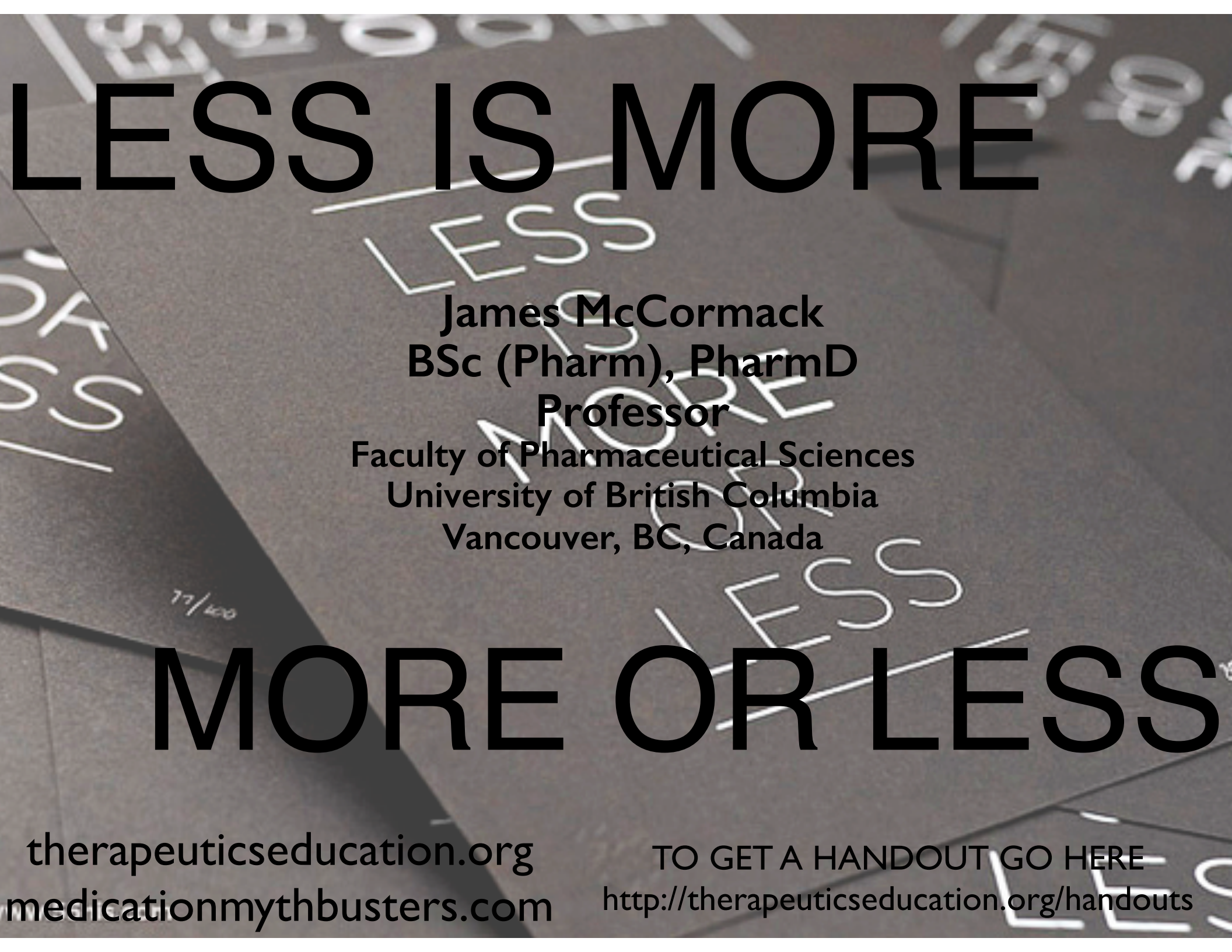

LESS IS MORE
James McCormack
BSc (Pharm), PharmD
Professor
Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, BC, Canada
MORE OR LESS
therapeuticseducation.org
medicationmythbusters.com
TO GET A HANDOUT GO HERE
http://therapeuticseducation.org/handouts

# 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"


DOING THE RIGHT THING
IS NOT A NEW IDEA

## IT'S NOT ABOUT SAVING MONEY

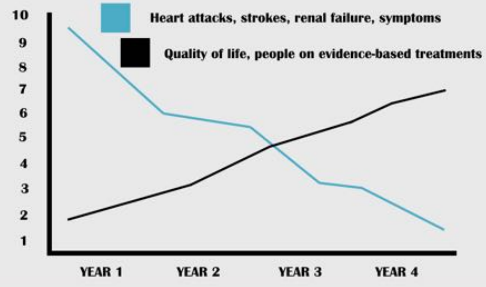
RATIONING
IS NOT THE MOTIVE

## 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

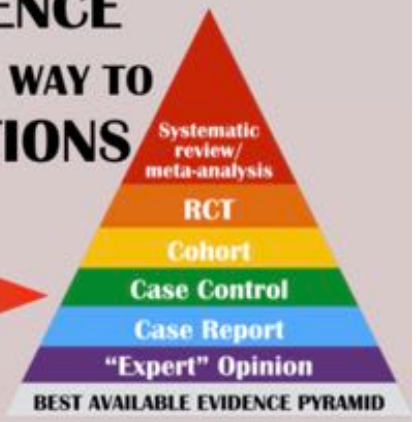
# WHAT IT IS

IT'S A WAY OF THINKING

# EVIDENCE-BASED PRACTICE

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

**P**atient
**I**ntervention
**C**omparator
**O**utcome




## USING CLINICAL EXPERTISE

Diagnostician
Knowledge Broker
Communicator
Being Kind & Careful


## INFORMING PATIENTS & ELICITING & INTEGRATING PREFERENCES

# 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?

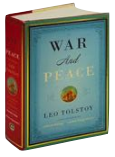
~100,000 pages

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

# How to assess CPGs

**Appraisal Tools for Clinical Practice Guidelines: A Systematic Review**

"the most comprehensively validated appraisal tool is the AGREE II instrument

PLoS ONE 8(12): e82915. doi:10.1371/journal.pone.0082915

# Appraisal of Guidelines for Research and Evaluation (AGREE) II

DOMAIN 1. SCOPE AND PURPOSE

DOMAIN 2. STAKEHOLDER INVOLVEMENT

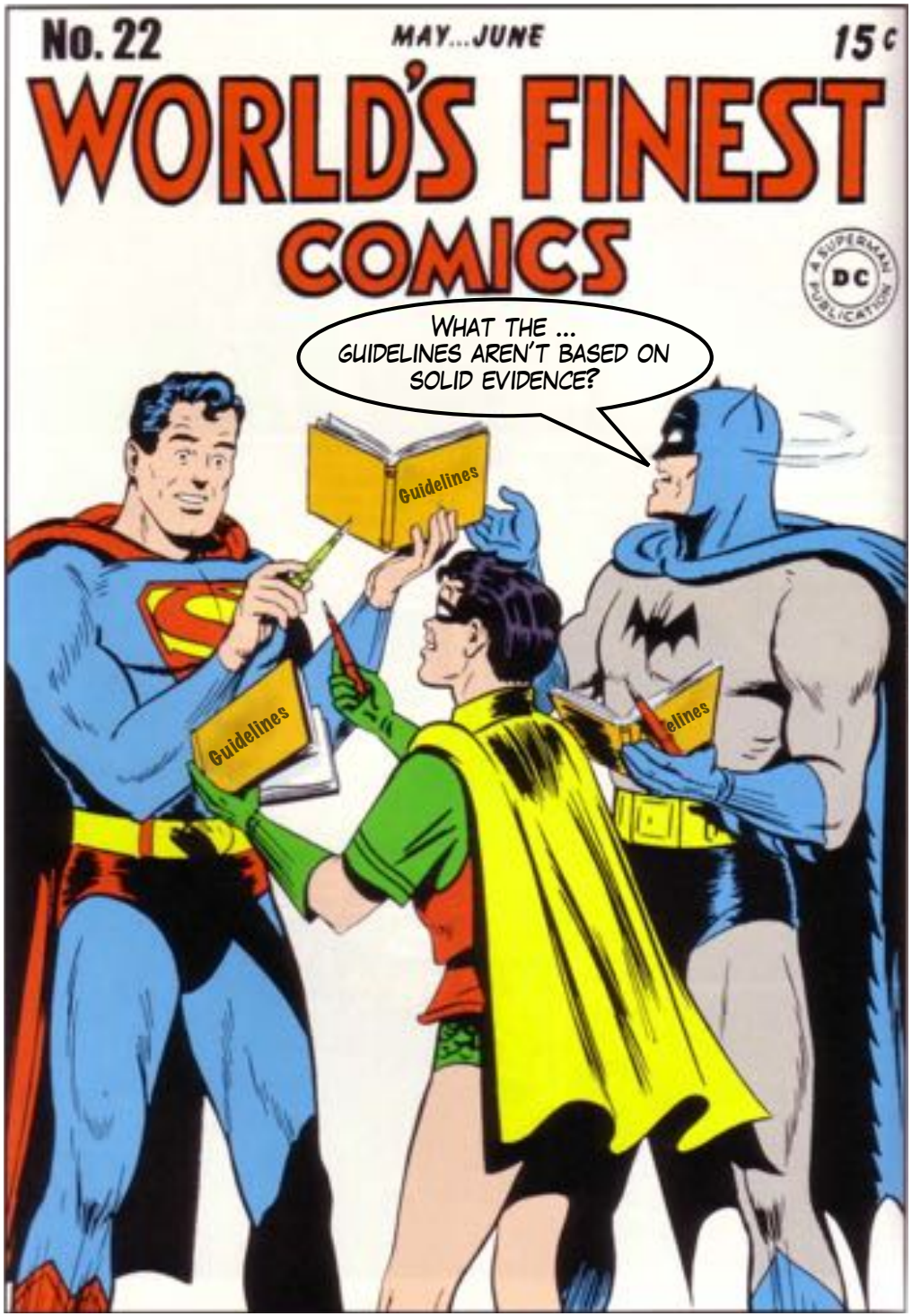
DOMAIN 3. RIGOUR OF DEVELOPMENT

DOMAIN 4. CLARITY OF PRESENTATION

DOMAIN 5. APPLICABILITY

DOMAIN 6. EDITORIAL INDEPENDENCE

OVERALL GUIDELINE ASSESSMENT




# 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 | | | | | |
| 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 |

***Top Score = 100%***

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

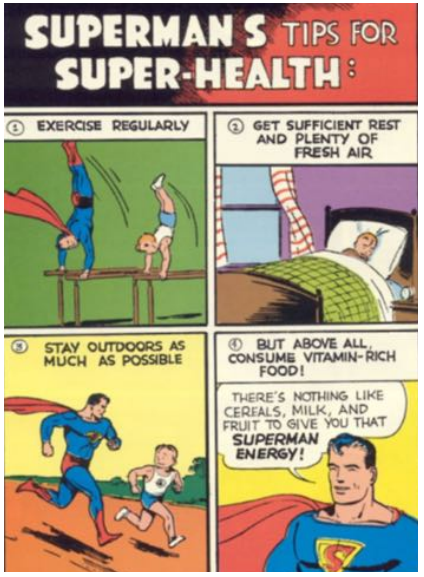
avg 48% - diabetes - 24 CPGs - range 0%-81% - PLoS ONE 2013 8(4): e58625

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



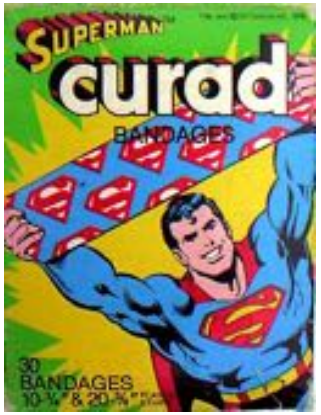





# Who writes/ sponsors guidelines?







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**

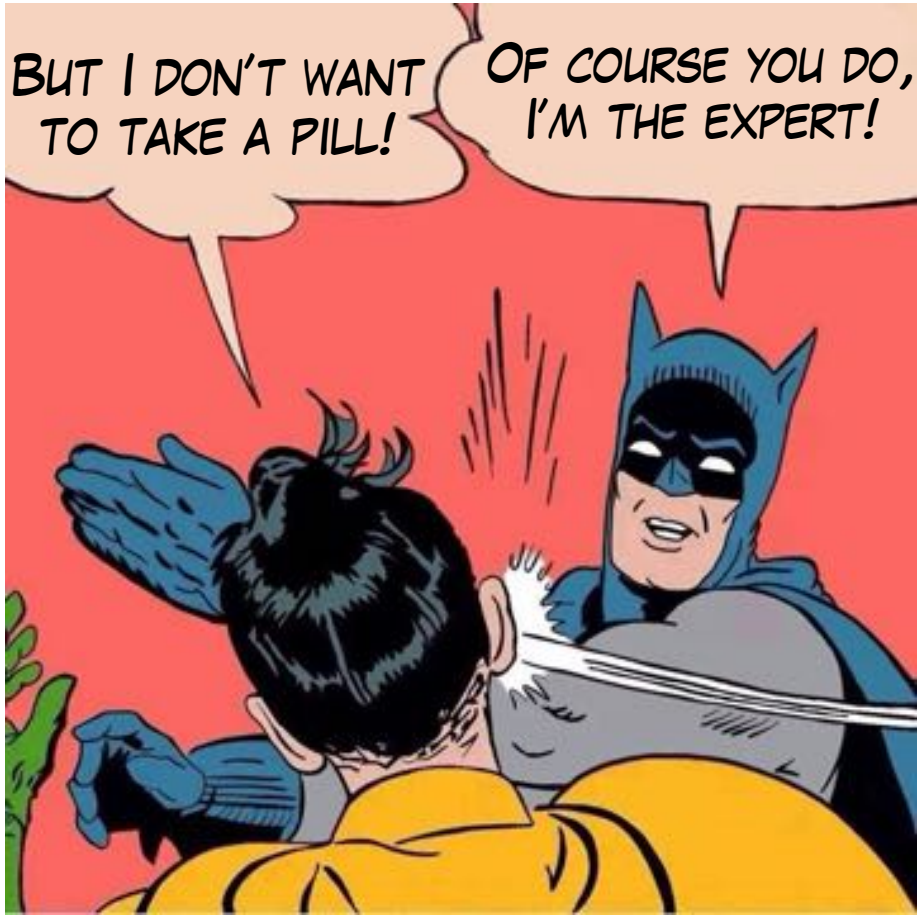
~50-80% of panel members on guidelines have financial COIs

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"

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"

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

2017

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

| The magnitude of the imprecision around routinely ordered medical measurements* | | | | | | |
|---|---|---|---|---|---|---|
| **MEASUREMENT** | Chloride<br>Sodium<br>Osmolality | Albumin<br>Bone density<br>Calcium<br>Hematocrit<br>Hemoglobin<br>HbA1c<br>INR<br>MCH<br>MCV<br>Total protein<br>Systolic BP | Creatinine<br>Globulins<br>Glucose<br>Magnesium<br>pC02<br>Potassium<br>PTT<br>Total cholesterol<br>T4 | AST<br>Alkaline phosphatase<br>BUN<br>HDL<br>LDH<br>LDL<br>Phosphorous<br>Platelets<br>Rheumatoid factor<br>Testosterone<br>Uric acid<br>WBC | GGT<br>Neutrophils<br>PSA<br>Vitamin D | Aldosterone<br>ALT<br>Bilirubin<br>Folate<br>Iron<br>Lactate<br>Triglycerides<br>TSH<br>Vitamin B12 |
| Approximate +/- range for a single measurement | ~1-3% | ~3-7% | ~7-15% | ~15-30% | ~30-50% | ~>50% |
| The magnitude of the change required between two serial measurements so one can be reasonably confident there has been a change** | ~2-5% | ~5-10% | ~10-20% | ~20-40% | ~40-60% | ~>60% |

* based on the analytic and biologic variation

** also known as the reference change value

Data collated primarily from here - https://www.westgard.com/biodatabase1.htm
but some also taken and confirmed from a few other sources - numbers rounded off for ease of use
James McCormack BSc.Pharm, Pharm D - therapeuticseducation.org


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."

CJD
Canadian Journal of Diabetes
A Publication of the Professional Sections of the Canadian Diabetes Association
Une publication des sections professionnelles de l'Association canadienne du diabète
CONTENTS: April 2013 ▪ Volume 37 ▪ Supplement 1

CMPA
Empowering
better healthcare

# The Bottom Line

Sep 2011

Even an authoritative CPG may NOT be found to be determinative of a standard of care.

It is prudent for physicians to be aware of authoritative clinical practice guidelines relevant to their practices. If a clinical decision may be perceived as being contrary to a recognized and accepted CPG, a physician, where appropriate, may consider the following steps: consult with a colleague or relevant specialist, discuss reasonable treatment options with the patient, and document the patient's consent for the chosen treatment.

If deviating from an established CPG, physicians should consider documenting the rationale for doing so, as well as any discussions with the patient about such variance.

# Many courts (UK, US, CA)

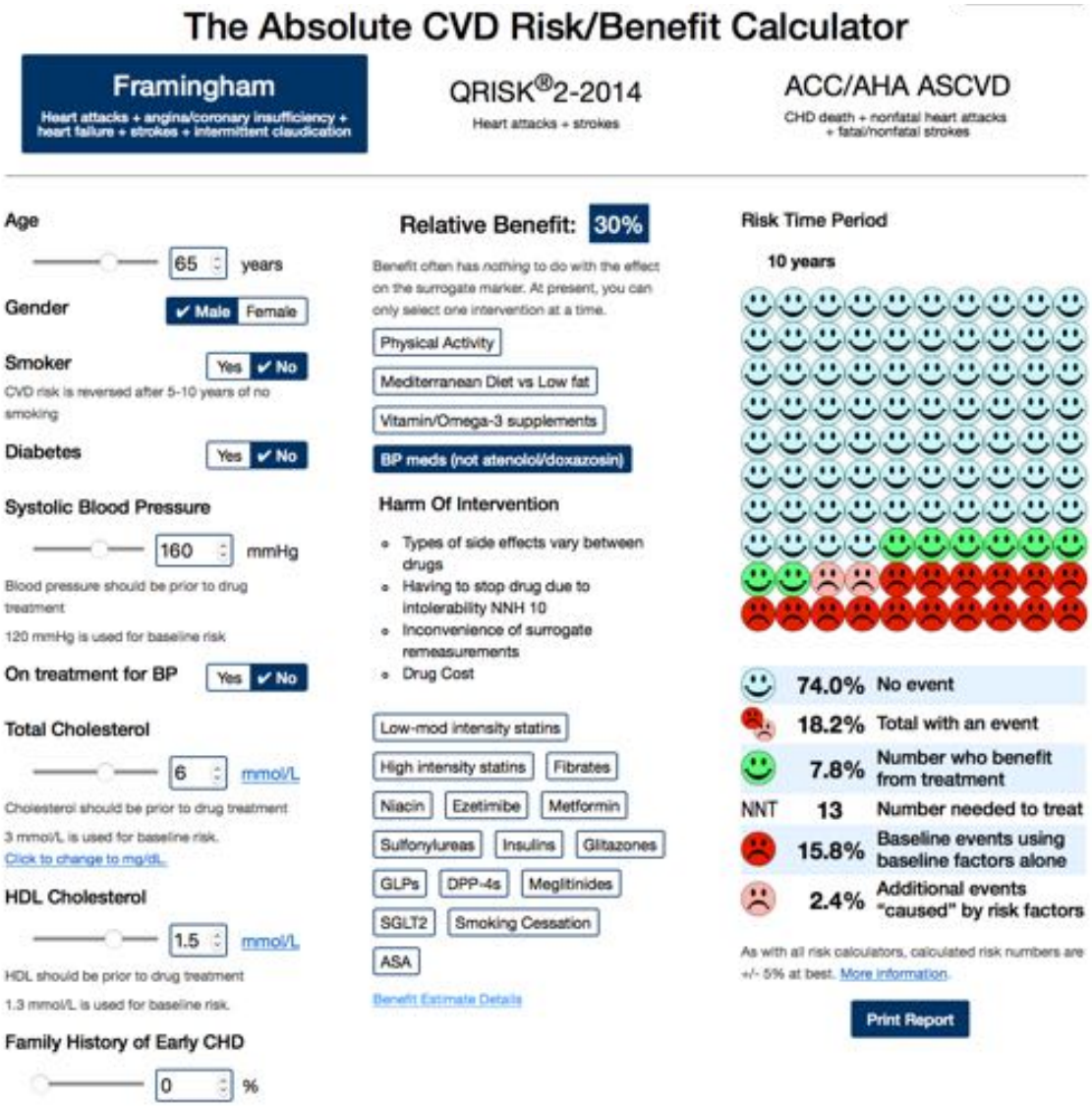
"The reasonable-patient standard … requires physicians and other health care practitioners to disclose all relevant information about the risks, benefits, and alternatives of a proposed treatment that an **OBJECTIVE PATIENT** would find material in making an intelligent decision as to whether to agree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

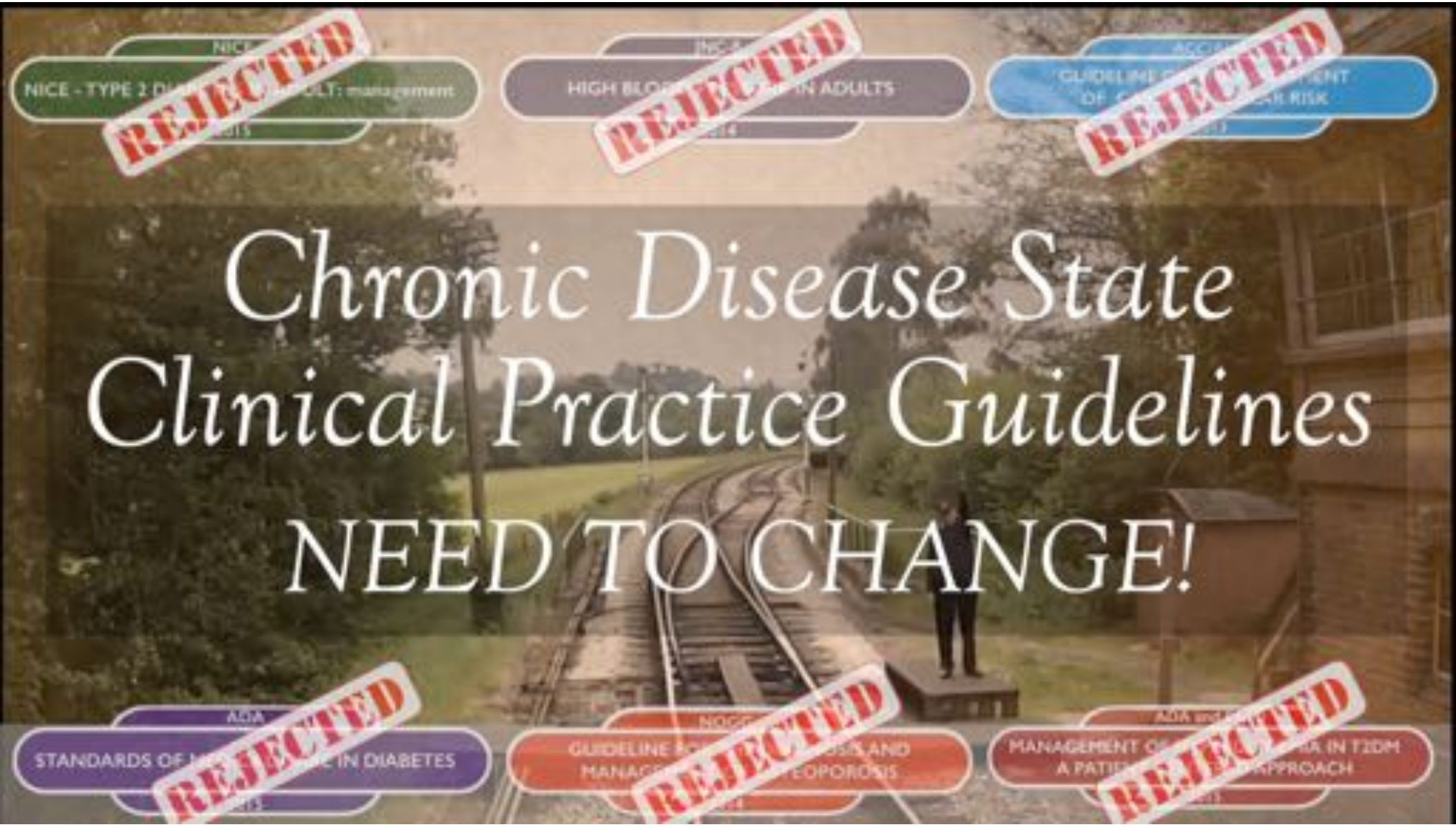



Calculate ballpark 10-yr risk of CVD - BP, chol, diabetes
Make estimate of benefit based on the best available evidence
Gives a list of adverse effects to discuss

cvdcalculator.com

# 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




End of Guidelines -
parody of Traveling Wilburys' End of the Line

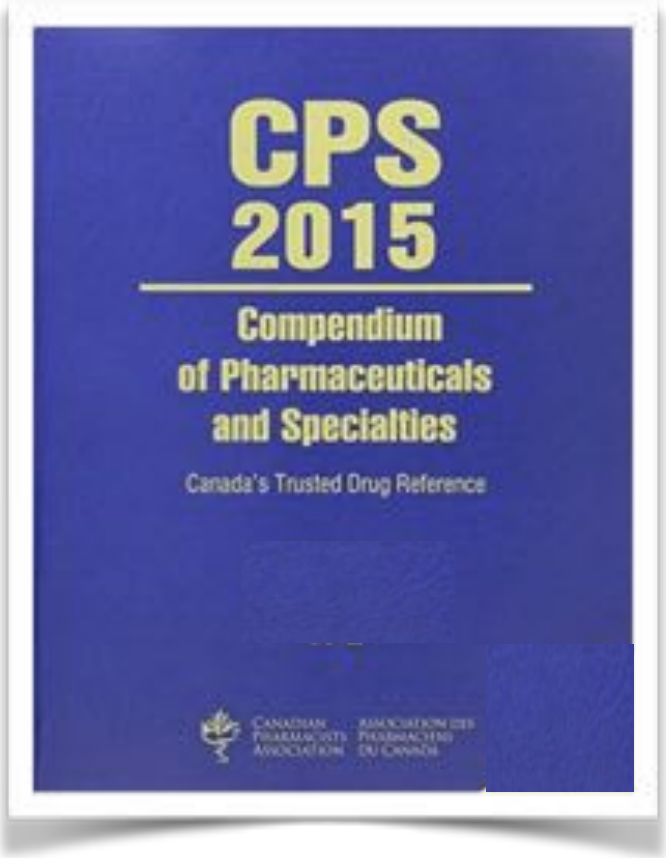
www.youtube.com/user/jmccorma1234

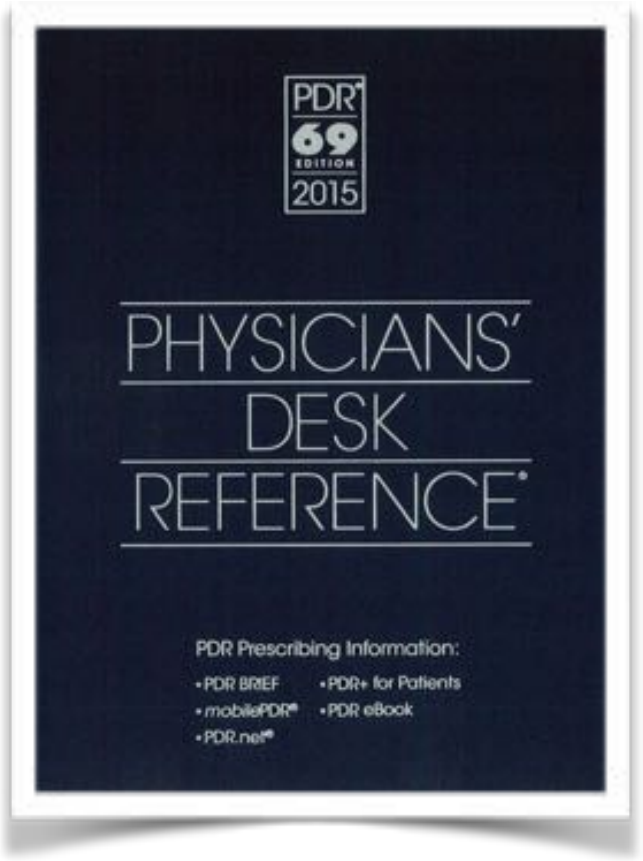

KEEP
CALM
AND
USE VERY
LOW DOSES

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)<br>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

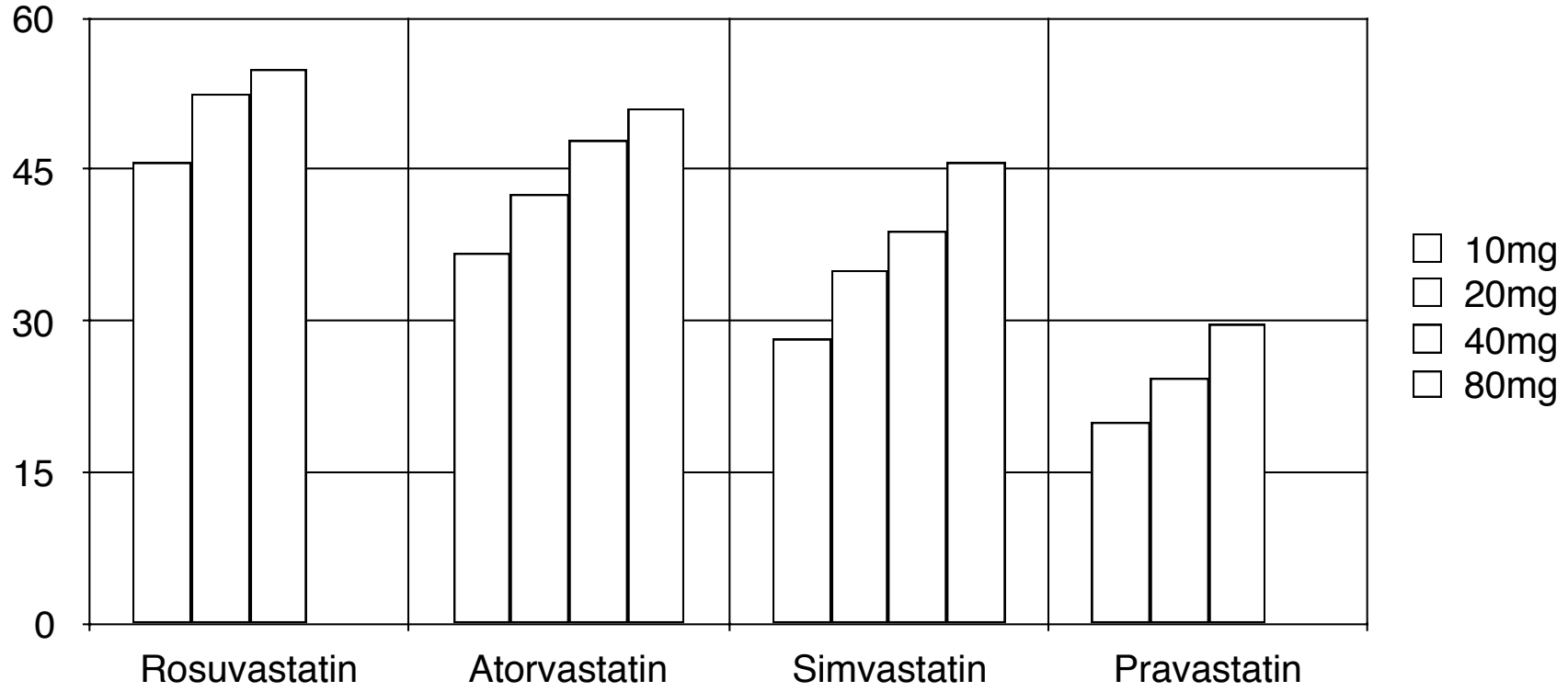
80% were dose decreases

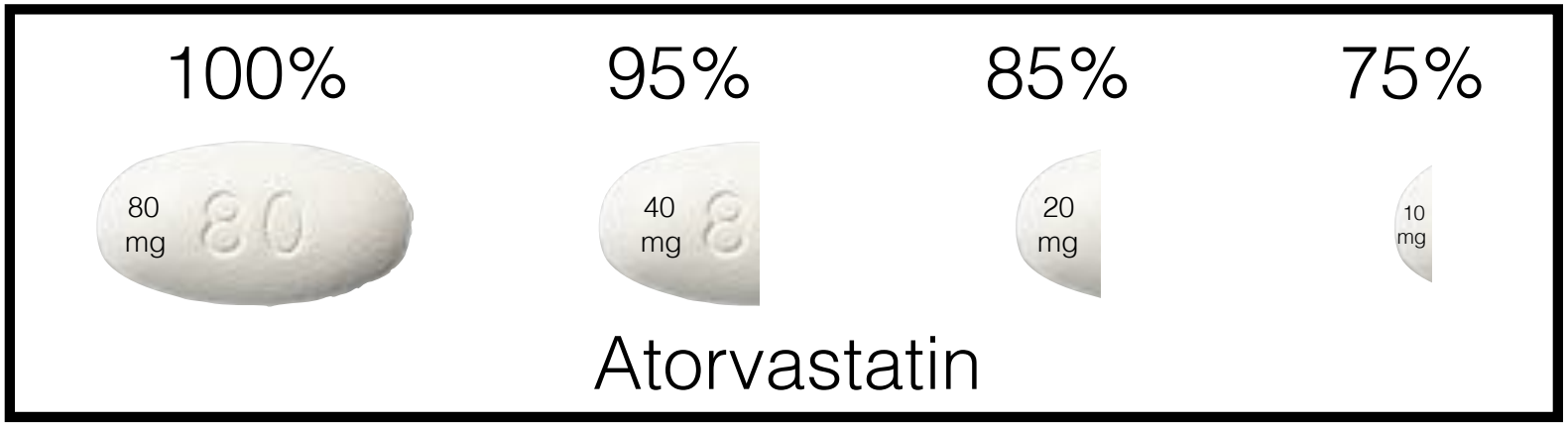
"this pattern may represent a systematic flaw in pre-marketing dosage evaluation; it has been common practice in the pharmaceutical industry to undertake phase III trials evaluating drug effectiveness at or near maximum-tolerated doses."

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 and DID it work

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

PPIs, sildenafil - NNT ~2

NSAIDs, opioids - pain NNT ~3-5

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

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

Antibiotics - acute COPD exacerbation - NNT ~5

Topical antibiotics - bacterial conjunctivitis - NNT ~7

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

| | If a person has responded, what is the % chance it was the medication | |
|---|---|---|
| Response in the placebo group | RCT Benefit 10% - NNT 10 | RCT Benefit 20% - NNT 5 |
| 0% | ~100% | ~100% |
| 10% | ~50% | ~66% |
| 20% | ~33% | ~50% |
| 30% | ~25% | ~40% |
| 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.

# The Risky Business of Risk Factor Modification

It’s Just a Numbers Game And So Much More

# Conditions requiring risk assessment

The main ones are hypertension, cholesterol, glucose/diabetes, osteoporosis/BMD, atrial fibrillation.

Levels of glucose, cholesterol, blood pressure, bone density are almost NEVER markers of disease - they are markers of risk

They all require value-laden decisions

Approximate risk of event over a time period

Approximate benefit

Include harm and costs and inconvenience

# Risk Factors versus Clinical Endpoints

"a risk factor/marker is a variable associated with an increased risk of disease"

| Not As Important | Very Important |
|---|---|
| blood pressure | symptoms |
| cholesterol | heart attacks |
| glucose/diabetes | strokes |
| bone density | heart failure |
| heart rate | death |
| CRP | dialysis |
| proteinuria | amputation |
| family history | fractures |
| age | blindness |
| gender | revascularization |
| race | angina |
| FEV1 | TIAs |

# It's all about figuring out

The Chance

WITH NO

TREATMENT

VS

The Chance

WITH

TREATMENT

**Ballpark risk estimate**
Epidemiological data/cohort data
- Framingham, QRISK, FRAX, CHA2DS2-VASc

**Ballpark benefit estimate**
RCT data
use the absolute benefit if people are similar to those in the studies or,
use the relative benefit and apply it to the baseline risk

# Absolute baseline risk, apply relative benefit, get absolute benefit

Baseline risk of a heart attack = 20% over 5 years
RR/Relative benefit = 0.75 or 25% reduction
With Treatment 20% drops to 15%
Absolute difference = 5%
NNT = 20

## INITIAL COST


Baseline risk

25% OFF SALE

Relative benefit

## NOW COSTS


New risk

## YOU SAVE


Absolute benefit

# Misguided beliefs

Patients believe CVD “prevention” drugs produce a 70% absolute benefit over 5 years when at most only ~ 20-30% benefit is possible over a lifetime



Clin Med 2002;2:527-33


# Risk of future illness
# CVD risk/benefit

(most people don't benefit despite a lifetime of treatment)

Challenging treatment thresholds

James McCormack PharmD, Aseem Malhotra MRCP and David Newman MD


Assume a person's lifetime risk of CVD is that of a male with two CVD risk factors - roughly 50% (NEJM 2012;366:321-9)


Assume that with multiple risk factor modification we can reduce that risk relatively by 60% (VERY optimistic)


Risk goes from 50% ➡ 20%


30% of individuals BENEFIT


70% DO NOT despite a LIFETIME of treatment

Prescriber September 2015

# Risks over short time periods

Assume a 5% (5/100) reduction in CVD over 5 years

~ 1% (1/100) reduction over one year

~ 0.1% (1/1000) per month

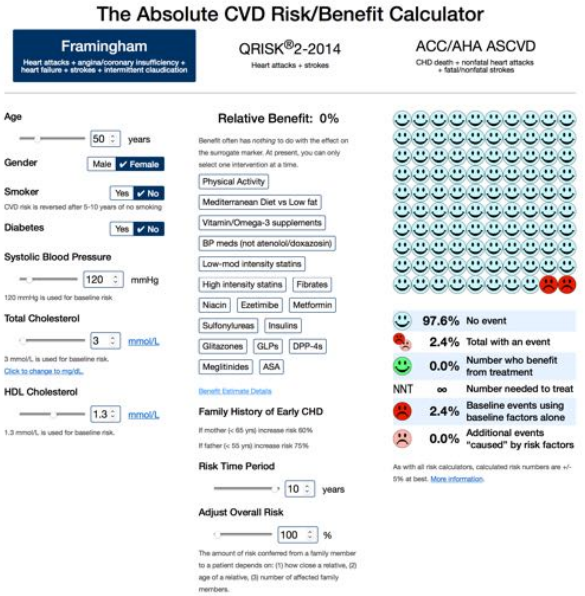
~ 0.02 (1/5000) per week

Patient

ACTIVITY AND NUTRITION!!!

Measure SBP/chol/glucose

Risk of cardiovascular disease




Patient decision


Treatment
Thiazides
ACE inhibitors
Statins etc

EVIDENCE FOR, AND MAGNITUDE OF, THE reduction in cardiovascular outcomes
SIDE EFFECTS

Repeat measurements?

Reevaluate need


# Every “measurement” will be different

Analytic variability
Biologic variability

# Actual LAB errors

# 0.3%

~60% pre-analytical
~15% analytical
~ 25% post analytical

**Table 1. Laboratory errors in stat testing.**

| Defects: detection steps | Defects found: No. | Defects found: Frequency, % |
|---|---|---|
| Preanalytical | | |
| Specimen collected from infusion route | 3 | 1.9 |
| Sample contaminated | 1 | 0.6 |
| Tube filling error | 21 | 13.1 |
| Empty tube | 11 | 6.9 |
| Inappropriate container | 13 | 8.1 |
| Nonrefrigerated sample | 3 | 1.9 |
| Missing tube | 5 | 3.1 |
| Digoxin test timing error | 1 | 0.6 |
| Patient identification error | 14 | 8.8 |
| Request procedure error | 12 | 7.5 |
| Data communication conflict | 6 | 3.8 |
| Physician's request order missed | 3 | 1.9 |
| Order misinterpreted | 2 | 1.3 |
| Check-in not performed (in the Laboratory Information Systems) | 4 | 2.5 |
| Subtotal | 99 | 61.9 |
| Analytical | | |
| Instrument-caused random error | 3 | 1.9 |
| Analytical inaccuracy not recognized | 21 | 13.1 |
| Subtotal | 24 | 15 |
| Postanalytical | | |
| Results communication breakdown | 32 | 20 |
| Lack of communication within laboratory | 3 | 1.9 |
| TAT excessive | 2 | 1.3 |
| Subtotal | 37 | 23.1 |

Clinical Chemistry 2007;53:1338-42

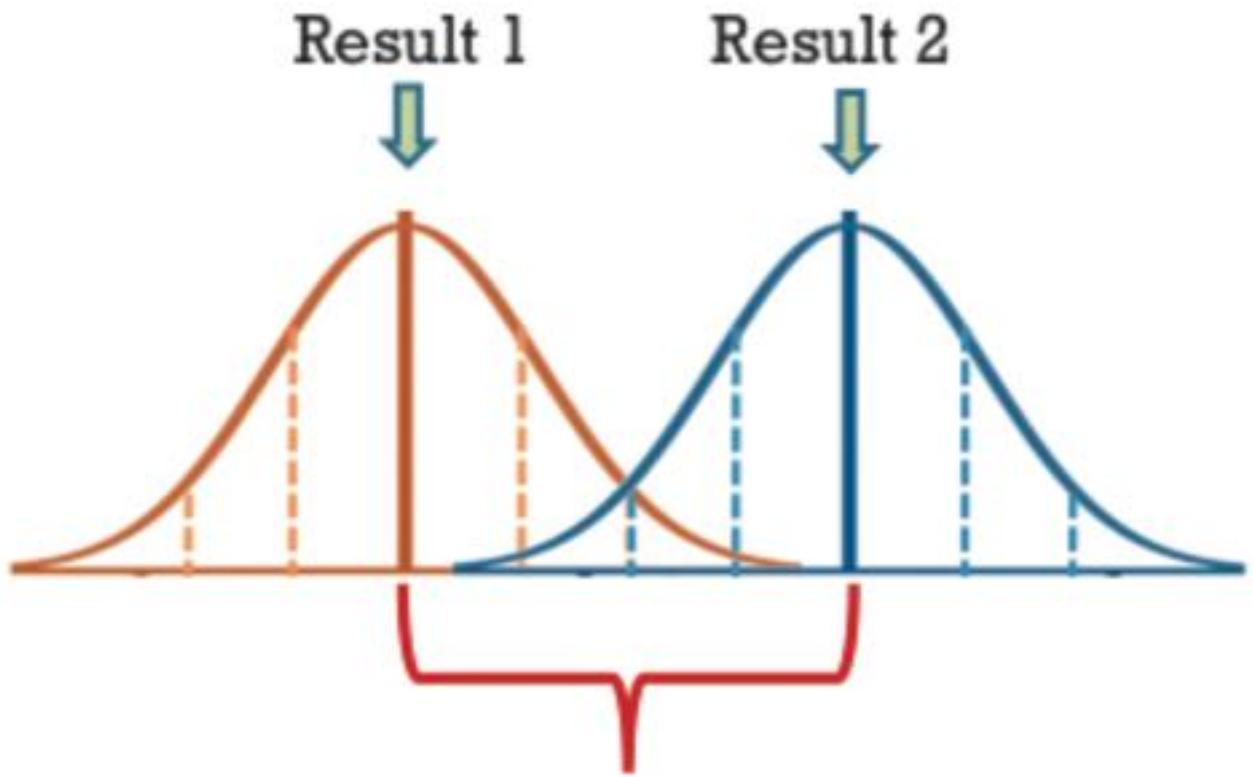
# Dispensing errors ~1-2%

Lab
Error

Analytic
variation

# Biologic
# variation

We believe these two results are different



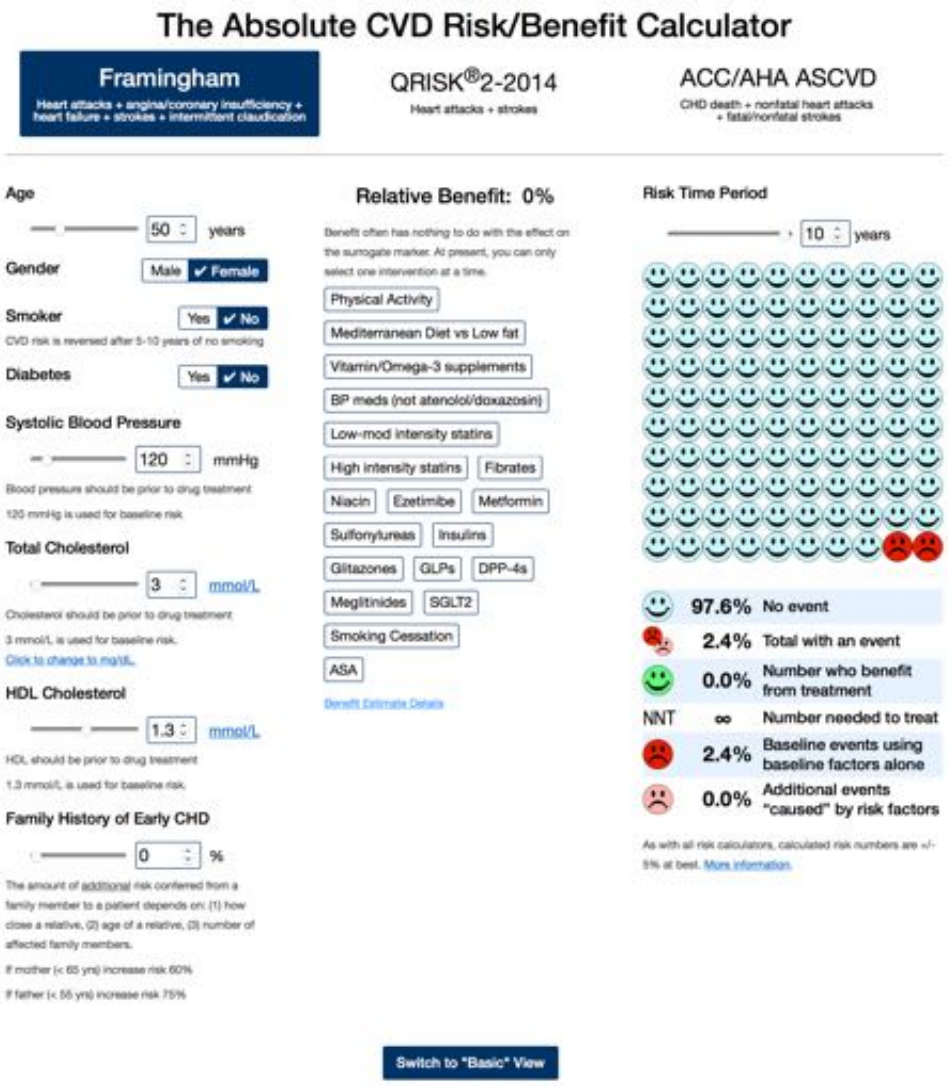

can’t necessarily quantify this difference with any precision

| The magnitude of the imprecision around routinely ordered medical measurements* | | | | | | |
|---|---|---|---|---|---|---|
| **MEASUREMENT** | Chloride<br>Sodium<br>Osmolality | Albumin<br>Bone density<br>Calcium<br>Hematocrit<br>Hemoglobin<br>HbA1c<br>INR<br>MCH<br>MCV<br>Total protein<br>Systolic BP | Creatinine<br>Globulins<br>Glucose<br>Magnesium<br>pC02<br>Potassium<br>PTT<br>Total cholesterol<br>T4 | AST<br>Alkaline phosphatase<br>BUN<br>HDL<br>LDH<br>LDL<br>Phosphorous<br>Platelets<br>Rheumatoid factor<br>Testosterone<br>Uric acid<br>WBC | GGT<br>Neutrophils<br>PSA<br>Vitamin D | Aldosterone<br>ALT<br>Bilirubin<br>Folate<br>Iron<br>Lactate<br>Triglycerides<br>TSH<br>Vitamin B12 |
| Approximate +/- range for a single measurement | ~1-3% | ~3-7% | ~7-15% | ~15-30% | ~30-50% | ~>50% |
| The magnitude of the change required between two serial measurements so one can be reasonably confident there has been a change** | ~2-5% | ~5-10% | ~10-20% | ~20-40% | ~40-60% | ~>60% |

* based on the analytic and biologic variation

** also known as the reference change value

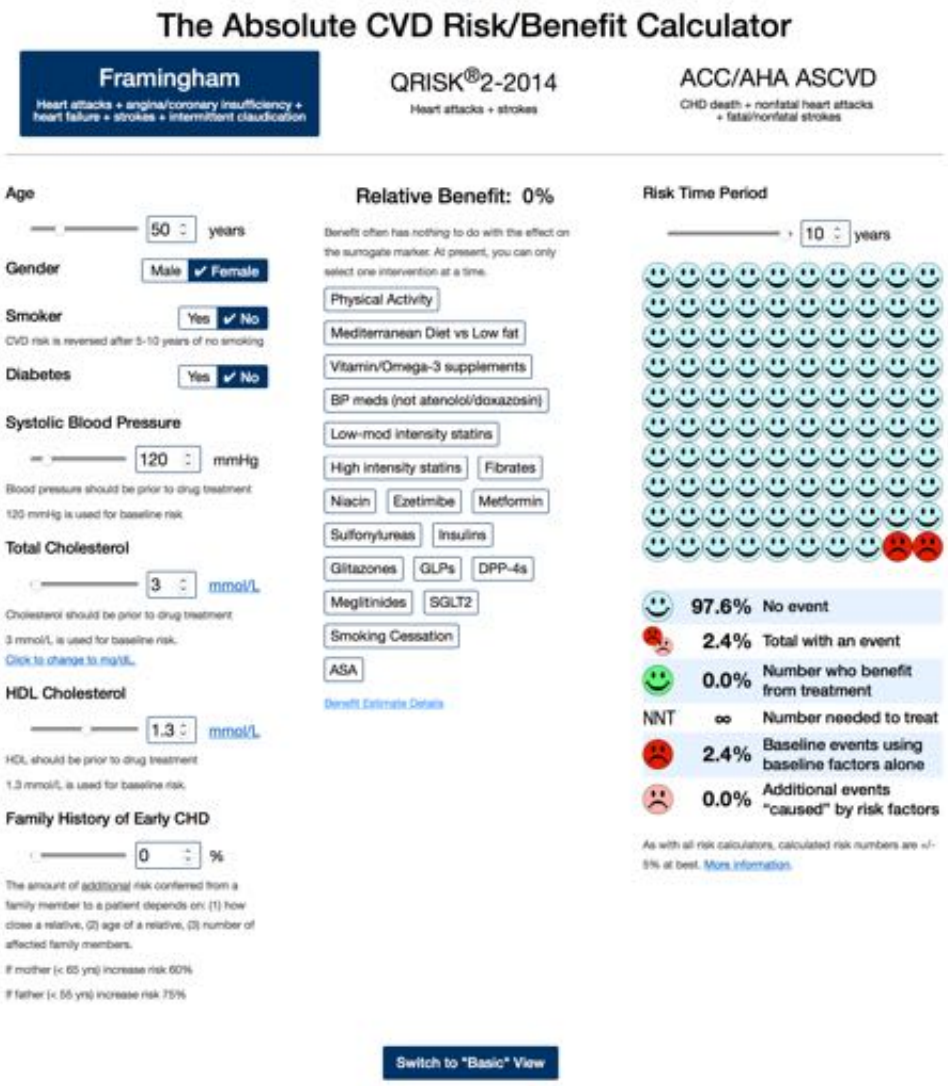
Data collated primarily from here - https://www.westgard.com/biodatabase1.htm
but some also taken and confirmed from a few other sources - numbers rounded off for ease of use
James McCormack BSc.Pharm, Pharm D - therapeuticseducation.org




cvdcalculator.com

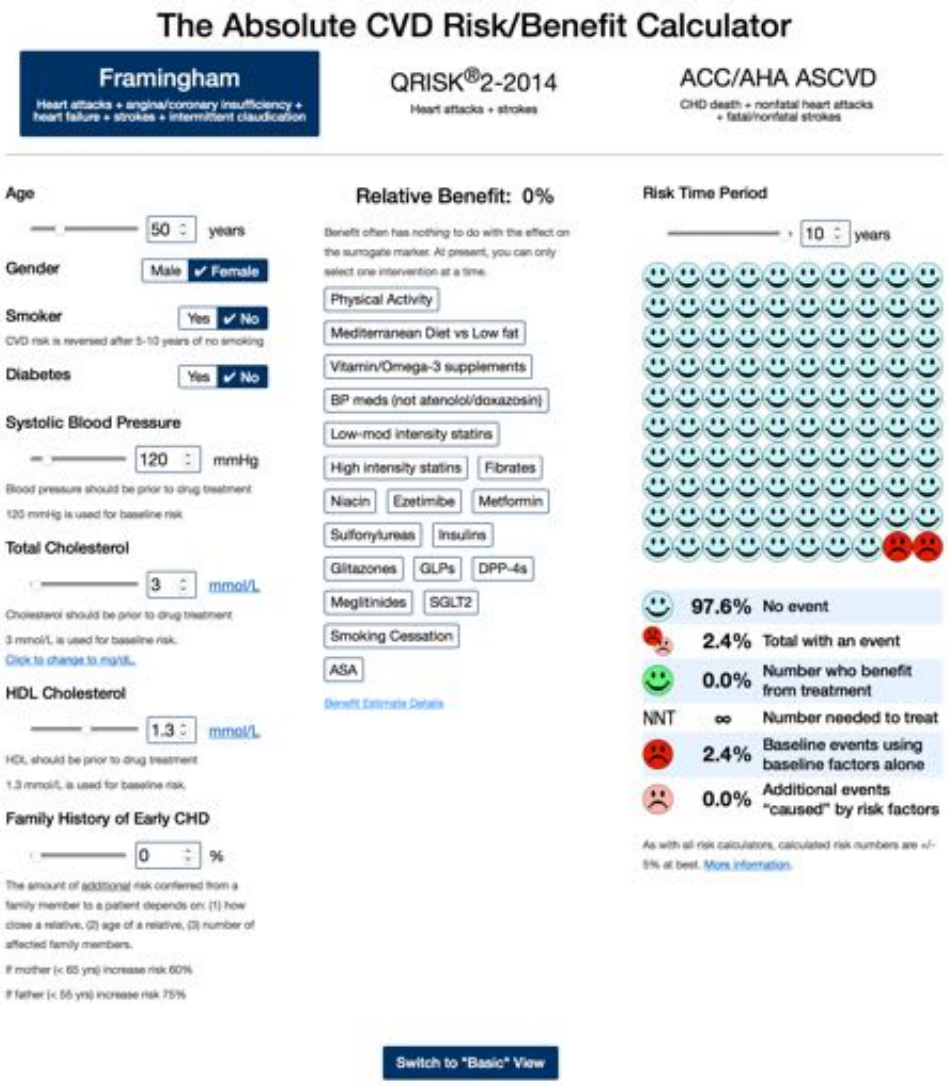
Oswald Chesterfield Cobblepot
AKA The Penguin
60 years old
Loves birds
Lives a luxurious lifestyle
Relatively inactive
PMH - Conduct disorder
Smoker
A1c 8
BP 150/90 mm/Hg
Total cholesterol 6 (240)
HDL 1 (40)

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)




cvdcalculator.com

Wonder Woman
Age 40 (OK she ages well)
BP 120/70 mmHg
Total cholesterol 6.8(270)
HDL 1.6 (65)
LDL 5.0 (200)
Trigs 1
Diet mostly caiman and anaconda (rich in cholesterol)
Non-diabetic
Not a smoker (but still smokin')
PMH: Charles Bonnet Syndrome
(suffers from visual hallucinations that are pleasant: in this case, a jet)
Wears bracelets as a defence but otherwise dresses more than appropriately!




cvdcalculator.com

# 10 year risk of complications from T2DM

60 y/o male, total chol 5, HDL chol 1, SBP 140, non-smoker

| Percentage Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| **A1C** | **Mortality** | **MI or stroke** | **Severe vision loss** | **RF/ ESRD** | **Pressure sensation loss** | **TOTAL** | **Additional risk vs 7** |
| **4** | 5 | 10 | 4 | 4 | 6 | 29 | -1.5/yr |
| **5** | 5 | 11 | 5 | 4 | 7 | 32 | -1.2/yr |
| **6** | 6 | 13 | 5 | 5 | 8 | 37 | -0.7/yr |
| **7** | 7 | 16 | 6 | 5 | 10 | 44 | - |
| **8** | 9 | 18 | 7 | 6 | 12 | 51 | +0.7/yr |
| **9** | 10 | 21 | 8 | 7 | 14 | 59 | +1.5/yr |
| **10** | 12 | 25 | 9 | 8 | 17 | 70 | +2.6/yr |

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

**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**

| | Stroke / Embolism | | Major Bleeding | |
|---|---|---|---|---|
| **THERAPY** | CHADS2 | CHA2DS2-VASc | 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

# A Suppository Guideline
# WHERE DO THEY FIT IN?


use. Remove the suppository from the foil and, lying on your back or your side with your knees bent up, push the suppository- pointed end first - up into your back passage. Lie still

**9** Insert the suppository, pointed end first, with your finger

Gently but firmly push the suppository into the rectum, pointed end first.

# Rectal suppository: commonsense and mode of insertion

K. H. ABD-EL-MAEBOUD T. EL-NAGGAR E. M. M. EL-HAWI
S. A. R. MAHMOUD S. ABD-EL-HAY


A = 83% needed to introduce finger - 3% expulsion

B = 1% needed to introduce finger - 0% expulsion - 98% found this method easier

Lancet 1991;338:798-800

Journal of
Clinical Nursing

REVIEW

# Rectal suppository insertion: the reliability of the evidence as a basis for nursing practice

Having reviewed the arguments for the best method to insert suppositories, it is clear that there is as yet little reliable evidence for supporting the method of blunt end foremost as opposed to what is described as the 'commonsense' method of pointed end foremost. Does this really matter?

The reason that this issue does matter lies in the law.

suppositories were used in this way'. Novartis 'cannot recommend the administration of the suppository blunt end first as it would be outside the terms of the licence'. This

information leaflets? As the manufacturer's instructions form the terms of the drug licence, where does the legal liability lie should an untoward event arise when the nurse has not followed their instructions? There is also one further issue to

Journal of Clinical Nursing 2007;16:98-103

BMJ : British Medical Journal
BMJ. 336(7647): 764-764 2008

# Getting to the bottom of evidence based medicine

Susan Bewley, consultant obstetrician

wide suppository guideline agreed, I decided to opt for a hospital-wide protocol. The chief pharmacist examined, and accepted, the arguments. We should indeed be inserting suppositories the other way, base first. The only problem was that all suppository packs contain the traditional, incorrect instruction, which would confuse patients. So, he concluded, it has to be an NHS-wide policy. I have written to the National