted: RR 1.25 (1.13 to 1.38), NNT = 558
- Restricted to depression: RR 1.12 (1.00 to 1.26)
- Fully adjusted & depression: RR 1.06 (0.93 to 1.22)

N Engl J Med. 2014 Jun 19;370(25):2397-407.

Bias of predisposition

- Two analyses of a large American cohort study (NHANES III) came to opposite conclusions:
- Every 1000 mg / day increase in sodium intake resulted in a trend towards:
  - Decreased (trend) all-cause mortality[1]
    - HR = 0.94 (0.88-1.01)
  - Increased all-cause mortality[2]
  - HR = 1.20 (1.03-1.41)

1) J Gen Intern Med. 2008; 23(9):1297-302. 2)Arch Intern Med. 2011; 171(13):1183-91.

Does pregnancy have a protective effect on depressive relapse?

1) Prospective observational Study 201 women[1]
Depression relapse with antidepressant discontinuation proximate to conception[1]:
- 68% vs 26% NNH = 3 (p<0.0001)

Limitations: HIGH risk women: mean depression 15 years, 44% had 5 or more prior recurrences, possible withdrawal effect

1) JAMA. 2006 Feb 1;295(5):499-507..

LEADER (U.S.)
DRUG INTERACTIONS

Financial Ties to Industry Cloud Major Depression Study

At Issue: Whether It's Safe For Pregnant Women To Stay on Medication

The study… failed to note that most of the 13 authors are paid as consultants or lecturers by the makers of antidepressants…In total, the authors failed to disclose more than 60 different financial relationships with drug companies.

Does pregnancy have a protective effect on depressive relapse?

1) Cohort 201 women[1]
Depression relapse with antidepressant discontinuation proximate to conception[1]:
- 68% vs 26% NNT = 3 (p<0.0001)

2) Cohort 778 women with hx of depression in past 5 years- no difference if on SSRI or not.[2]

3) Sys Rev, 27 RCTs, all GSK data, paroxetine mean improvement = 2.5 pts on the Hamilton Rating Scale for Depression[3]
- Minimum 3 pts is clinically significant.[4]

1) JAMA. 2006 Feb 1;295(5):499-507. 2) Epidemiology. 2011 Nov;22(6):848-54 3) PLoS One. 2014 Aug 27;9(8):e106337. .4) National Institute for Clinical Excellence (2004) Depression: Management of depression in primary and secondary care.

SSRIs & Pregnancy

- Dec 2005 - FDA: paroxetine use may increase risk for fetal heart defects by 2-fold
- Oct 2009 – First paxil lawsuit awarded $2.5 million for CVD deformations
- By 2010 – 800 Paxil lawsuits for birth defects settled at ~$1 billion[1]

- Bottom Line: Most studies report risk of cardiac malformation with paroxetine RR ~ 1-2,
- Baseline risk ~1% [2,3]
- If real, risk would increase from ~1% to 2%.

1) Paxil birth defects.www.lawyersandsettlements.com/case/paxil-heart-defects-newborn.html. Accessed Sept 16, 2014. 2) Clin Ther. 2007 May;29(5):918-26. 3) Am J Epidemiol. 1985 Jan;121(1):31-6.

Tina Korownyk

Reported Exposures and Congenital Cardiovascular Defects

Maternal Illness	Defect	RR
Pregestational Diabetes	Any	3.1-18[1]
Febrile Illness	Any	1.8-2.9[1]
Influenza	Any	2.1[1]
Ibuprofen	Any	1.86[1]
Marijuana	VSD	1.9[1]

Circulation. 2007 Jun 12;115(23):2995-3014. Epub 2007 May 22.

Risk of spontaneous abortion (sys reviews observational data)

Exposure	OR	CI	Congenital Malformation
Smoking[1]	1.32	1.21-1.44	
Obesity (BMI >30)[2]	1.31	1.18-1.46	
Working Fixed Nights[4]	1.51	1.27-1.78	
Poor glycemic control in DM[3]	3.23	1.64-6.36	3.44 (2.30 to 5.15).
Thyroid antibodies (normal thyroid function)[5]	3.90	2.48-6.12	
Work in Columbian Floriculture[6]	2.24	1.87-2.68	1.31 (1.95-1.64).

1) Am J Epidemiol. 2014 Apr 1;179(7):807-23 2) Semin Reprod Med. 2011 Nov;29(6):507-13. 3) BMC Pregnancy Childbirth. 2006 Oct 30;6:30. 4) Scand J Work Environ Health. 2013 Jul;39(4):325-34.5) BMJ. 2011 May 9;342:d2616. 6) Biomedica. 2007 Dec;27(4):490-7

Smoking Cessation

- 2 RCTs in 2014: 1050[1] & 476[2] women, NRT patch
  - 10-30mg/16hr vs placebo
  - At 1 month: NRT better 21.3% vs 11.7% (NNT = 11)[1]
  - At delivery and 2 yrs: No difference[1,2]
- 2012 Sys Rev 6 RCTs, 1745 women
  - No diff in quit rates with NRT RR 1.33(0.93 –1.91)[3]
  - No RCTs looking at bupriopion or varenicline
  - Sys Rev demonstrated improvement with counseling interventions (RR 1.44, CI 1.19-1.75)[4]

1) Efficacy and safety of nicotine replacement therapy for smoking cessation in pregnancy: systematic review and meta-analysis. Addiction 2011;106 :52– 61 2) BMJ. 2014;348:g1622/ACP Journal club 3) Cochrane Database Syst Rev. 2012 Sep 12;9:CD010078. 4) Cochrane Database Syst Rev. 2013 Oct 23;10:CD001055.

Another vitamin to the Rescue?

- RCT, double blind, 2007-2011, 159 pregnant smokers, Vitamin C 500mg/d vs placebo.[1]
- Vit C Group had significant improvement in:
- 1° Outcome: Newborn Pulmonary Function Testing Measures ~10% improvement, p=0.006
- 2° Outcome: At least 1 episode wheezing <1yr
- 21% vs 40%, NNT = 6
- Limitations: small size, PFTs similiar at 1yr, needs to be replicated
- Bottom Line: Smoking cessation best, possible harm reduction

1) Jama. 2014;311(20):2074-2082 2) Cochrane Database Syst Rev. 2013 Oct 23;10:CD001055.

Folic Acid & Neural Tube Defects 2 RCTs

1) 1817 women with history NTD, Folic acid 4mg/day vs placebo[1]
- Folic acid RR 0.28, NNT = 40

2) 4753 women, Folic acid 0.8mg/day (multivitamin), 1° prevention[2]
- RR 0.08 (0.00 - 1.33) no cases in folic acid group, NNT* = 399

Sys Review, 5 RCTs, (4 were 2° prevention), 6105 women [3]
- Significant ↓ Neural Tube Defects: RR 0.28 (0.15-0.52)

Bottom Line: decreased risk of NTD, particularly with history of NTD.

1) Lancet. 1991 Jul 20;338(8760):131-7. 2) Arch Gynecol Obstet (1994) 255:131-139 3) Cochrane Database Syst Rev. 2010 Oct 6;(10):CD007950.

Preconception ASA to prevent pregnancy loss

- Cochrane 2014, 9 RCTs, 1228 women with 2 or more unexplained losses (with or without hereditary thrombophilia)[1]
  - ASA vs Placebo RR 0.94 (CI 0.8-1.11)
  - LMWH vs ASA RR 1.08 (CI 0.93-1.26)
  - LMWH & ASA vs no treatment RR 1.01 (CI 0.87-1.16)
- RCT (not included in sys rev), 1228 women, low dose ASA vs placebo[2]
- No difference live births (58% vs 53%, p=0.0984)
- Bottom Line: Low dose ASA or LMWH not recommended for prevention of pregnancy loss

1) Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD004734 2) Lancet. 2014 Jul 5;384(9937):29-36.

Tina Korownyk

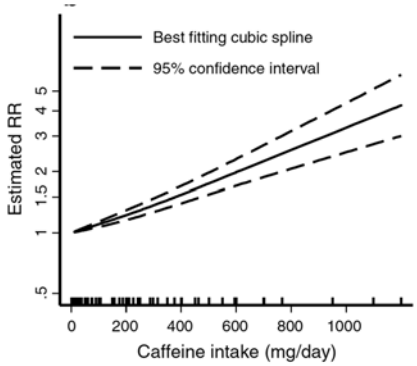
Caffeine

- Sys Review 2014, 53 cohort and case control studies[1]
- Each increment 100 mg caffeine =
- 14% ↑ spontaneous abortion,
- 19% ↑ stillbirth
- 7% ↑ low birth weight
- Non sign difference preterm birth
- Possible confounders: inverse correlation with nausea and caffeine intake, smoking, stress…etc

1) Eur J Epidemiol. 2014 Sep 2. [Epub ahead of print]

Daily Caffeine Intake & Miscarriage

Dose Response Curve



Caffeine

RCT 1207 Pregnant women <20wks, ≥3 cups coffee/day

- Regular vs decaffeinated coffee
- Results: Mean caffeine: 317mg vs 117mg (182mg diff)
- No difference: mean birth weight (3539g vs 3519g)
- length of gestation (279d vs 280d)
- Limitations: compliance unknown, 49% guessed in noncaffeinated group, questionnaire, 2nd half of pregnancy only
- Bottom Line: In excess, most things are bad for you

BMJ, doi:10.1136/bmj.39062.520648.BE (published 26 January 2007)

Thank You

Rita McCracken

Dementia

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

CFPC CoI Templates: Slide 1

Faculty/Presenter Disclosure

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

CFPC CoI Templates: Slide 2

Disclosure of Commercial Support

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

CFPC CoI Templates: Slide 3

Mitigating Potential Bias

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

26th Annual Best Science Medicine Course: Slide 4

Learning Outcome Objective Slide

1. Describe levels of **dementia** severity
   - Practice using one (easily applied) tool to asses
2. Brief review of how severity of dementia affects lifespan and and how dementia is linked to frailty.
3. Discuss effectiveness of dementia medications versus side effects.

Alzheimer's	7
Vascular Dementia	13
Severe Alzheimer's dementia with BPSD	1
Dementia	41
Severe dementia	3
Alzheimer's type and ischemic	1
Advanced dementia	2
Dementia with agitation, labile mood	1
Cognitive impairment with personality traits	1
Decreased cognitive function	2
Alzheimer's dementia/Alzheimer's-type dementia	10
Dementia with BPSD	1
Cognitive impairment	11
Lewi Body dementia	2
Dementia NOS	1
Likely Alzheimer's	1
Mild cognitive impairment	10
Frontal lobe dementia	1
Dementia – mixed etiology	1
Multi-infarct dementia	2
Advanced vascular dementia	1
Memory impairment	1
Dementia (mod-severe cognitive impairment)	1
Dementia-minimal verbal output	1
Dementia not Alzheimer's	2
Mild dementia	3
Moderate dementia	2
Dementia – small vessel ischemia	1
CVA with cognitive decline and behavior changes	1

How do we describe dementia now?

Variable?
Spotty?
Inconsistent?
Useful?

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Why do we need to know about this?

- Help patient and family plan for future and give accurate advice about prognosis. (Dementia is a fatal disease)
- Make reasonable recommendations about dementia medications.

A 2 minute dementia staging scale

DEMENTIA STAGE: BRIEF COGNITIVE RATING SCALE

Dementia Stage		Cognition (CURE)	FAST (IRAN) N/A (If function impaired for physical reasons)
1	Normal	○ Cognition intact	○ Function intact
2	Subjective complaints only		
3	MCI	○ Deficits on high level tasks	○ Difficulty with high level tasks, such as planning a dinner party
4	Mild dementia	○ Difficulty remembering current events or recent events. Record details:	○ IADLs impaired
5	Moderate dementia	○ Cannot name US President	○ Re-wears clothes (tends to wear the same clothes day after day)
6	Severe dementia	○ Difficulty remembering names of first degree relatives (children, spouse)	○ BADLs impaired
7	Very severe dementia	○ Difficulty remembering everything	○ Non-verbal, non-ambulatory

Reisberg B, Ferris S.H. Brief Cognitive Rating Scale (BCRS). Psychopharmacol Bull. 1988; 24:629-636

Moorhouse P, Mallery LH. J Am Geriatr Soc. 2012;60(12):2326-32.

(unofficial) equivalence of dementia measures

Global Deterioration Scale (GDS) [1],	MMSE [2], (out of 30)	Severity label [3]
1-2	28-30	No dementia
3	23-28	MCI
4	18-23	Mild
5	10-17	Moderate
6	0-9	Severe
7	0-9	Very Severe

References

1. Sclan SG, Reisberg B. Functional assessment staging (FAST) in Alzheimer's disease: reliability, validity, and ordinality. International psychogeriatrics / IPA. 1992;4 Suppl 1:55-69.
2. Rizzuto D, Bellocco R, Kivipelto M, Clerici F, Wimo A, Fratiglioni L. Dementia after age 75: survival in different severity stages and years of life lost. Current Alzheimer research. 2012;9(7):795-800.
3. Moorhouse P, Mallery LH. Palliative and therapeutic harmonization: a model for appropriate decision-making in frail older adults. J Am Geriatr Soc. 2012;60(12):2326-32.

How long at each dementia stage?

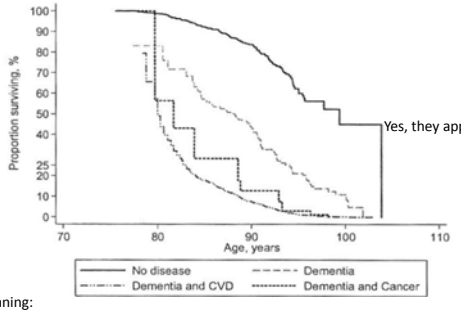
Severity label [3]	Years lived at each stage of dementia
No dementia	
MCI	5 months
Mild	23 months
Moderate	14 months
Severe/Very Severe	12 months

Mean survival time from time of diagnosis = 4.1 years (SD 2.61)

- If < 85 yo at diagnosis = 4.8
- If > 85 yo at diagnosis = 3.8
- Mean age of this population was 81 years old

Rizzuto D, et al., Current Alzheimer research. 2012;9(7):795- 800
Helmer, C, et al., Am J Epidemiol. 2001; 152(7): 642-8
Knopman, DS, et al., Arch Neurol 2003; 60(1):85-90

If you have dementia, do other diseases influence time to death?



Yes, they appear to.

Meaning:
If you have dementia and heart disease, you die sooner than anyone else.
If you have dementia, you die sooner than if you don't.

Rizzuto D, et al., Current Alzheimer research. 2012;9(7):795- 800

Medications for dementia

- LOTS of research on Alzheimer's medications.
- Studies primarily use a measure called ADAS-COG (sometimes also MMSE)
- ADAS-COG is a score out of 70 (need special training to administer it)
- "Clinically meaningful" improvement generally considered (by trials) to be >4 point change on ADAS-COG (that is 4/70…)

Burns A. 2002. Meaningful treatment outcomes in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **73**: 471–472.

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Pfizer's press release (when they received FDA approval to market Aricept in 1996) noted:

"Alzheimer's disease is a family tragedy. Aricept will benefit patients and families alike by improving or maintaining patient function, which in turn may help ease the burden for caregivers and help maintain personal dignity… **Aricept represents a significant step forward in addressing the therapeutic needs of the Alzheimer's disease community**…This therapy will help to change the approach to the management of Alzheimer's disease."

Global sales of Aricept were approximately $1.1 billion for 2008 alone

http://www.sciencebasedmedicine.org/dont-believe-the-hype-cholinesterase-inhibitors-as-a-treatment-for-dementia/

NNT

(20 meta-analyses have been published)

NNT for ADAS-Cog score change >4
= **6-18**

Not so bad…?

Candy Marcet and G. Michael Allan. Cholinesterase Inhibitors and treatment of Alzheimer's dementia. Alberta College of Family Physicians: Tools for Practice [Internet]. 2014.

NNH

- Number needed to HARM
  - Adverse event leading to study drop out=10
- Specific AE's (if using donepezil)
  - Anorexia, NNH = 17
  - Diarrhea, NNH = 10
  - Nausea, NNH = 11
  - Vomiting, NNH = 13

Birks, J Cochrane database Syst. Rev. 2006: (1):CD005593
Birks, J, Harvey RJ, Cochrane database Syst. Rev. 2006: (1):CD001190

Outcomes NOT demonstrated

- No difference in time to nursing home admission (Courtney, Lancet 2003)
- No reduction in caregiver burden
- Preservation of meaningful cognitive function (hold conversations, enjoy TV/radio, reading & writing skills)

TI Letter #56, Drugs for Alzheimer's Disease

Bias?

- Drop out rates typically 35%
  - Analyzed as if cognition was stable LCOF=last observation carried forward
  - As opposed to using assumption that dementia is progressive, so gives "better score".
- Only non-drug company funded study (Courtney, C. Lancet, 2004), plagued with issues (recruitment and dropouts).
- Why so many meta-analyses?

Practical advice

1. Know your patient's health, do the FAST screen (dementia, function, frailty)
2. Know your patient's values (Gawande, Being Mortal, 2014)
   1. What is your understanding of where you are and of your illness?
   2. Your fears or worries for the future
   3. Your goals and priorities
   4. What outcomes are unacceptable to you? What are you willing to sacrifice and not?

   And later,
   5. What would a good day look like?
3. If GDS is 4-6, and/or MMSE is 10-26, may consider a short trial (8 weeks)
   1. get good collateral hx (don't prescribe if you can't find out if it harms or helps)
   2. be ready to redo FAST assessment.
   3. Start LOW, go SLOW
4. STOP drugs if side effects, or if not better, or if dementia progresses to very severe (7).

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Resources

- Therapeutics Letter #56, Drugs for Alzheimer's Disease, TI
- Book: "Being Mortal", Atul Gawande
- PATH CLINIC for frailty specific treatment guidelines for chronic disease
  - www.pathclinic.ca/resources
- BC Alzheimer's Drug Therapy Initiative
  - http://www.health.gov.bc.ca/pharmacare/adti/clinician/

Thanks for your questions and discussion.

Thanks for completing your course evaluations.