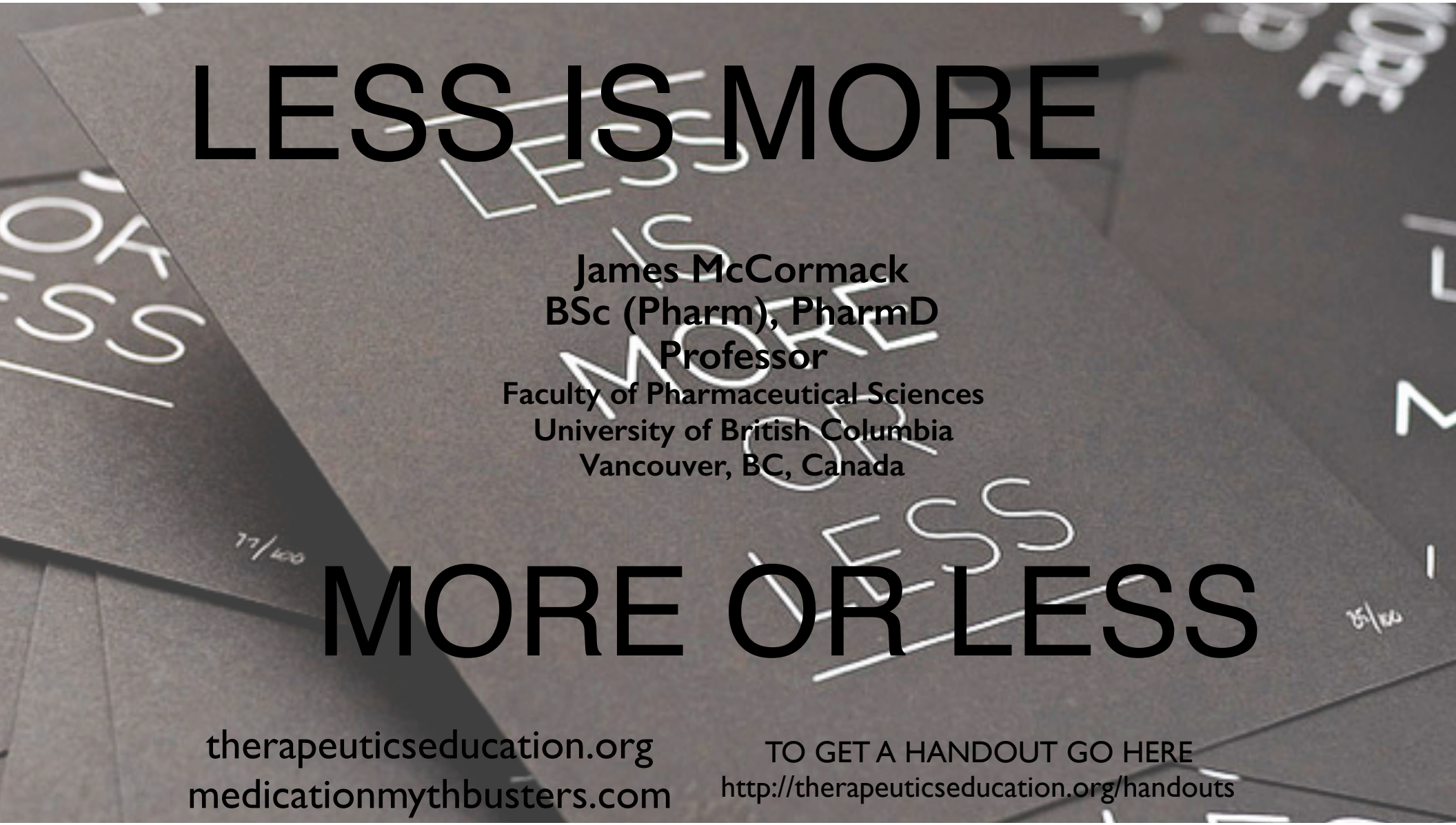


James McCormack
BSc (Pharm), PharmD
Professor
Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, BC, Canada

therapeuticseducation.org
medicationmythbusters.com

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

We all need to do a better job when it comes to medications

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

IT'S NOT ABOUT GUIDELINES

140/90
< 6.5%
< 2.0

GUIDELINES RARELY CONSIDER
PATIENT PREFERENCES

IT'S NOT CHECKBOX MEDICINE

PEOPLE DON'T FIT INTO BOXES

IT'S NOT SOMETHING "NEW"

NEW APPROACH AHEAD

DOING THE RIGHT THING IS NOT A NEW IDEA

IT'S NOT ABOUT SAVING MONEY

$

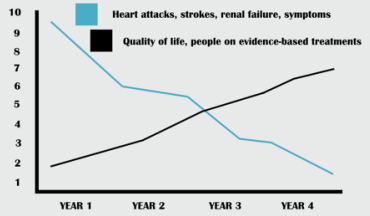
RATIONING IS NOT THE MOTIVE

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 NECESSARILY ABOUT INFLUENCING OUTCOMES



IT'S NOT ABOUT IGNORING BASIC SCIENCE

WE NEED TO UNDERSTAND HOW IT WORKS

IT'S NOT ABOUT ZERO COMPETING INTERESTS

RESEARCH COSTS MONEY SOMEBODY HAS TO PAY FOR IT

WE NEED TO UNDERSTAND BIAS IS EVERYWHERE

BEST AVAILABLE EVIDENCE
USED IN A HIERARCHICAL WAY TO ANSWER CLINICAL QUESTIONS

Patient
Intervention
Comparator
Outcome

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

What is a Clinical Practice Guideline (CPG)?

The Institute of Medicine definition:

"…statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options”

Clinical Practice Guidelines in Practice and Education

Alfred O. Berg, MD, MPH, David Atkins, MD, MPH, William Tierney, MD

1997 - THE REASONS FOR INTEREST IN QUALITY CLINICAL PRACTICE GUIDELINES

“medical history is littered with clinical practice guidelines that have been fatally incorrect”

“the physician's ability to keep up with the medical literature erodes with each year's burden”

“costly and unexplained variability in medical practice”

“growing demand from patients for greater participation in medical decisions”

J Gen Intern Med 1997;12(Suppl 2):S25–S33

National Guideline Clearinghouse

The Number of Guidelines

Diseases/conditions - 2,983

Treatments/interventions - 7,364

~10,000 guidelines ~10 pages each?

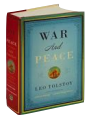
~100,000 pages

500 pages ~ 2 inches

400 inches ~ 33 feet ~10 meters

Highest pole vaulter ~ 20 feet ~ 6 meters

War and Peace is ~1500 pages ~ 70 copies



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

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]

"guideline reliability is largely over-stated, and guidelines still suffer methodological flaws, limited panel composition and conflicts of interests, making their conclusions often untrustworthy. Even when evidence-based methodology is claimed, it is often not fully adopted and the 'evidence-based quality mark' gets misappropriated by vested interests"

EBM 2017;22:1-3

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]

"Furthermore, no official, publicly accountable, reliable, independent and unconflicted rating agency of published guidelines exists."

EBM 2017;22:1-3

Spectrum of Decisions

Immediate life-threatening issues or very "technical" work - surgery, dispensing etc - YES
Guidelines, even policies, are likely very useful

Symptom treatment - SORT OF
Each person is an experiment - need to know just what has the potential to work and the safety

Risk factor interventions - NO
At least not what CPGs are now

Guidelines would be awesome if they…

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

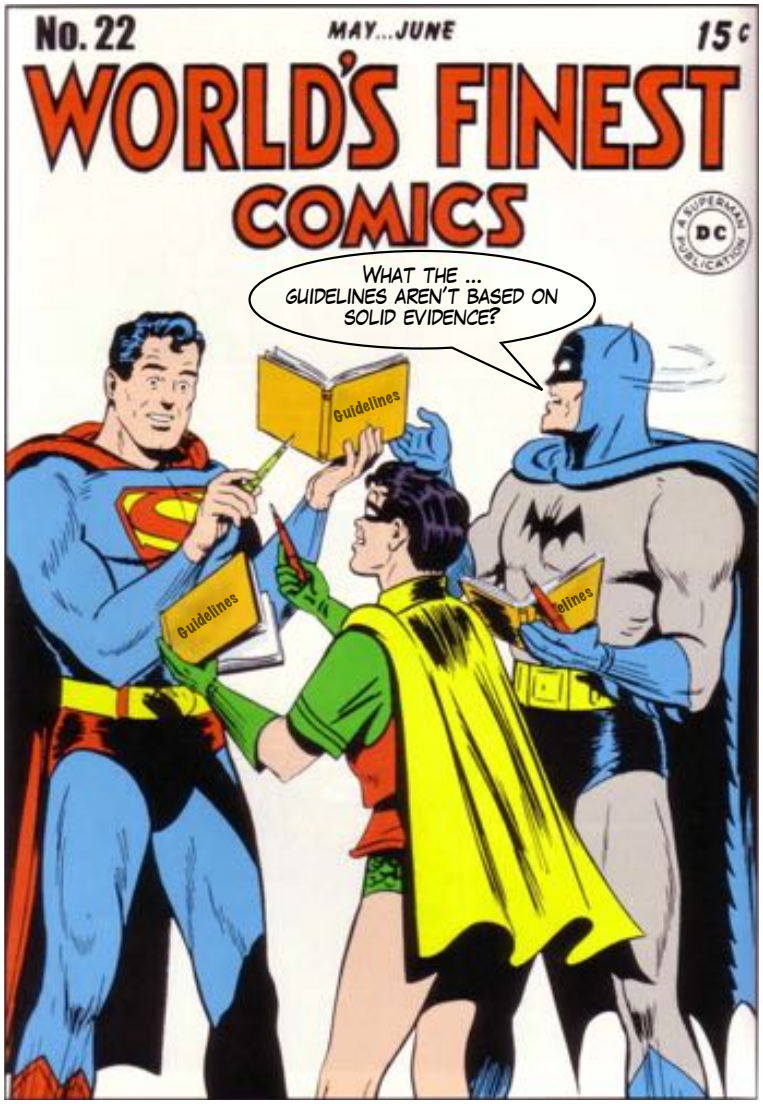
Were a credible synopsis of the best available evidence presented in a way that clinicians could easily access and interpret

Allowed patient values and preferences to be taken into account

Combine Evidence with Common Sense

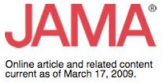
Common Sense

"So rare
that it's a
superpower"



How evidence-based are CPGs?

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



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%

BMJQS

The quality of clinical practice guidelines over the last two decades: a systematic review of guideline appraisal studies

Table 2 Appraisal of Guidelines, Research and Evaluation domain scores of guidelines over time (total sample=608)

	1988–1992 (n=9)	1993–1997 (n=102)	1998–2002 (n=291)	2003–2007 (n=206)	p Value for trend
Domain scores		***Top Score = 100%***			
Scope and purpose	44	61	60	71	<0.001
Stakeholder involvement	18	38	33	37	0.01
Rigour of development	14	41	43	44	0.003
Clarity and presentation	32	56	55	68	<0.001
Applicability	10	30	18	23	<0.001
Editorial independence	17	30	28	33	0.26

Engaging the right people, quality of evidence appraisal, providing useful tools, and competing interests have not improved in 14 years (1993-2007)

Qual Saf Health Care 2010;19:e58. doi:10.1136/qshc.2010.042077

Recent examples of Guideline **Quality/Rigour**

AGREE II (Appraisal of Guidelines for Research and Evaluation)

is the instrument typically used ***- 207 guidelines***

avg 55% - neuropathic pain - 16 CPGs - range 27%-88% - BMC Anesthesiology 2016;16:12

avg 30% - hypertension - 11 CPGS - range 8%-86% - PLoS ONE 2013 8(1): e53744

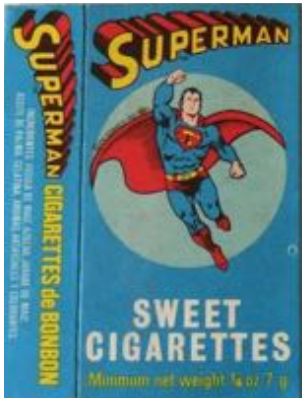
avg 32% - asthma - 18 CPGs - range 8%-64% - Chest 2013 144: 390-7

avg 48% - diabetes - 24 CPGs - range 0%-81% - PLoS ONE 2013 8(4): e58625

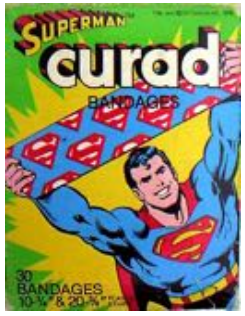
avg 20% - vancomycin - 12 CPGs - range 4%-73% - PLoS ONE 2013 9(6): e99044

avg 18% - hypertension (China) - 17 CPGs - range 1-36% - BMJ Open 2015;5:e008099

avg 8% - respiratory (China) - 109 CPGs - range 0%-27%- Chest 2015;148:759-766



Who writes/ sponsors guidelines?



Research

Contributors to primary care guidelines

What are their professions and how many of them have conflicts of interest?

G. Michael Allan MD CCFP Roni Kraut Aven Crawshay Christina Korownyk MD CCFP
Ben Vandermeer MSc Michael R. Kolber MD CCFP MSc

176 PRIMARY CARE guidelines in the CMA database

CONTRIBUTORS

54% non–family physician specialists
17% family physicians - 8% if industry sponsored
11% other clinicians
8% non-clinician scientists
6% nurses
3% pharmacists

69% of guidelines didn't report conflicts of interest

Can Fam Physician 2015;61:52-8

Guideline sponsorship

2009 - 2,300 guidelines in the National Guideline Clearinghouse

Guideline development

- 41% - medical speciality societies
- 22% - government agencies/nonprofit
- 17% - professional associations
- 9% - disease specific societies
- 4% - independent expert panels

at least 2/3 are being developed by groups with a clear potential for important biases

http://www.ncbi.nlm.nih.gov/books/NBK22928/

Prevalence of financial conflicts of interest among panel members producing clinical practice guidelines in Canada and United States: cross sectional study

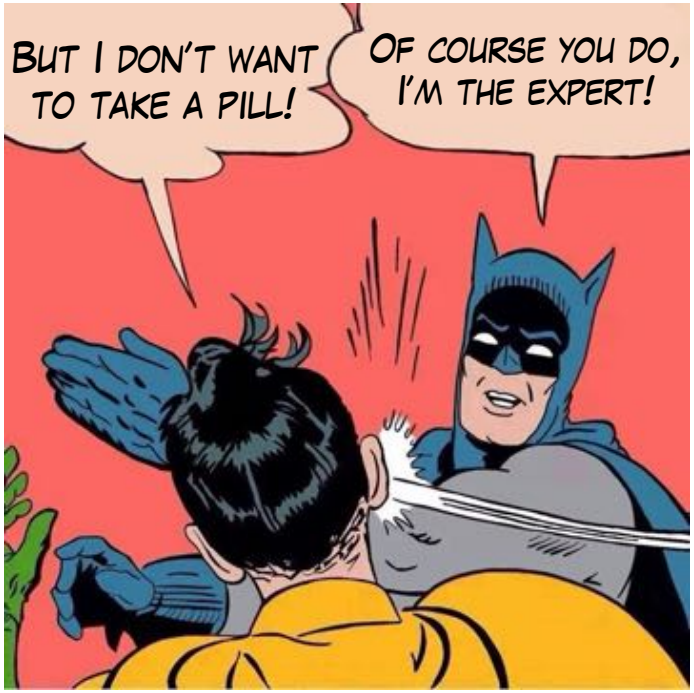
~50-80% of panel members on guidelines have financial COIs

BMJ 2011;343:d5621 doi: 10.1136/bmj.d5621

EVIDENCE BASED MEDICINE

Why we can't trust clinical guidelines BMJ;2013:346

Despite repeated calls to prohibit or limit conflicts of interests among authors and sponsors of clinical guidelines, the problem persists. **Jeanne Lenzer** investigates



How well do guidelines address patient values and preference?

Adding "value" to clinical practice guidelines

James P. McCormack PharmD Peter Loewen PharmD

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

197 PAGES - 90,000 WORDS

99(0.1%) words - relevant to
patients' values and preferences

Can Fam Physician 2007;53:1326-27

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441

Diabetes Care
THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION
January 2015 Volume 38, Supplement 1

Standards of Medical Care in Diabetes—2015

Diabetes Care January 2015

113 PAGES

Looked for info on

- Risk estimation (magnitude)
- Impact of treatment on risk
- Potential harms (magnitude)

"The information presented in these documents is glucose-centric and not organized or presented in a way that could be construed as supporting shared decision making"

Their response

“would like to thank McCormack et al for their thoughtful letter regarding the American Diabetes Association’s Standards of Medical Care in Diabetes”

“agrees that shared decision making is a valuable aspect of diabetes care … that process would be incredibly labor intensive and would make the Standards long and unwieldy”

“Clinical guidelines are the foundation for evidence-based medicine”

Guidelines

Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension

~11,800 words - 20 pages

Total mention of values and preferences - 0.19% of the words

"Practitioners are advised to consider patient preferences, values, and clinical factors when determining how to best apply these recommendations at the bedside"

"In the absence of Canadian data to determine the accuracy of risk calculations, **avoid using absolute levels of risk** to support treatment decisions"

Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults

~8,300 words - 20 pages

The following were unfortunately not mentioned anywhere in the guidelines

the magnitude of the risk associated with hypertension in either absolute or relative terms
the magnitude of the potential benefit of treatment in either absolute or relative terms or NNT
a list of any side effects of the medications and no mention of the magnitude of side effects
the costs associated with treating hypertension
the inconvenience of treating hypertension
starting with low doses and titrating up based on tolerability
the pill burden associated with treatment
the concern of labelling people with a condition such as hypertension
when to consider discontinuing or re-evaluating treatment or,
the promotion of shared-decision making

Total mention of values and preferences - ~ 0.2% of the words

"Practitioners are advised to consider patient preferences, values,

ACP American College of Physicians™ Leading Internal Medicine, Improving Lives **2017** CLINICAL GUIDELINE

Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians

~8,700 words - 27 pages

Benefits

No numbers whatsoever for fracture risk or fracture benefit

Do present info in an appendix - new studies

Harms

2017

28 numeric mentions of side effects

6 absolute numbers

22 relative numbers

One mention of patient preferences

Recommendation 6: *ACP recommends that clinicians should make the decision whether to treat osteopenic women 65 years of age or older who are at a high risk for fracture based on a discussion of patient preferences, fracture risk profile, and benefits, harms, and costs of medications. (Grade: weak recommendation; low-quality evidence)*

ACP American College of Physicians℠
Leading Internal Medicine, Improving Lives

2017

CLINICAL GUIDELINE

Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians

Recommendations: Recommendation 1: *ACP recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (Grade: strong recommendation; high-quality evidence)*

"Evidence is insufficient to determine the comparative effectiveness of pharmacologic therapy or the superiority of one medication over another, within the same class or among classes, for prevention of fractures"

2017

ACP American College of Physicians
Leading Internal Medicine, Improving Lives

CLINICAL GUIDELINE

Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians

2017

"The data do not support monitoring BMD during the initial 5 years of treatment in patients receiving pharmacologic agents to treat osteoporosis."

THE COURT ACTUALLY LIKES SHARED DECISION-MAKING

Guidelines and the Law

Guidelines and the Law

"As per the Canadian Medical Association Handbook on Clinical Practice Guidelines, guidelines should NOT be used as a legal resource in malpractice cases as "their more general nature renders them insensitive to the particular circumstances of the individual cases."

Many courts (UK, US, CA)

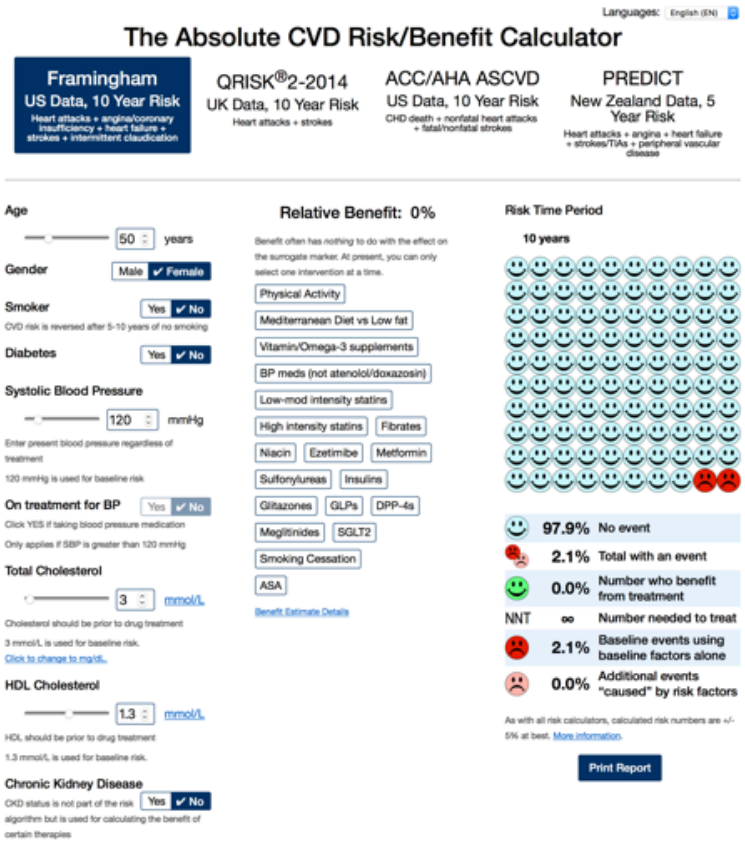
"The reasonable-patient standard … requires physicians and other health care practitioners to disclose all relevant information about the risks, benefits, and alternatives of a proposed treatment that an **OBJECTIVE PATIENT** would find material in making an intelligent decision as to whether to agree to the proposed procedure"

JAMA 2016;315:2063-4

On ALL NICE guidelines

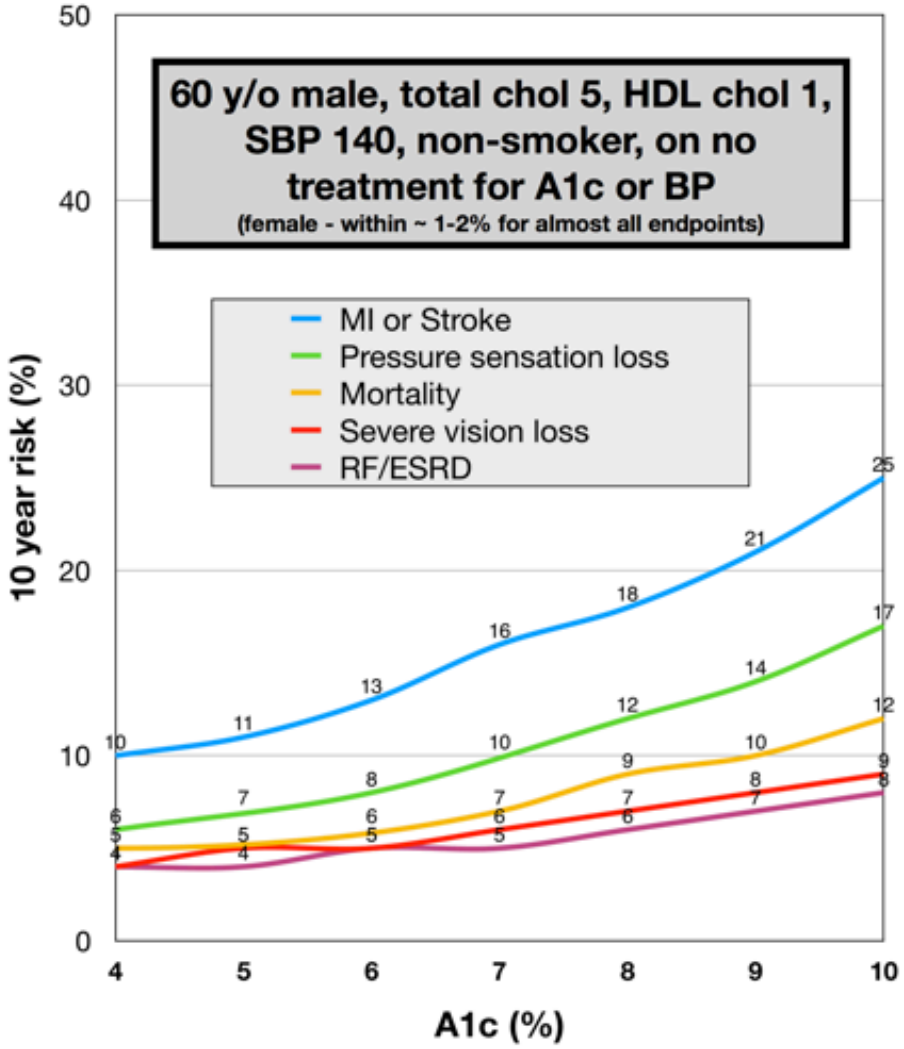
“Disclaimer: The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.”

Guidelines should provide
ballpark estimates
of what happens if
you DON'T treat/test/screen
and if
you DO treat/test/screen



Calculate ballpark 5/10-yr risk of CVD - BP, chol, diabetes
Make estimate of benefit based on the best available evidence
Gives a list of adverse effects to discuss

cvdcalculator.com



T2DM risk should not be categorized as YES or NO

https://sanjaybasu.shinyapps.io/recodesi/ - from the ACCORD study

Ballpark benefits - over 5 years

Primary prevention

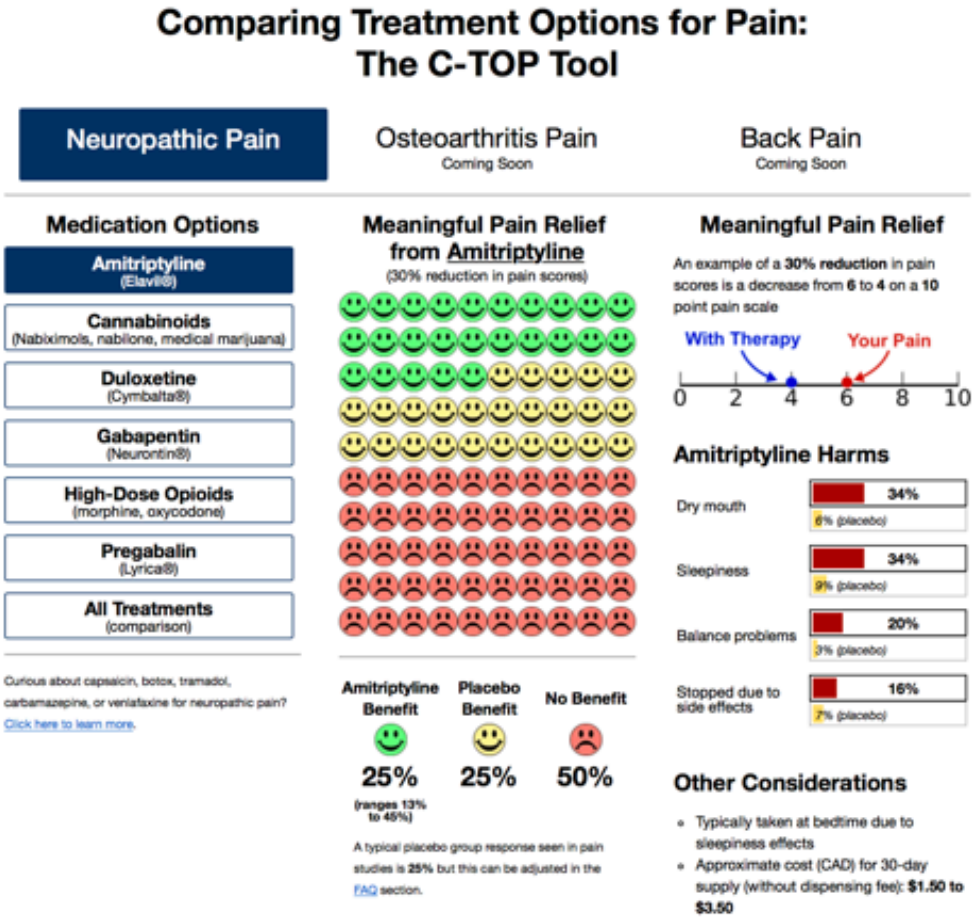
- Cardiovascular events
  - BP ~2-5% ARR
  - Statins ~1-2% ARR
- Mortality
  - <1% ARR

Secondary prevention/Heart failure (not class 4)

- Cardiovascular events, worsening HF
  - Betablockers, ACEI, ARBs, statins ~ 5-10% ARR
- Mortality
  - Betablockers, ACEI, ARBs, statins ~ 2-5% ARR

T2DM

- Cardiovascular events
  - Most meds - no benefits
  - SGLT2, GLP, metformin? ~ 2-5% ARR
- Mortality
  - Most meds - no benefits
  - SGLT2, GLP, metformin? ~ 1–2% ARR



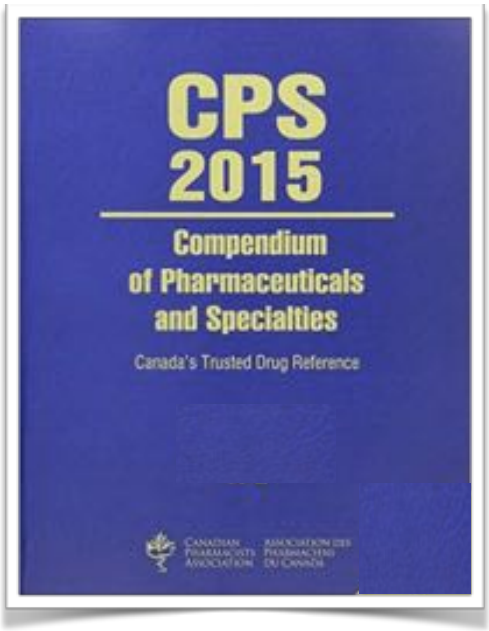
pain-calculator.com

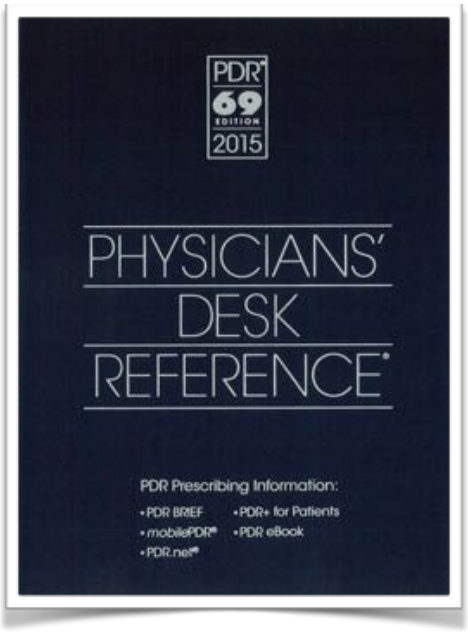

KEEP
CALM
AND
USE VERY
LOW DOSES

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"

INSOMNIA

Sleep 2007; 30: 1555–61

Efficacy and Safety of Three Different Doses of Doxepin in Adults with Primary Insomnia

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

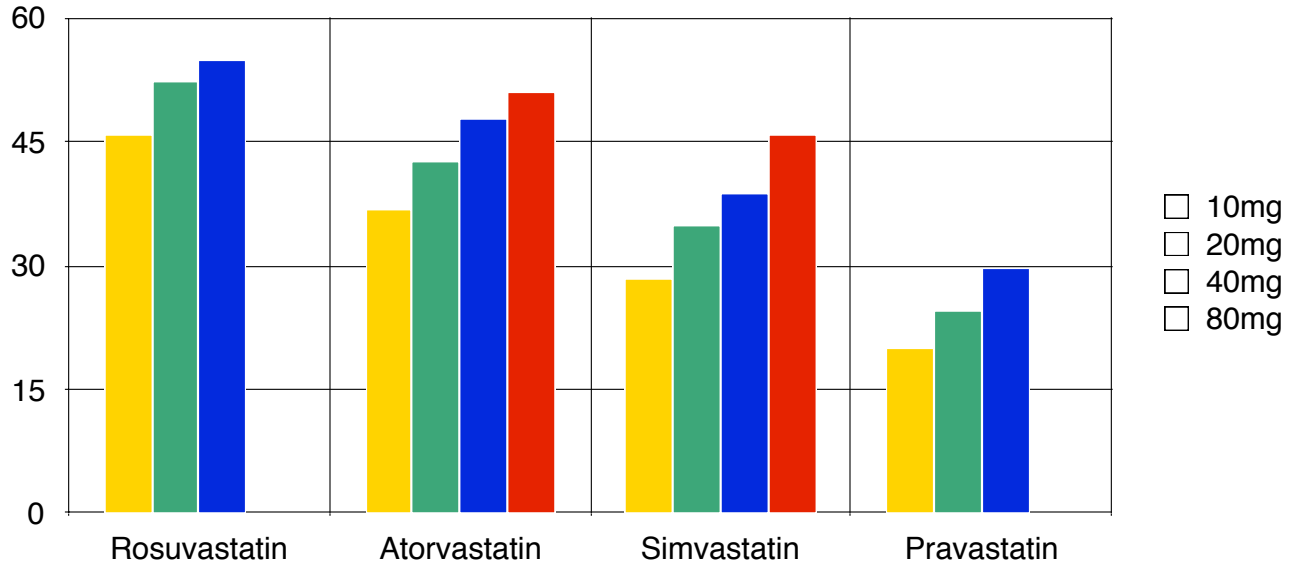
80% were dose decreases

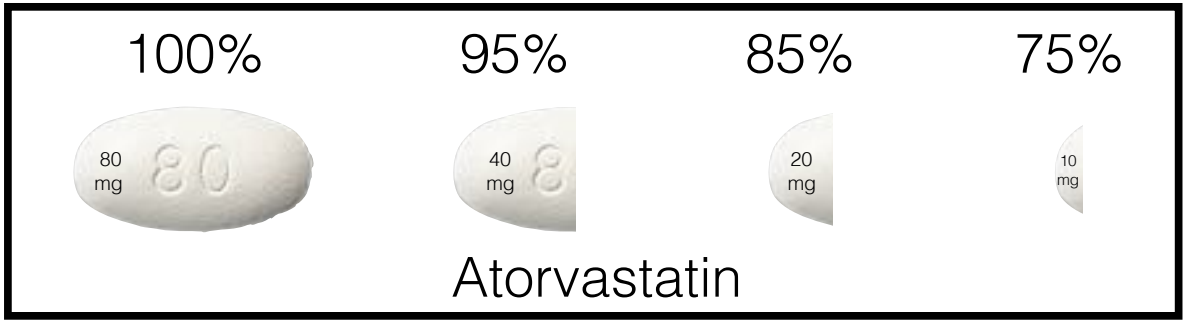
"this pattern may represent a systematic flaw in pre-marketing dosage evaluation; it has been common practice in the pharmaceutical industry to undertake phase III trials evaluating drug effectiveness at or near maximum-tolerated doses."

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

Symptoms

You primarily need to know IF it works

Safety, cost and convenience

Older medications first - safety

Head-to-head studies are uncommon

Doses in the CPS are “wrong”

N-of-1 studies

Let the patient tell you

Symptom NNTs

General anesthesia/local anesthesia - NNT ~1

PPIS, sildenafil - heartburn/“successful” intercourse NNT ~2

NSAIDs, opioids - pain NNT ~3-5

Steroids - sore throat - NNT ~3, Bell’s palsy - NNT ~10

Antibiotics - acute COPD exacerbation - NNT ~5

Topical antibiotics - bacterial conjunctivitis - NNT ~7

Antidepressants - severe depression - NNT ~10

Ipratropium - asthma attack - NNT ~11

Cholinesterase inhibitors - ADAS-Cog >4 - NNT ~10

Sleeping pills - improvement in sleep quality - NNT ~13

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 of 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.