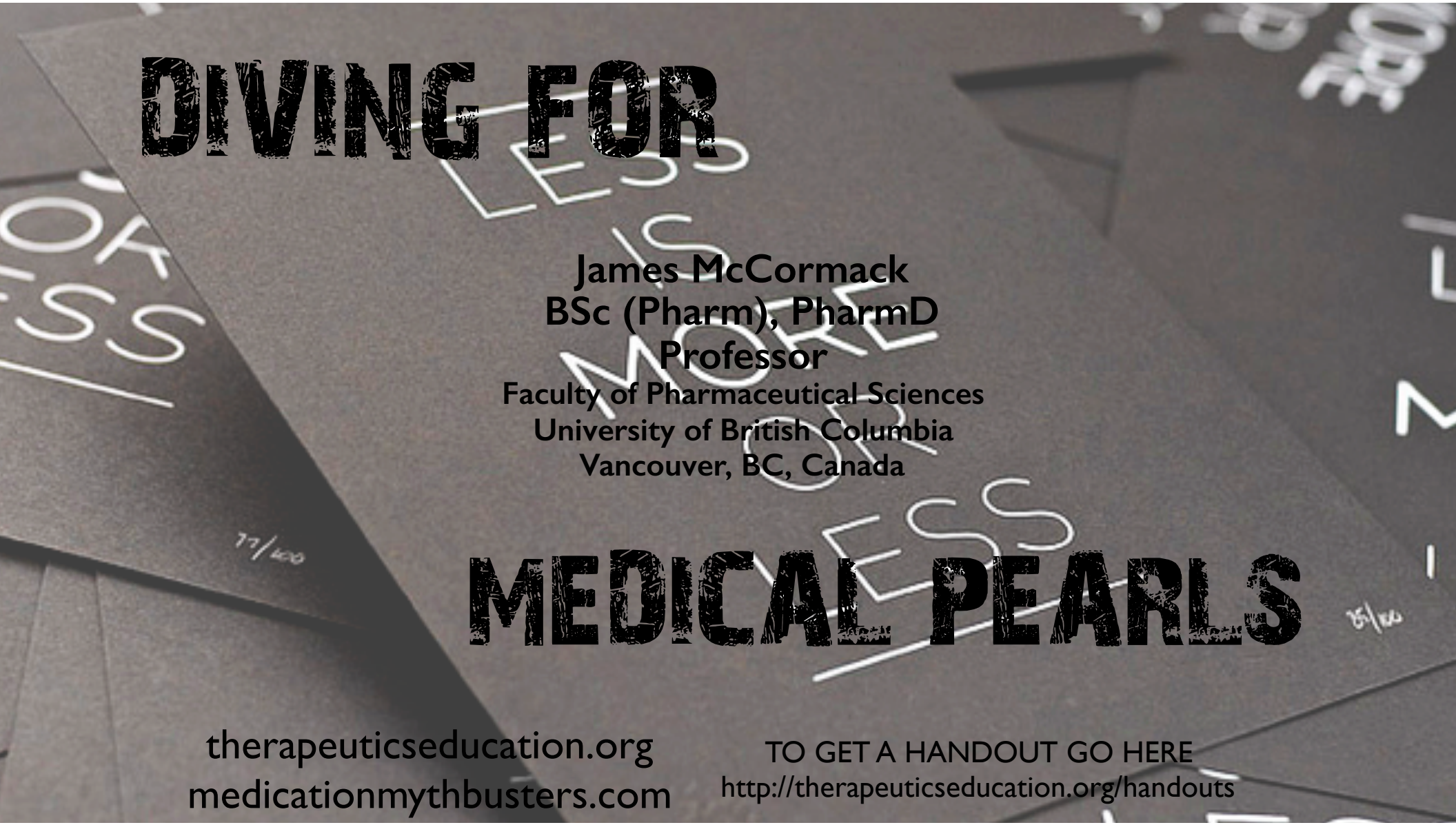


DIVING FOR MEDICAL PEARLS

James McCormack
BSc (Pharm), PharmD
Professor
Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, BC, Canada

therapeuticseducation.org
medicationmythbusters.com

TO GET A HANDOUT GO HERE
http://therapeuticseducation.org/handouts

Guidelines would be awesome if they…

Were developed primarily by, and definitely for, the people that ultimately end up using them

Were a credible synopsis of the best available evidence presented in a way that clinicians could easily access and interpret

Allowed patient values and preferences to be taken into account

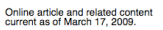
Wrong guidelines: why and how often they occur

Primiano Iannone,[1] Nicola Montano,[2] Monica Minardi,[3] James Doyle,[3] Paolo Cavagnaro,[4] Antonino Cartabellotta[5]

"Unfortunately, depending on how their reliability is measured, up to 50% of guidelines can be considered untrustworthy. This carries serious consequences for patients' safety, resource use and health economics burden."

EBM 2017;22:1-3

Typically “evidence-based” guideline recommendations are not based on “solid” evidence



Online article and related content current as of March 17, 2009.

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci; Joseph M. Allen; Judith M. Kramer; et al.

JAMA. 2009;301(8):831-841 (doi:10.1001/jama.2009.205)

Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines

Dong Heun Lee, MD; Ole Vielemeyer, MD *Arch Intern Med*. 2011;171(1):18-22

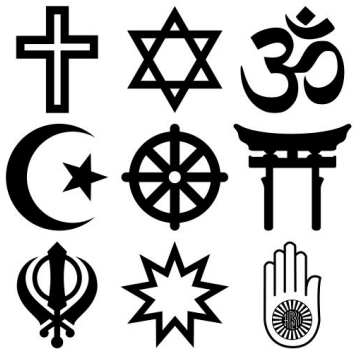
Clinical Endocrinology (2013) **78**, 183–190 doi: 10.1111/j.1365-2265.2012.04441.x

METHODOLOGICAL ASSESSMENT IN ENDOCRINOLOGY

A comparative quality assessment of evidence-based clinical guidelines in endocrinology

EVIDENCE LEVEL	Cardiology	Infectious disease	Endocrinology
1 or A based on RCTs	11%	14%	6%
3 or C based on opinion	48%	55%	35%

MY BELIEF

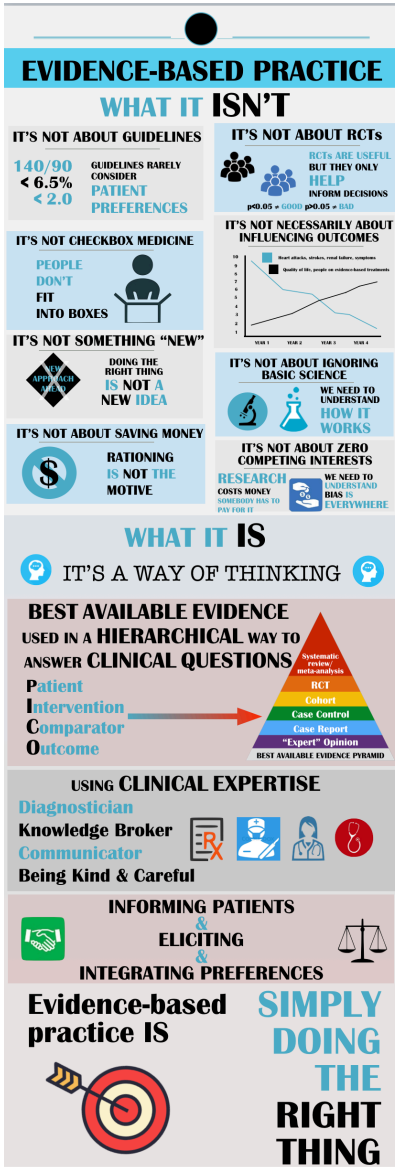


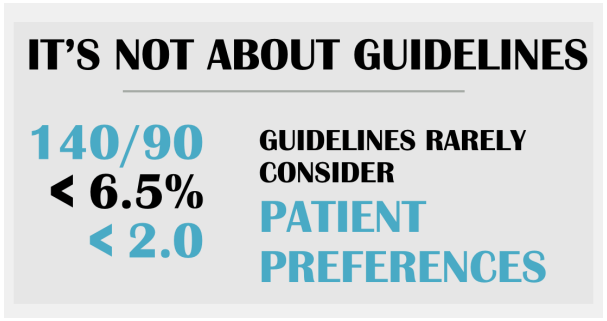
All Health Care Providers should have their practice underpinned by the best available evidence

Evidence-Based Practice (EBP)

Best Available Evidence

Nothing in there about guidelines


EVIDENCE-BASED PRACTICE
WHAT IT ISN'T
IT'S NOT ABOUT GUIDELINES
140/90
< 6.5%
< 2.0
GUIDELINES RARELY CONSIDER
PATIENT PREFERENCES
IT'S NOT ABOUT RCTs
RCTs ARE USEFUL BUT THEY ONLY HELP INFORM DECISIONS
p<0.05 ≠ GOOD p>0.05 ≠ BAD
IT'S NOT CHECKBOX MEDICINE
PEOPLE DON'T FIT INTO BOXES
IT'S NOT NECESSARILY ABOUT INFLUENCING OUTCOMES
IT'S NOT SOMETHING "NEW"
NEW APPROACH AHEAD
DOING THE RIGHT THING IS NOT A NEW IDEA
IT'S NOT ABOUT IGNORING BASIC SCIENCE
WE NEED TO UNDERSTAND HOW IT WORKS
IT'S NOT ABOUT SAVING MONEY
RATIONING IS NOT THE MOTIVE
IT'S NOT ABOUT ZERO COMPETING INTERESTS
RESEARCH
COSTS MONEY
SOMEBODY HAS TO PAY FOR IT
WE NEED TO UNDERSTAND BIAS IS EVERYWHERE
WHAT IT IS
IT'S A WAY OF THINKING
BEST AVAILABLE EVIDENCE
USED IN A HIERARCHICAL WAY TO ANSWER CLINICAL QUESTIONS
Patient
Intervention
Comparator
Outcome
Systematic review, meta-analysis
RCT
Cohort
Case Control
Case Report
"Expert" Opinion
BEST AVAILABLE EVIDENCE PYRAMID
USING CLINICAL EXPERTISE
Diagnostician
Knowledge Broker
Communicator
Being Kind & Careful
INFORMING PATIENTS
&
ELICITING
&
INTEGRATING PREFERENCES
Evidence-based practice IS
SIMPLY DOING THE RIGHT THING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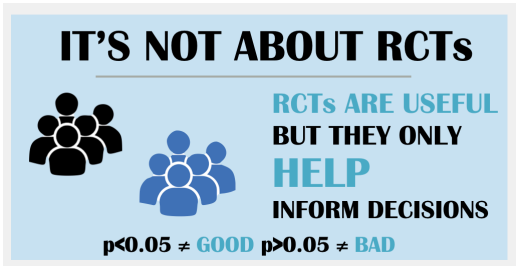
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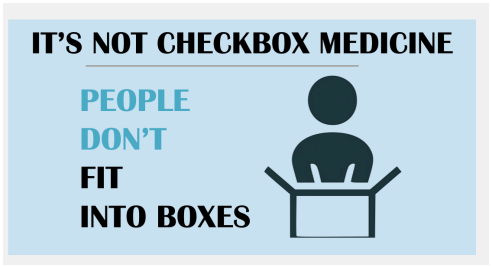
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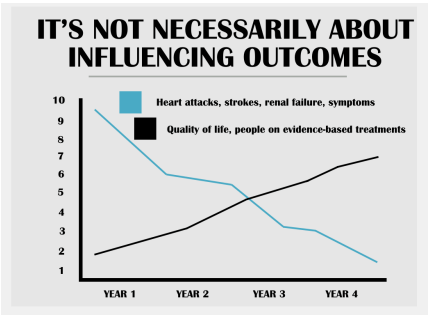
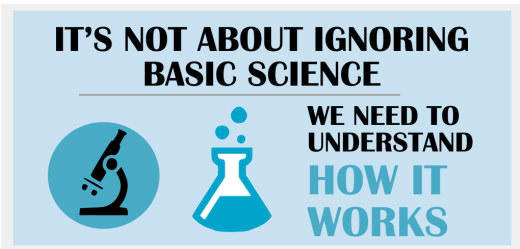

IT'S NOT NECESSARILY ABOUT INFLUENCING OUTCOMES
Heart attacks, strokes, renal failure, symptoms
Quality of life, people on evidence-based treatments
10
9
8
7
6
5
4
3
2
1
YEAR 1
YEAR 2
YEAR 3
YEAR 4


IT'S NOT SOMETHING "NEW"
NEW APPROACH AHEAD
DOING THE RIGHT THING
IS NOT A NEW IDEA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USING CLINICAL EXPERTISE

Diagnostician
Knowledge Broker
Communicator
Being Kind & Careful

INFORMING PATIENTS
&
ELICITING
&
INTEGRATING PREFERENCES

WHAT IT IS

IT'S A WAY OF THINKING

EVIDENCE-BASED PRACTICE

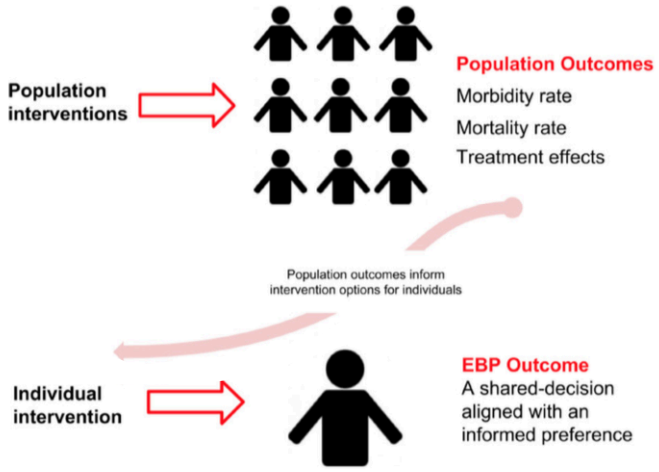
EBM analysis

OPEN ACCESS

Shared decision is the only outcome that matters when it comes to evaluating evidence-based practice

James McCormack,[1] Glyn Elwyn[2]

"in the vast majority of circumstances, the only outcome of relevance for EBP is to measure whether a shared decision was made"



doi:10.1136/ bmjebm-2018-110922

Simplified lipid guidelines

Prevention and management of cardiovascular disease in primary care

G. Michael Allan MD CCFP Adrienne J. Lindblad ACPR PharmD Ann Comeau MN NP CCN(C) John Coppola MD CCFP
Brianne Hudson MD CCFP Marco Mannarino MD CCFP Cindy McMinis Raj Padwal MD MSc
Christine Schelstraete Kelly Zarnke MD MSc FRCPC Scott Garrison MD PhD CCFP Candra Cotton
Christina Korownyk MD CCFP James McCormack PharmD Sharon Nickel Michael R. Kolber MD CCFP MSc

Can Fam Phy 2015;61:857-67

Simplified guideline for prescribing medical cannabinoids in primary care

G. Michael Allan MD CCFP Jamil Ramji Danielle Perry Joey Ton PharmD Nathan P. Beahm PharmD
Nicole Crisp RN MN NP-Adult Beverly Dockrill RN Ruth E. Dubin MD PhD FCFP DCAPM Ted Findlay DO CCFP FCFP
Jessica Kirkwood MD CCFP Michael Fleming MD CCFP FCFP Ken Makus MD FRCPC Xiaofu Zhu MD FRCPC
Christina Korownyk MD CCFP Michael R. Kolber MD CCFP MSc James McCormack PharmD Sharon Nickel
Guillermina Noël MDes PhD Adrienne J. Lindblad ACPR PharmD

Can Fam Phy 2018;64:111-120

They can only really do 5 things - and only 2 of these are good

Help with symptoms

Reduce risk of future health issues

Cause side effects

Cost money

Be inconvenient

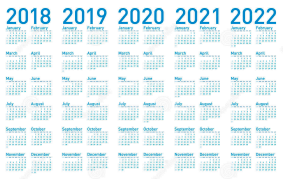
Have A Purpose

You are looking for numbers (%s)

In general who is it for - young/older, primary/secondary

TIME FRAME - 1 dose, 1 day, 1 week, 1 month, 1 year, 1 decade?

Is it for symptoms?



Clinically relevant endpoints

Is it for prevention?

CVD, fractures, exacerbations, infections

- anything as long as it isn't a surrogate marker (BP, cholesterol, glucose, FEV1, bone density)

It’s all about figuring out

The Chance of “X”

WITH NO

TREATMENT/TEST

The Chance “X”

WITH

TREATMENT/TEST

Progress in evidence-based medicine: a quarter century on

Benjamin Djulbegovic, Gordon H Guyatt

"Few clinicians would ever have the skill - or time - to conduct sophisticated assessment of the evidentiary basis for their practice"

Now - "directing clinicians to processed sources of evidence, and aiding decision making by advancing the science of trustworthy clinical practice guidelines that would be available to clinicians at the point of care delivery"

Lancet 2017;390:415–23

Tools For Practice

TOOLS FOR PRACTICE

Total articles found: 233

#233 Drink Up: Increasing Fluid Intake to Prevent Recurrent UTIs

Author(s): Adrienne J Lindblad, Rodger Craig
Publication Date: April 15, 2019
Collection: Tools for Practice
Categories: General, Obstetrics-Gynecology, Urology
Clinical Question: Does increasing water intake prevent recurrent urinary tract infections (UTIs)?

Tags: water, water intake, low fluid, UTI, urinary track, infection, women, female, antibiotics, non-pregnant , premenopausal , cystitis, cranberry juice, vaginal estrogen, oral estrogens, antibiotic prophylaxis,

View Article

Begin Reflective Exercise
(to launch a reflective exercise, you must be logged into GoMainpro)

#232 Muscling out molluscum contagiosum: Which treatments work?

Author(s): Danielle Perry, G. Michael Allan, Nicolas Dugré
Publication Date: April 01, 2019
Collection: Tools for Practice
Categories: Dermatology, General, Infectious Disease
Clinical Question: How effective are commonly used therapies for molluscum contagiosum?

Tags: molluscum contagiosum, lesion, potassium hydroxide, cryotherapy, curettage, cantharidin, imiquimod, virus, immune system, infection, pediatric, immunocompetent, burn, self-limiting

View Article

Begin Reflective Exercise
(to launch a reflective exercise, you must be logged into GoMainpro)

#231 Does an ASA a day really keep the doctor away?

Author(s): Paul Fritsch, Michael R Kolber
Publication Date: March 18, 2019
Collection: Tools for Practice
Categories: Cardiology, Gastroenterology, General, Oncology
Clinical Question: Is ASA effective for reducing cardiovascular events in patients without pre-existing cardiovascular disease?

Tags: ASA, cardiovascular, cardiovascular disease, elderly, diabetic, gastrointestinal, cancer, colon, CVD, transfusion, hemodynamic, circulatory system, primary prevention, aspirin, bleeding , bleeds

View Article

https://www.bmj.com/rapid-recommendations

Dual vs single antiplatelet therapy

The BMJ Practice: Dual antiplatelet therapy with aspirin and clopidogrel for acute high risk transient ischaemic attack and minor ischaemic stroke

BMJ Research: Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack

Oxygen therapy for acutely ill medical patients

The BMJ Practice: Oxygen therapy for acutely ill medical patients: a clinical practice guideline

The Lancet research: Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis

MAGICapp: Expanded version of the results

Prostate cancer screening

The BMJ Practice: Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline

The BMJ research: Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis.

BMJ Open research: Values and preferences of men for undergoing prostate-specific antigen screening for prostate cancer: a systematic review

The BMJ editorial: What should doctors say to men asking for a PSA test?

Comparing Treatment Options for Pain: The C-TOP Tool

Neuropathic Pain | Osteoarthritis Pain (Coming Soon) | Back Pain (Coming Soon)

Medication Options

- **Amitriptyline** (Elavil®)
- **Cannabinoids** (Nabiximols, nabilone, medical marijuana)
- **Duloxetine** (Cymbalta®)
- **Gabapentin** (Neurontin®)
- **High-Dose Opioids** (morphine, oxycodone)
- **Pregabalin** (Lyrica®)
- **All Treatments** (comparison)

Curious about capsaicin, botox, tramadol, carbamazepine, or venlafaxine for neuropathic pain? Click here to learn more.

Meaningful Pain Relief from Amitriptyline

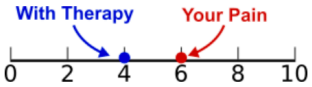
(30% reduction in pain scores)

Amitriptyline Benefit	Placebo Benefit	No Benefit
25% (ranges 13% to 45%)	25%	50%

A typical placebo group response seen in pain studies is **25%** but this can be adjusted in the FAQ section.

Meaningful Pain Relief

An example of a **30% reduction** in pain scores is a decrease from **6** to **4** on a **10** point pain scale



Amitriptyline Harms

Dry mouth	34%	6% (placebo)
Sleepiness	34%	9% (placebo)
Balance problems	20%	3% (placebo)
Stopped due to side effects	16%	7% (placebo)

Other Considerations

- Typically taken at bedtime due to sleepiness effects
- Approximate cost (CAD) for 30-day supply (without dispensing fee): **$1.50 to $3.50**

http://pain-calculator.com

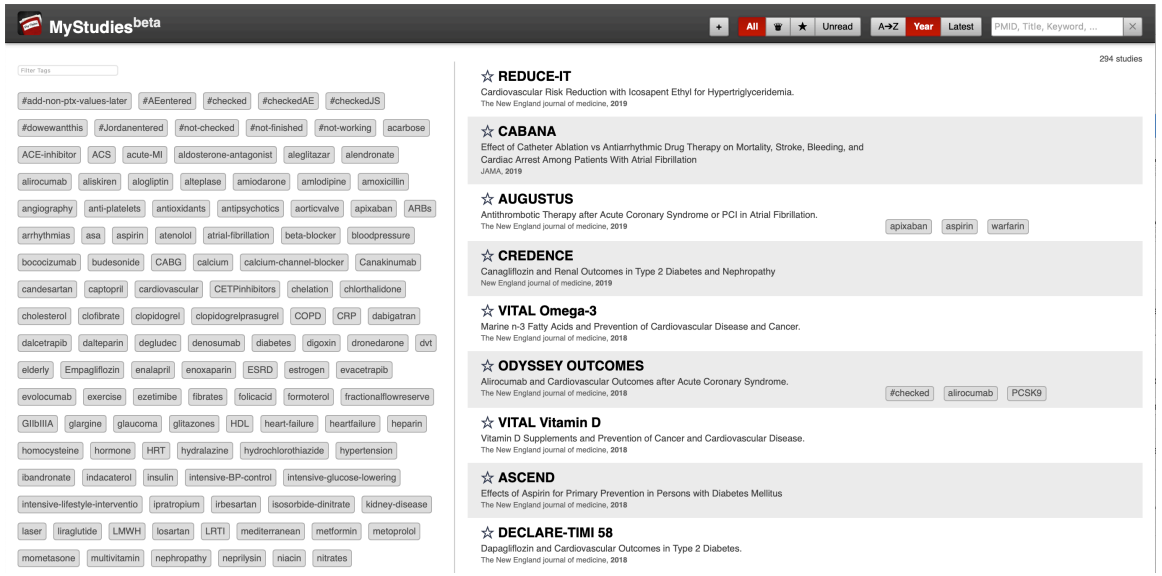
mystudies.org ~300 studies

MyStudies beta — Load studies

Study Results at Your Fingertips

You want to use evidence in your clinical practice from the landmark studies – those studies that change practice. Your patient comes in and asks you about the latest greatest study. How can you quickly and easily get all that information? **Let MyStudies help.**

You are at a presentation and you start to wonder if the presenter is really telling you everything you need to know about a study. Did they just present relative numbers? Did they only present the benefits with no mention of harms? Did they come up with conclusions that don't really match the results? **MyStudies can help.**



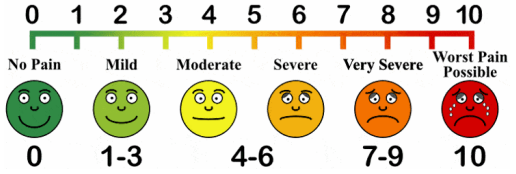
All the large RCTs evaluating the impact of glucose lowering medications on CVD Outcomes

RCTs evaluating the impact of medications on CVD outcomes in T2DM						
YEAR	NAME		MEDICATION	RESULT	OUTCOME CHANGED	ABSOLUTE DIFFERENCE/TIME
1970	UGDP	SU	tolbutamide (Orinase)	NEGATIVE	CVD mortality	↑8%/5 years
1971		BG	phenformin (DBI)	NEGATIVE	Mortality	↑ 6%/5-8 years
1976		SU	tolbutamide (Orinase)	NEGATIVE	Fatal MI	↑ 5%/5 years
1982		IN	insulin	NEUTRAL		
1998	UKPDS 33/34	IN,SU	insulin, chlorpropamide, glyburide/glibenclamide, glipizide	NEUTRAL		
1998		IN,SU,BG	metformin, insulin, chlorpropamide, glyburide/glibenclamide, glipizide	NEUTRAL except POSITIVE for metformin	Mortality MI	↓7%/11 years ↓ 6%/11 years
2003	STOP-NIDDM	OTH	acarbose (Precose)	POSITIVE	MI	↓ 1.5%/3 years
2005	PROACTIVE	GLIT	pioglitazone (Actos)	POSITIVE	MI	↓ 1.5%/3 years
2007	RECORD	GLIT	rosiglitazone (Avandia)	NEGATIVE	Heart failure	↑ 1%/4 years
2012	ORIGIN	IN	insulin	NEUTRAL		
2013	EXAMINE	DPP4	alogliptin (Nesina)	NEUTRAL		
2014	SAVOR-TIMI 53	DPP4	saxagliptin (Onglyza)	NEGATIVE	Heart failure	↑ 1%/2 years
2014	ALECARDIO	OTH	aleglitizar	NEUTRAL		
2015	ELIXA	GLP	lixisenatide (Adlyxin)	NEUTRAL		
2015	TECOS	DPP4	sitagliptin (Januvia)	NEUTRAL		
2015	EMPA-REG	GLIF	empagliflozin (Jardiance)	POSITIVE	Mortality Heart failure	↓ 2.5%/3 years ↓ 1.5%/3 years
2016	SUSTAIN 6	GLP	semaglutide (Ozempic)	POSITIVE	Combined outcome	↓ 2%/2 years
2016	LEADER	GLP	liraglutide (Victoza)	POSITIVE	Mortality Combined outcome	↓ 1%/4 years ↓ 2.5%/4 years
2017	CANVAS	GLIF	canagliflozin (Invokana)	POSITIVE	Combined outcome Heart failure Amputations	↓ 2%/3.5years ↓ 1%/3.5 years ↑ 1%/3.5 years
2017	EXSCEL	GLP	exenatide (Bvetta)	NEUTRAL		
2017	ACE	OTH	acarbose (Procose)	NEUTRAL		
2017	Omarigliptin	DPP4	omarigliptin	NEUTRAL		
2018	HARMONY	GLP	albiglutide (Tanzeum)	POSITIVE	Combined outcome	↓ 2%/2 years
2018	CARMELINA	DPP4	linagliptin (Tradjenta)	NEUTRAL		
2018	DECLARE-TIMI 58	GLIF	dapagliflozin (Farxiga)	POSITIVE	Combined outcome (primarily heart failure)	↓ 1%/4 years
2019	REWIND	GLP	dulaglutide (Trulicity)	POSITIVE	Combined outcome Renal outcomes	↓ 1.5%/5.4 years ↓ 2.5%/5.4 years
2019	PIONEER 6	GLP (oral)	semaglutide (Ozempic)	POSITIVE	CVD mortality Mortality	↓ 1%/1.5 years ↓ 1.5%/1.5 years
2019	CREDENCE		canagliflozin (Invokana)	POSITIVE	Combined CVD outcome Combined renal outcome outcomes	↓ 2.5%/2.6 years ↓ 3%/2.6 years

mystudies.org

Symptom Pearls

Symptoms



Scales - VAS, QOL, SGRQ - then what is the MICD

% of people who benefit in the treatment arm - that will be what you see in practice over placebo

% of people who benefit in the placebo arm - subtract that from the treatment to see how many actually benefit from the medication

Head-to-head studies are relatively uncommon

6-8 weeks	No longer depressed
Medication	50%
Placebo	40%
Medication benefit	50-40 = 10%
If person responds, the chance it is the medication	10/50 = 20%

But you need to know what goes on in the placebo group

	If person “responds”, what is the % chance it was the medication	
Response in the placebo group	If Benefit 10% - NNT 10	If Benefit 20% - NNT 5
0%	~100%	~100%
20%	~33%	~50%
40%	~20%	~33%

The Placebo Group Effect

not the placebo effect and these are ballpark numbers

~0% - general anesthesia

~5% - psychosis

~10% - sildenafil, OCD

~20% - Alzheimer's meds, acetaminophen for headaches, side effects

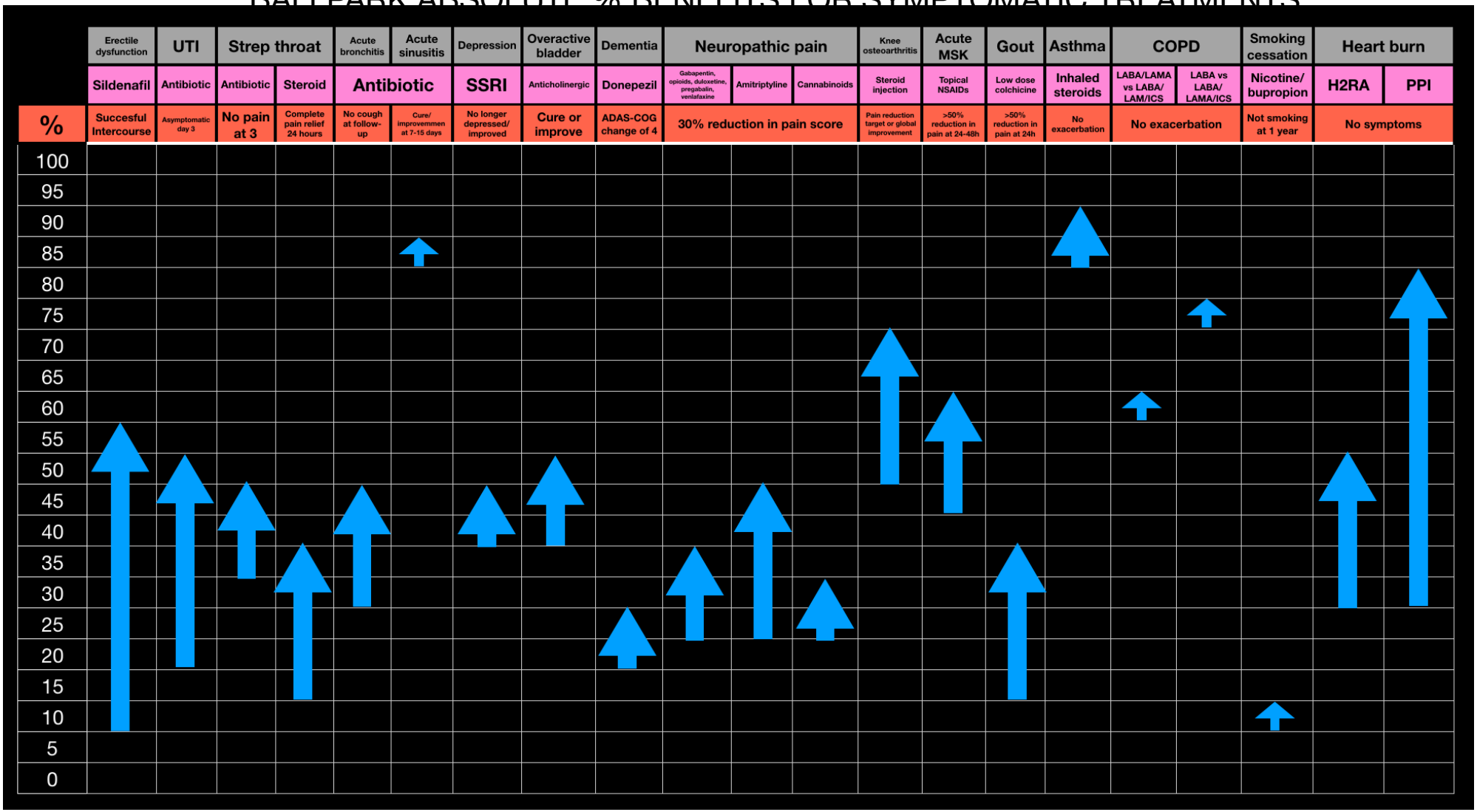
~25% - menopausal symptoms, migraine (frequency/severity)

~30% - blood pressure goal, depression, anxiety, PTSD, PPIs/H2RA, sore throat, NSAIDs for OA, inhalers for COPD

~40% - panic disorders

When a medication has “worked”, if you were a betting person you would bet that it probably wasn't because the medication worked.

BALLPARK ABSOLUTE % BENEFITS FOR SYMPTOMATIC TREATMENTS



Prevention Pearls

Math 101 - actually grade 5

REMEMBER - X% of Y - "OF" means multiply

WHAT IS THE ABSOLUTE BENEFIT %?

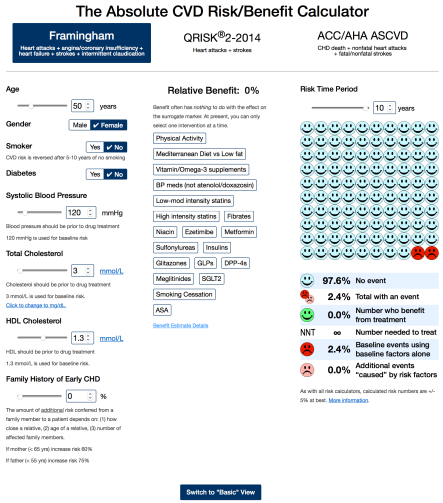
	Relative benefit (%)				
BASELINE RISK (%)	10	15	20	25	30
10					
15					
20					
30					

WHAT IS THE NNT?

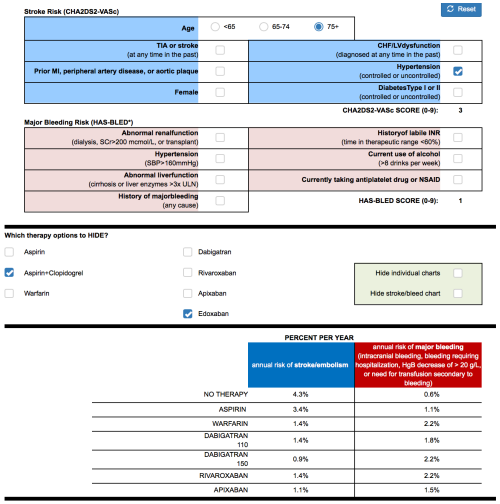
Absolute benefit	0.5%	1%	2%	3%	4%	5%	6%	7%	8%	9%	10%
NNT											

Ballpark Risks (CVD, fractures etc)

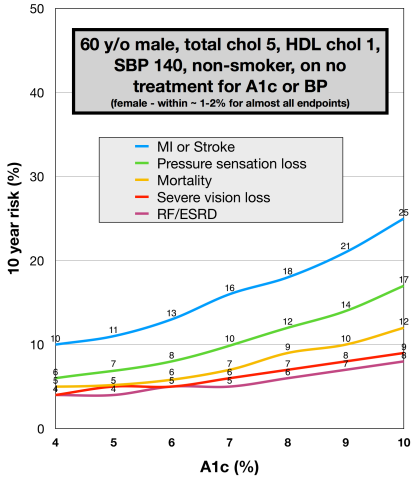
https://therapeuticseducation.org/tools



cvdcalculator.com



sparctool.com



https://sanjaybasu.shinyapps.io/recodesi/

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

It's all about figuring out

The *Ballpark* Chance
WITH NO TREATMENT

VS

The *Ballpark* Chance
WITH TREATMENT

What are the important endpoints?

It's all about figuring out

The *Ballpark* Chance
WITH NO TREATMENT

VS

The *Ballpark* Chance
WITH TREATMENT

Risk of What and Over How Long

WHAT

CVD is cardiovascular disease

Typically = CHD + cerebrovascular

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

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

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

HOW LONG - 5 or 10 years

Oswald Chesterfield Cobblepot
AKA The Penguin
60 years old
Loves birds
Lives a luxurious lifestyle
Relatively inactive
PMH - Conduct disorder
Smoker
A1c 8
BP 150/90 mm/Hg
Total cholesterol 6 (240)
HDL 1 (40)

Languages: English (EN)

The Absolute CVD Risk/Benefit Calculator

Framingham
US Data, 10 Year Risk
Heart attacks + angina/coronary insufficiency + heart failure + strokes + intermittent claudication

QRISK®2-2014
UK Data, 10 Year Risk
Heart attacks + strokes

ACC/AHA ASCVD
US Data, 10 Year Risk
CHD death + nonfatal heart attacks + fatal/nonfatal strokes

PREDICT
New Zealand Data, 5 Year Risk
Heart attacks + angina + heart failure + strokes/TIAs + peripheral vascular disease

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Age
50 years

Gender
Male ✔ Female

Smoker
Yes ✔ No
CVD risk is reversed after 5-10 years of no smoking

Diabetes
Yes ✔ No

Systolic Blood Pressure
120 mmHg
Enter present blood pressure regardless of treatment
120 mmHg is used for baseline risk

On treatment for BP
Yes ✔ No
Click YES if taking blood pressure medication
Only applies if SBP is greater than 120 mmHg

Total Cholesterol
3 mmol/L
Cholesterol should be prior to drug treatment
3 mmol/L is used for baseline risk.
Click to change to mg/dL.

HDL Cholesterol
1.3 mmol/L
HDL should be prior to drug treatment

Relative Benefit: 0%

Benefit often has *nothing* to do with the effect on the surrogate marker. At present, you can only select one intervention at a time.

- Physical Activity
- Mediterranean Diet vs Low fat
- Vitamin/Omega-3 supplements
- BP meds (not atenolol/doxazosin)
- Low-mod intensity statins
- High intensity statins
- Fibrates
- Niacin
- Ezetimibe
- Metformin
- Sulfonylureas
- Insulins
- Glitazones
- GLPs
- DPP-4s
- Meglitinides
- SGLT2
- Smoking Cessation
- ASA

Benefit Estimate Details

Risk Time Period

10 years

97.9%		No event
2.1%		Total with an event
0.0%		Number who benefit from treatment
NNT	∞	Number needed to treat
2.1%		Baseline events using baseline factors alone
0.0%		Additional events "caused" by risk factors

As with all risk calculators, calculated risk numbers are +/- 5% at best. More information.

cvdcalculator.com

Bruce Banner
AKA The Hulk
Age 45
Scientist
Easily agitated,
and emotionally withdrawn
SBP 160 mm/Hg
Non-smoker
Non-diabetic
Total cholesterol 4.4 (180)
HDL 1.5 (60)
AM testosterone: 330 nmol/L (N 6.7-29)
Urine catechol: +ve (no urine found)

10 year risk

Framingham (HA, angina, HF, stroke, int claud) = 64%

ASCVD (HA, stroke) = 41%

Smoker - stop ~15% absolute
A1c 8 ?
BP 150/90 mm/Hg ~ 30-50% RR
Total cholesterol 6 (240) ~ 25% RR
HDL 1 (40)

10 year risk

Framingham (HA, angina, HF, stroke, int claud) = 7%

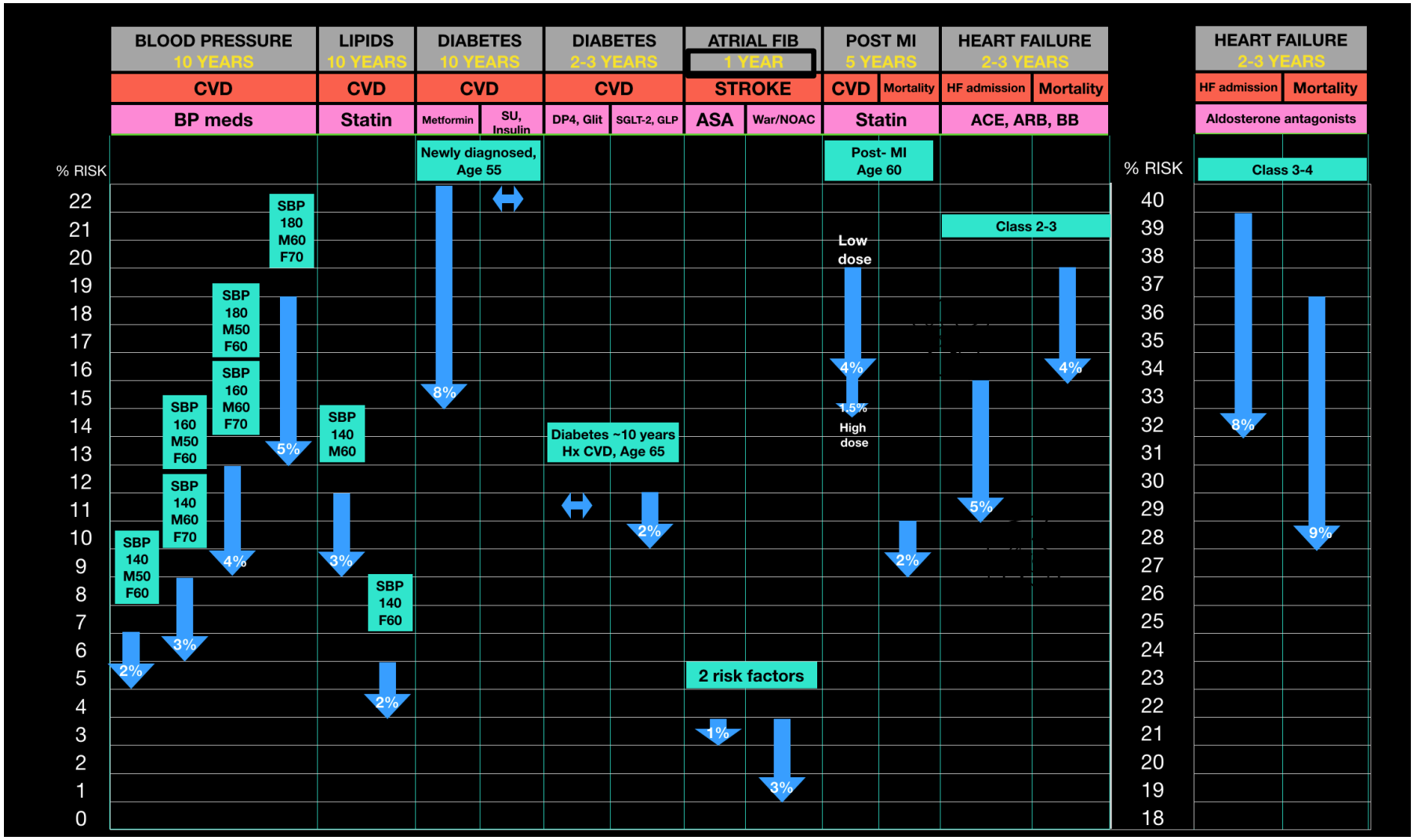
ASCVD (HA, stroke) = 2%

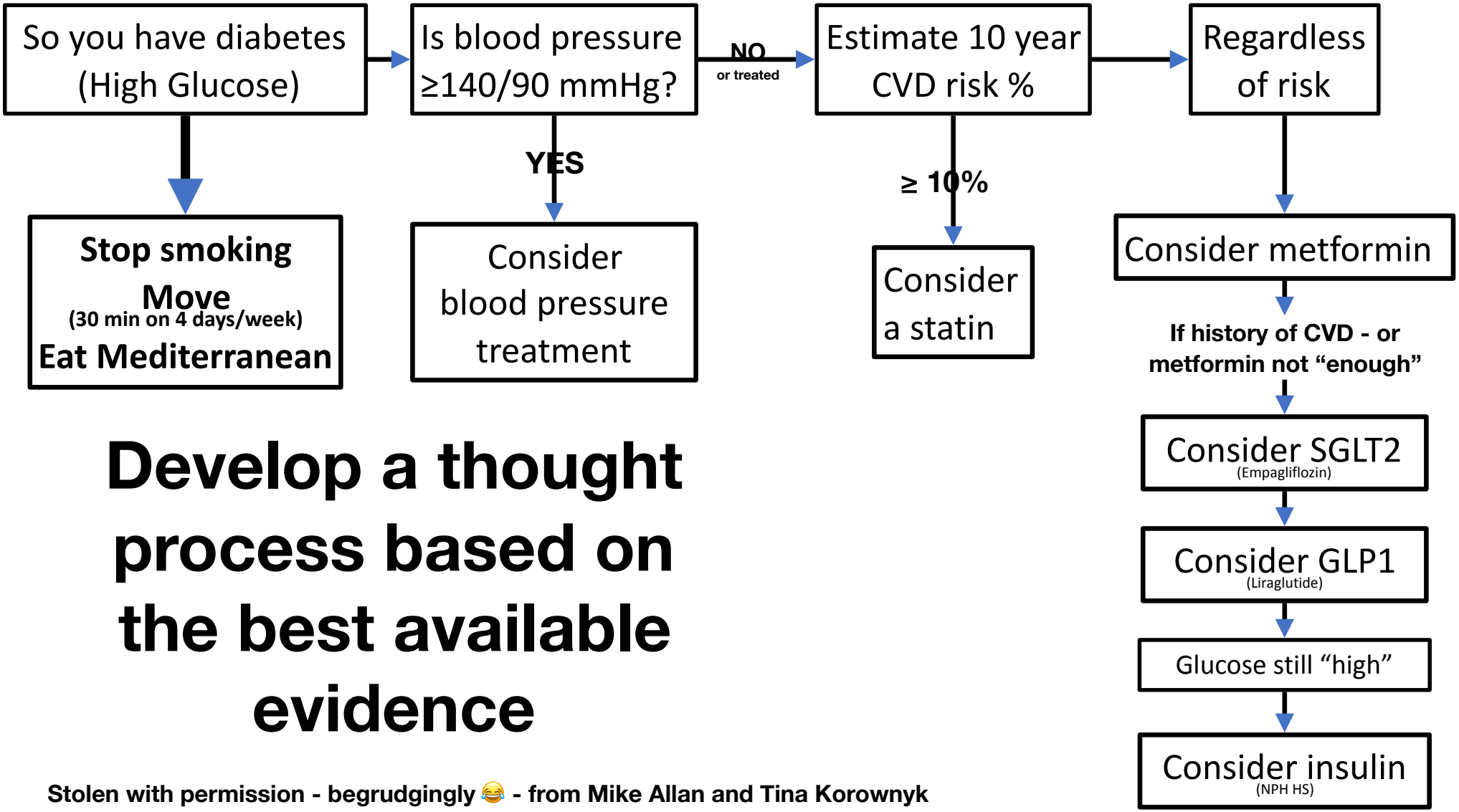
SBP 160 mm/Hg ~ 30% RR
Non-smoker
Non-diabetic
Total cholesterol 4.4 (180) ~ 25% RR
HDL 1.5 (60)

BALLPARK RELATIVE % BENEFITS FOR CARDIOVASCULAR PREVENTATIVE TREATMENTS

	Lifestyle	**Cholesterol**	**Blood pressure**	**Glucose**	**A fib**	**Heart failure**
RRR%	Cardiovascular events				Stroke	Mortality
100	Stopping smoking (obviously no RCTs) CVD but also cancer and lung issues					
95						
90						
85						
80						
75						
70						
65					Warfarin/NOACS	
60						
55						
50			Blood pressure diabetes			
45						
40						
35		Statins		Metformin?		
30	Mediterranean diet		Blood pressure			
25	Physical Activity plus QOL				Aspirin	ACEI, BB, Aldo antag
20						
15		PCSK9 Monoclonal antibodies		SGLT2, GLP		
10		Aspirin				
5		Ezetimibe				
0		Fibrate, niacin		DPP4, SU, insulin, glitazone		

BALLPARK ABSOLUTE % BENEFITS FOR PREVENTATIVE TREATMENTS





Develop a thought process based on the best available evidence

Stolen with permission - begrudgingly 😂 - from Mike Allan and Tina Korownyk

A Reasonable Side Effect List

An unsolvable problem?

They are not captured well/completely/understandably in studies - but likely the best we have

Rarely can we figure out rare side effects

Many monographs, books, studies, websites just list a variety of symptoms, often with no numbers, no context, no idea of the duration, severity, frequency, statistical significance?

The NEW ENGLAND JOURNAL of MEDICINE

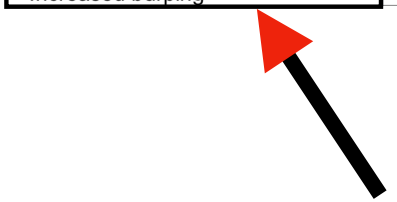
ORIGINAL ARTICLE

Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

This is a !@#$%
5.3 year study

Table S7. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Safety and Adverse Events by Randomized Assignment to Omega-3 Fatty Acids (n-3) compared to Placebo

	No. of Events				
Outcome	**n-3 (N = 12,933)**	**Placebo (N = 12,938)**	**HR**	**95% CI**	**P-value**
Monitored safety conditions					
Gastrointestinal bleeding	370	374	0.99	0.86-1.14	0.89
Blood in urine	919	874	1.06	0.96-1.16	0.25
Easy bruising	3443	3399	1.02	0.97-1.07	0.48
Frequent nosebleeds	465	491	0.95	0.83-1.07	0.40
Kidney failure or dialysis	85	88	0.97	0.72-1.30	0.82
Other symptoms and side effects					
Stomach upset or pain	4887	4843	1.01	0.97-1.05	0.72
Nausea	3558	3550	1.00	0.96-1.05	0.94
Constipation	5184	5111	1.01	0.97-1.05	0.51
Diarrhea	5599	5580	1.00	0.97-1.04	0.77
Skin rash	3331	3367	0.99	0.94-1.03	0.58
Bad taste in mouth	2240	2245	1.00	0.95-1.06	0.92
Increased burping	2217	2158	1.03	0.97-1.10	0.29



How are these not 100%

Key steps to communicating evidence

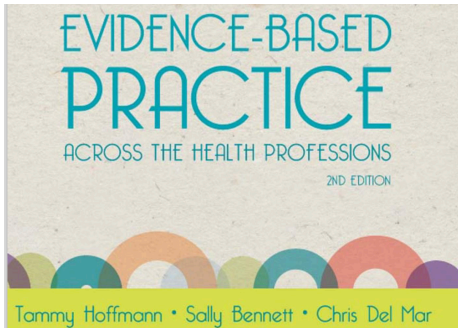
Understand the patient's (and family members') experiences and expectations.

Build partnerships.

Discuss the evidence, including a balanced discussion about uncertainties.

Present recommendations.

Check for understanding and agreement.



Risky Relative Adjectives

HOW

low is low

moderate is moderate

high is high

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

Need a time frame, main endpoints, ask what they know

GENERAL SUGGESTIONS - these are “relative”
use percentages (5%) or natural frequencies (5 out of 100) - BOTH?
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

Three “sobering” but very empowering concepts

SYMPTOMS

If a patient seems to be getting a benefit from a medication for symptoms they likely aren't

PREVENTION

If a patient is on a medication for risk reduction (BP, chol, glucose BMD) the benefit they are receiving is likely not large enough for them to make up for the cost, inconvenience and adverse effects

DOSE

If a patient is on a medication they are likely on too high a dose

Costs

Generic Name	Brand name	Strength	Dosing	90 Day Cost (unless otherwise noted)	Coverage
HYPOGLYCEMIC AGENTS					
Biguanides					
Metformin	Glucophage	500mg	2 BID	**$30**	BC / IA covered
Metformin SR	**Glumetza SR**	1000mg	2 QD	**$255**	NC by BC or IA
Sulfonylureas					
Glyburide	Diabeta	5mg	BID	**$25**	BC / IA covered
Gliclazide, Gliclazide MR	Diamicron/MR	80mg/30mg MR	BID, 2 QD MR	**$30**	BC / IA covered
Meglitinides					
Repaglinide	Gluconorm	1mg	TID	**$35**	BC / IA covered
Dipeptidylpeptidase-4 Inhibitors (DPP-4)					
Linagliptin	**Trajenta**	5mg	QD	**$265**	SA req'd for BC and IA
Saxagliptin	**Onglyza**	5mg	QD	**$295**	SA req'd for BC and IA
Sitagliptin	**Januvia**	100mg	QD	**$310**	SA req'd for BC and IA
Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors					
Empagliflozin	**Jardiance**	10mg	QD	**$270**	SA req'd for BC and IA
Canagliflozin	**Invokana**	100mg	QD	**$280**	SA req'd for BC and IA
Glucagon-like Peptide 1 Agonist (GLP-1)					
Liraglutide	**Victoza**	1.2mg SQ	QD	**$575**	NC by BC or IA
Liraglutide	**Victoza**	1.8mg SQ	QD	**$855**	NC by BC or IA
Insulin (Prices may vary between pharmacies, relative differences likely consistent. Max allowable price for 1500 Units of penfill insulin)					
Regular insulin	**Novolin Toronto/ Humulin R**	100U/mL	As dir	**$60**	BC / IA covered
Long-acting insulin	**Novolin NPH/Humulin N**	100U/mL	As dir	**$65**	BC / IA covered
Rapid-acting insulin	**Novorapid/Humalog**	100U/mL	As dir	**$75**	BC / IA covered
Basal insulin (Glargine)	Basaglar	100U/mL	As dir	**$90**	BC covered, NC by IA
Basal insulin (Glargine)	**Toujeo**	300U/mL	As dir	**$110**	NC by BC or IA
Basal insulin (Glargine)	**Lantus**	100U/mL	As dir	**$115**	BC / IA covered
Basal insulin (Detemir)	**Levemir**	100U/mL	As dir	**$130**	BC / IA covered
OBESITY					
Orlistat	**Xenical**	120mg	TID	**$505**	NC by BC or IA
Liraglutide	**Saxenda**	3mg SQ	QD	**$1,165**	NC by BC or IA

LEGEND:
BC = Alberta Blue Cross, IA = Indian Affairs, NC = Not covered, SA = special authorization, SR = sustained release, OTC = over the counter, SQ = subcutaneous injection, SS=Social Services

https://www.acfp.ca/wp-content/uploads/2018/03/ACFPPricingDoc2018.pdf

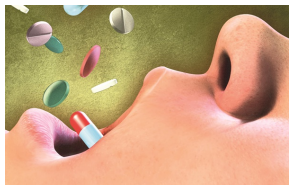
Inconvenience

Get the prescription

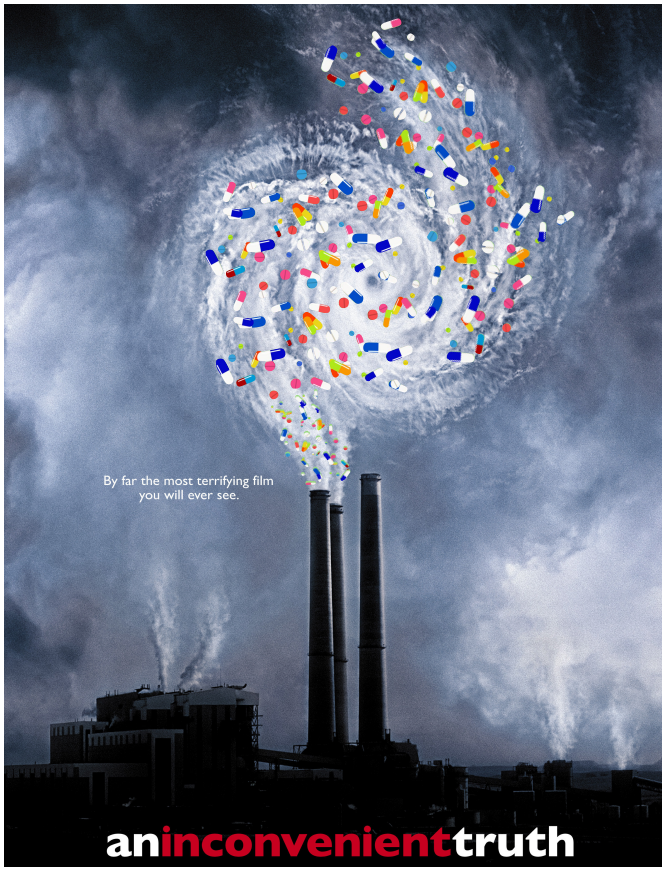
Fill the prescription

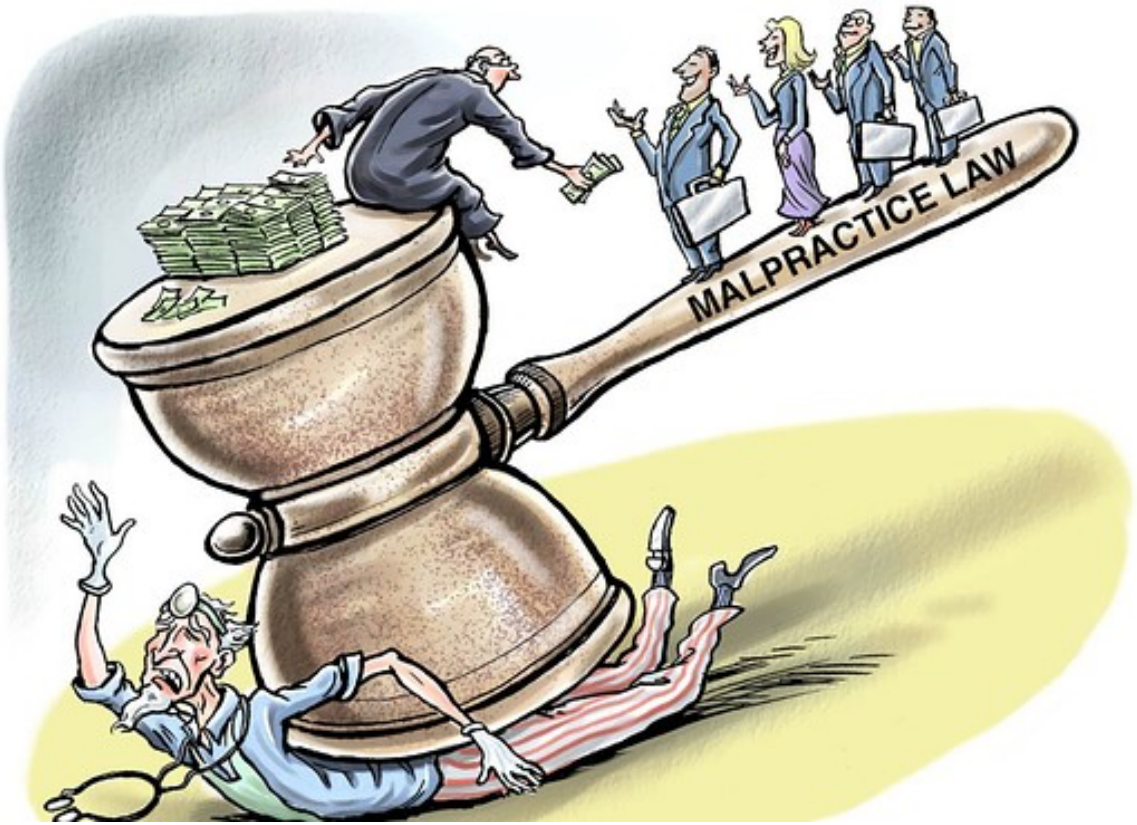
Pay for the prescription

Take the prescription



Labelling/worry




MALPRACTICE LAW

Durand *et al. BMC Health Services Research* (2015) 15:167
DOI 10.1186/s12913-015-0823-2

BMC
Health Services Research

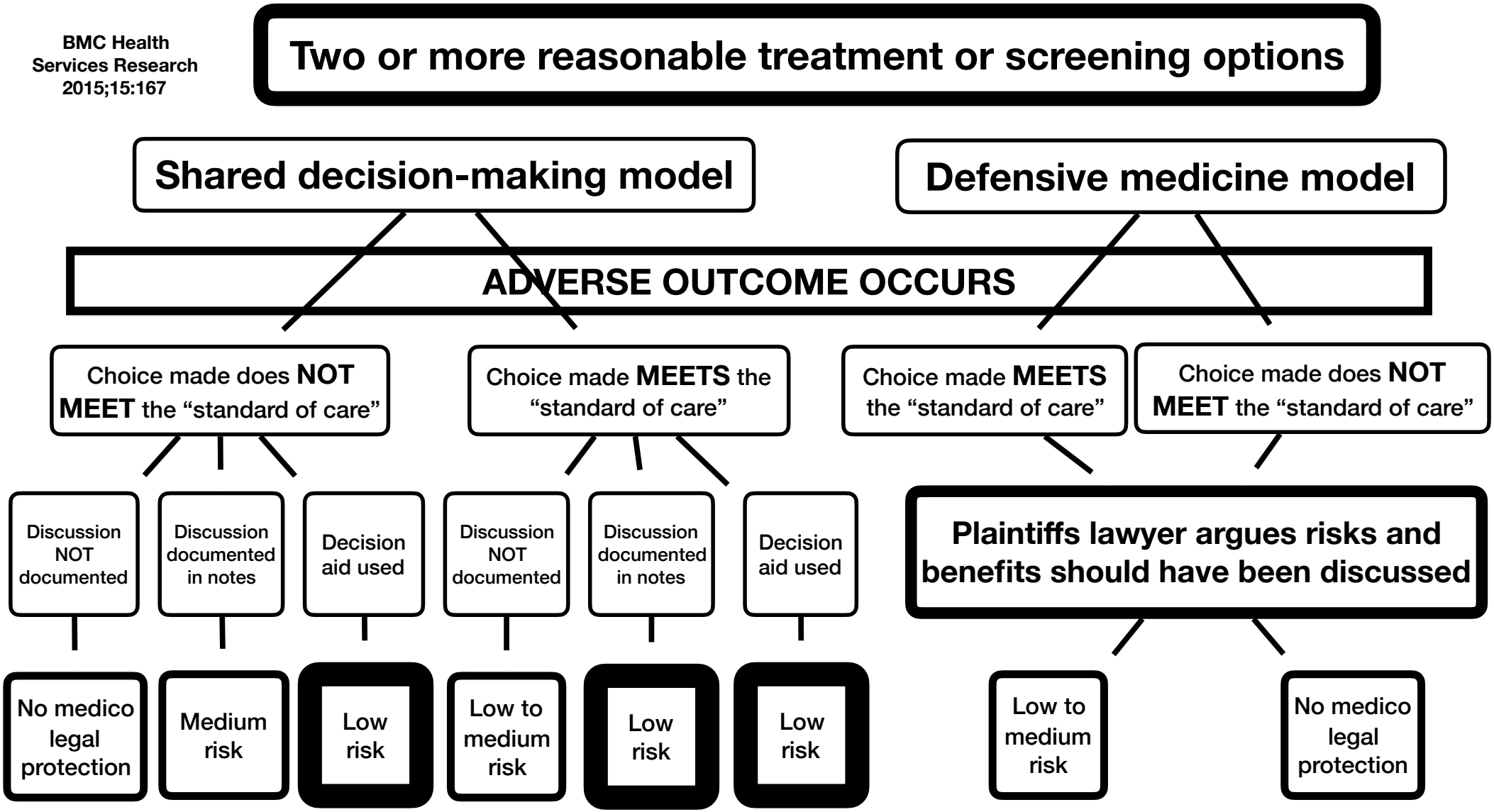
RESEARCH ARTICLE Open Access

Can shared decision-making reduce medical malpractice litigation? A systematic review

Marie-Anne Durand[1,2*], Benjamin Moulton[3,4,5], Elizabeth Cockle[2], Mala Mann[6] and Glyn Elwyn[1,7]

"There is insufficient evidence to determine whether or not shared decision-making and the use of decision support interventions can reduce medical malpractice litigation. Further investigation is required."

BMC Health Services Research 2015;15:167



Defensive model (guidelines/standard of care)

NEVER get to a low litigation risk

Reducing litigation risk

2 THINGS to DO

Shared decision-making model

1) Use a decision aid

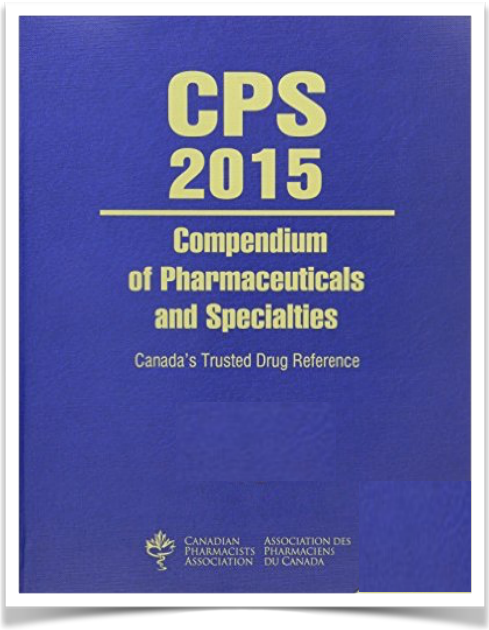
2) Document decision

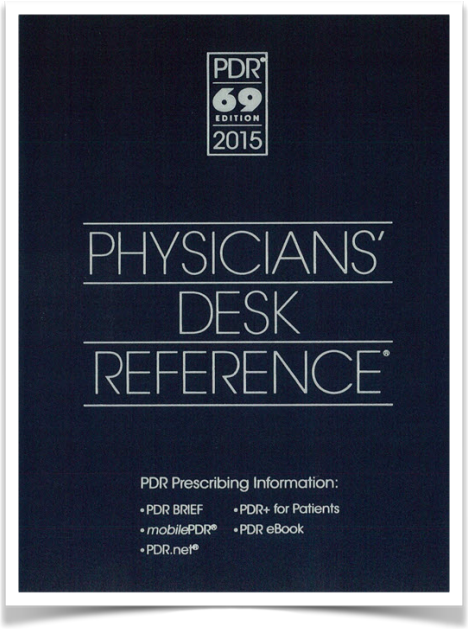

KEEP
CALM
AND
USE VERY
LOW DOSES

This simple concept can eliminate most medication problems

USE VERY LOW DOSES

The doses in these books





are all "WRONG" for individual patients

Everyone is a genetic mongrel

It's a dose thing

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

Br J Clin Pharmacol 2004; 57:121–6

CMAJ ANALYSIS

Is bigger better? An argument for very low starting doses

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

”Unless the condition is severe or life-threatening, drug treatment can be started at a very low dose (half or one-quarter the recommended starting dose)”

CMAJ 2011. DOI:10.1503 /cmaj.091481

Most of the effect of a medication comes from the “low” starting doses AND doubling a dose never doubles the effect - in fact it sometimes has no additional effect

A sample of Low-Dose RCT Evidence

6.25 mg hydrochlorothiazide	first marketed at 50 to 200 mg daily
6.25 mg captopril	25 mg PO TID is still a commonly recommended initial starting dose for hypertension
25 mg sildenafil (Viagra)	effective dose for erectile dysfunction
25 mg sumatriptan (Imitrex)	works as well as100 mg
5 mg daily fluoxetine (Prozac)	similar effects to those seen at 20 mg and 40 mg daily
0.25 mg ezetimibe (Ezetrol)	1/40th of the recommended initial starting dose provides 50% of the LDL lowering effect
15 mg elemental iron daily	as effective for anemia in elderly as 50 mg and 150 mg with a lower incidence of side effects
150 mg daily bupropion (Zyban) 0.5 mg BID varenicline (Champix)	produces the same rate of smoking cessation at one year as 300 mg daily (1.0 mg BID)
10 mg atorvastatin	produces 2/3 of the effect on cholesterol as that seen with an 80 mg (8-fold increase) dose
200 mg ibuprofen (Motrin)	as effective as 400 mg for migraine headache
25 mg ranitidine (Zantac)	as effective as 125 mg for heartburn relief
1.8 mg colchicine	as effective as 4.8mg for acute gout with less adverse events

Doxepin (Sinequan)

Depression - start 25-50 mg - optimal 75mg -150mg up to 300mg

Doxepin in the Treatment of Primary Insomnia:
A Placebo-Controlled, Double-Blind,
Polysomnographic Study

J Clin Psychiatry
2001;62:453-63

"The results support the effectiveness of low doses (25-50 mg) of doxepin to improve sleep"

All three doses worked better than placebo
AND
NO side effects over placebo

A recommended low dose was still 25-50 times TOO HIGH

A Dose of Reality

When a new drug comes on the market almost never have more than 2 doses been studied

To get a drug on the market you have to show it works therefore one has to choose a dose that is high enough that if it is going to work it will work

Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980–1999†

dosage changes occurred in 21%
of all new molecular entities

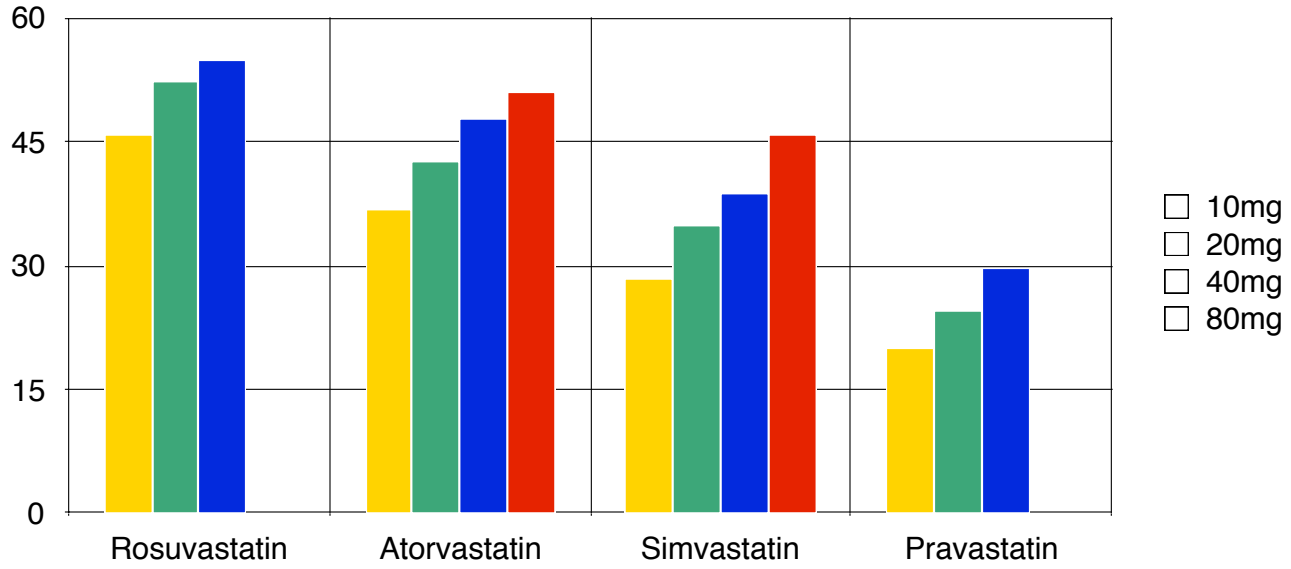
80% were dose decreases

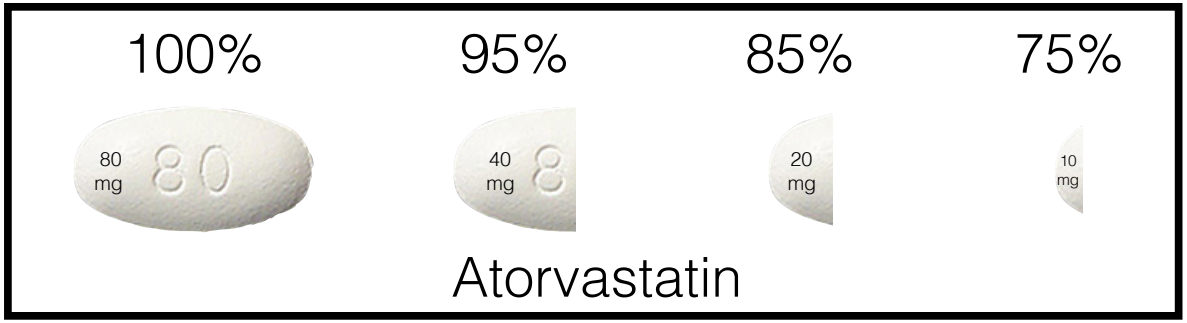
"this pattern may represent a systematic flaw in pre-marketing dosage evaluation; it has been common practice in the pharmaceutical industry to undertake phase III trials evaluating drug effectiveness at or near maximum-tolerated doses."

Pharmacoepidemiology and Drug Safety 2002;11:439–446

DOSE reductions do not lead
to proportional EFFECT reductions

% reduction in LDL cholesterol





Advantages of starting with “very” low doses

Get the potential “placebo group effect” without deception

Patients are engaged in the process of finding the best dose for them

Cost savings can be considerable and most adverse events can be minimized

Most clinically relevant drug interactions can be avoided

Approaches differ depending on outcome

Every patient is an experiment - dose and effect

SYMPTOMS - we can usually figure out if it is working - but it is tricky

PREVENTION - one will never know if it worked

Expectations