

# Baffled, Befuddled, and Bemused

How not to get fooled again, and again, and ,...

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therapeuticseducation.org  
medicationmythbusters.com

antibiotics  
thiazides  
many vaccines  
ACE inhibitors  
proton pump inhibitors  
H2 receptor antagonists  
contraceptives



corticosteroids  
beta-agonists  
insulin  
anesthetics  
adrenalin  
narcotics  
chemotherapy  
warfarin

## Drugs Removed from the Market

### 1950-70s

Thalidomide  
Teratogenicity  
LSD (psych cure-all)  
Used recreationally  
Diethylstilbestrol  
Teratogenicity  
Phenformin/Buformin  
Lactic acidosis

### 1980s

Ticrynafen  
Hepatitis  
Zimeldine  
Guillain-Barré syndrome  
Phenacetin  
Cancer/  
kidney disease  
Methaqualone  
Addiction/overdose  
Nomifensine (Merital)  
Hemolytic anemia

### 1990s

Triazolam  
UK - psychiatric reactions  
Terodiline (Micturin)  
Prolonged QT interval  
Tetrafluoracetate  
Allergic reactions/  
hemolytic anemia  
Flosequinan (Manoplax)  
Increased hospitalization/  
death  
Alpidem (Ananxyl)  
Hepatotoxicity  
Chlormezanone (Trancopal)  
Toxic epidermal necrolysis  
Dexfenfluramine/fenfluramine  
Heart valve disorder  
Tolrestat (Alfredase)  
Hepatotoxicity  
Terfenadine (Seldane)  
Cardiac arrhythmias  
Mibefradil (Posicor)  
Dangerous interactions  
Ethinamate  
Birth defects  
Tolcapone (Tasmar)  
Hepatotoxicity  
Temazepam (Restoril)  
Sweden and Norway - diversion,  
abuse, overdose  
Asenitole (Hismanal)  
Arrhythmias  
Grepafloxacin (Raxar)  
Prolonged QT interval

### 2000s

Troglitazone (Rezulin)  
Hepatotoxicity  
Alosetron (Lotronex)  
Fatal complications of constipation  
Reintroduced 2002 on a restricted basis  
Cisapride (Propulsid)  
Cardiac arrhythmias  
Amineptine (Survector)  
Hepatotoxicity  
Dermatological  
Abuse potential  
Phenylpropanolamine (Dexatrim)  
Stroke  
Trovafoxacin (Trovan)  
Liver failure  
Carvastatin (Baycol)  
Rhabdomyolysis  
Rapacuronium (Raplon)  
Fatal bronchospasm  
Rofecoxib (Vioxx)  
Myocardial infarction  
Co-proxamol (Distalgic)  
Overdose dangers  
Hydromorphone ER (Palladone)  
Overdose dangers  
Thioridazine (Mellaril)  
UK - cardiotoxicity  
Pemoline (Cylert)  
Hepatotoxicity  
Ximelagatran (Exanta)  
Hepatotoxicity  
Pergolide (Permax)  
US - heart valve damage  
Tegaserod (Zelnorm)  
Heart attack and stroke  
Aprotinin (Trasylol)  
Death  
Inhaled insulin (Exubera)  
Long-term safety and too high a cost  
Lumiracoxib (Prexige)  
Liver damage  
Rimonabant (Accompia)  
Severe depression and suicide  
Efalizumab (Raptiva)  
Progressive multifocal leukoencephalopathy  
Sibutramine (Reductil)  
Cardiovascular risk  
Gemtuzumab (Mylotarg)  
US - no benefit and venoocclusive disease  
Rosiglitazone (Avandia)  
Europe - heart attacks and death

## Outcomes Are Not Created EQUAL Surrogate - Subjective - Objective

Ask yourself: Can a patient feel the outcome?

If No - it is a surrogate marker

## A Medical Tale: The Surrogate Heart



	Encainide/ Flecainide	Placebo
Mortality	7.7%	3%
Arrhythmia death or cardiac arrests	4.5%	1.2%

NEJM 1989;321:406-12

## Surrogates: The Never-ending Consistently Inconsistent Story

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

N Engl J Med 2007;357:2109-22

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

**JAMA**  
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):851-841 (doi:10.1001/jama.2009.209)

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

Dong Huan Lee, MD, Ole Videmeyer, MD Arch Intern Med. 2011;171(1):18-22

Cardiology	LEVEL	Infectious disease
11%	Evidence Level (I or A) based on RCTs	14%
48%	Evidence Level (3 or C) based on opinion	55%

2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations

TARGETS OF THERAPY		
Risk level	Primary target: LDL-C	Class level
High	<2 mmol/L CAD, PVD, atherosclerosis or Most patients with diabetes FRS ≥20% apoB <0.80 g/L FRS ≥20%	Class I level A
Moderate	<2 mmol/L* or LDL-C >3.5 mmol/L TC/HDL-C ≥5.0 hs-CRP >2 mg/L in men >50 years and women >60 years of age Family history and hs-CRP modulate risk	Class IIa, level A
Low	≥50% ↓ LDL-C	Class IIb, level A
FRS <10%		

Level A = recommendation based on evidence from multiple randomized trials or meta-analyses

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

“The Expert Panel was unable to find RCT evidence to support titrating cholesterol-lowering drug therapy to achieve target LDL-C or non-HDL-C levels, as recommended by ATP III”

## 20 “NEGATIVE” STUDIES IN A ROW

### LIPIDS

AIM-HIGH, HPS2-THRIVE (niacin)  
ACCORD (fibrates)  
dalOUTCOMES (dalcetrapib)  
STABILITY (darapladib)

### DIABETES

ACCORD, ADVANCE, VADT  
(aggressive A1c lowering)  
ROADMAP (olmesartan)  
ORIGIN (insulin)  
SAVOR-TIMI 53 (saxagliptin)  
EXAMINE (alogliptin)  
ALECARDIO (aleglitazar)

### BLOOD PRESSURE

ALTITUDE (aliskiren)  
VALISH, AASK, ACCORD  
(aggressive BP lowering)

### GENERAL

ACTIVE (irbesartan/afib)  
CRESCENDO (rimonabant)  
VISTA-16 (varespladib)

182,000+ patients



## 1967 Effects of Treatment on Morbidity in Hypertension

Results in Patients With Diastolic Blood Pressures  
Averaging 115 Through 129 mm Hg

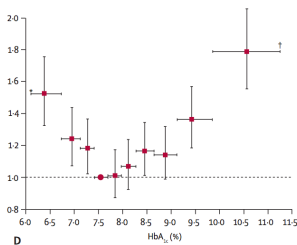
Veterans Administration Cooperative Study Group on Antihypertensive Agents

Lower BP in patients with average DBP of 121 mmHg - 19 months

Placebo - 70 patients - 27 CVD events - 4 deaths

Drug - 73 patients - 2 events - 0 deaths

## What goes down must come up



BMI<sup>3</sup> over 65

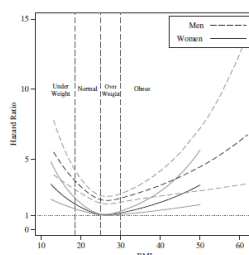
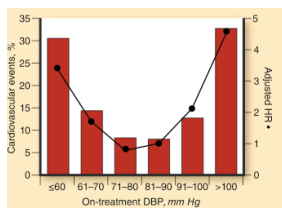


Figure 1. Hazard ratios of all-cause mortality according to body mass index (BMI) in men and women aged 70 to 75 (lines are 95% confidence intervals).

Similar data for  
25-59 years of age  
JAMA 2007;298:2028-37

Diastolic BP<sup>2</sup>



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

632

JAMA, Feb 23, 1963

## Effectiveness of Estrogens for Therapy of Myocardial Infarction in Middle-Age Men

JAMA  
1963;183:106-12

10 mg versus placebo - over 5 years

Cardio/renal event - first 3 months - 22% vs 5% - but

mortality lower at 5 years therefore a new trial suggested

“Feminizing effect” - 40% vs 30%

## The Coronary Drug Project

Terminated  
early

Initial Findings Leading to  
Modifications of Its Research Protocol

The Coronary Drug Project Research Group

JAMA 1970;214:1303-13

5 mg versus placebo - over 18 months

Definite non-fatal MI - 6.2% vs 3.2%

Pulmonary embolism - 1.5% vs 0.4%

Excessive shopping - 80% vs 3%

**IMPORTANT!**  
Finish all medication  
unless otherwise  
directed by prescriber.



BMJ

EDITORIALS

**A prescription for improving antibiotic prescribing in primary care**  
Comprehensive education programmes can reduce antibiotic prescriptions, but the impact on clinical outcomes is unclear.  
James McCormack professor<sup>1</sup>, G Michael Allan associate professor<sup>2</sup>

**If you say it enough  
it becomes the truth**

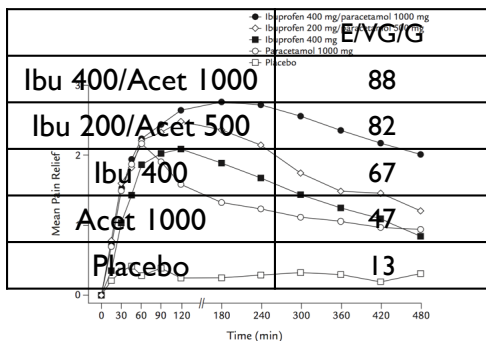
“a reasonable approach for most primary care infections would be to tell the patient to continue the antibiotic until they have been asymptomatic or afebrile for 72 hours and then to stop”

## The “Best” Painkiller for postoperative dental pain

	Excellent	E/VG/G
Ibu 400/Acet 1000	24	85
Ibu 200/Acet 500 mg	14	82
Ibu 400/codeine 25mg	16	78
Acet 1000/codeine 15mg	6	73
Placebo	2	11

Pain 2011;152:632–42

## The “Best” Painkiller for postoperative dental pain



Clinical Therapeutics 2010;32:882-95

## The “Best” Painkiller for postoperative dental pain

	Pain Nil/Mild
Ibu 150/Acet 500	68
Ibu 150	54
Acet 500	38

Br J Anaesth 2010;104:80–8

## Risk: Relative, Absolute & NNT

If you don't know where you start, it's hard to know where you finish.  
If you don't know where you start, it's hard to know where you finish.

Zoster vaccine reduces shingles up to 70%

Study	Placebo	Zoster Vac	Benefit	NNT (3 yrs)
Age 50-59 (3 yrs)	2.03%	0.62%	1.41%	71
Age ≥60 (3 yrs)	3.42%	1.67%	1.75%	58

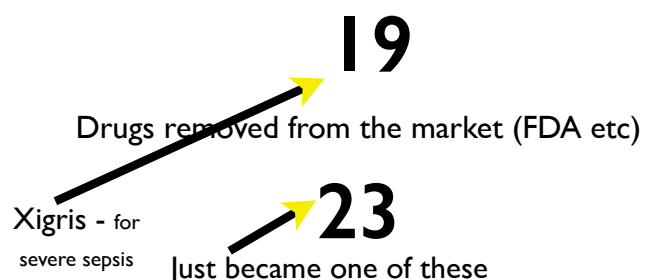
Bottom-Line: Over 3 years, one in 60-70 patients will avoid shingles due to the vaccine

- One in 350 for post-herpetic neuralgia

Tools for Practice Nov 12, 2012

## New and improved Unsafe/withdrawn The last decade (2000s)

Drugs considered to provide substantial improvements (PMPRB)



## 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 Adult 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*

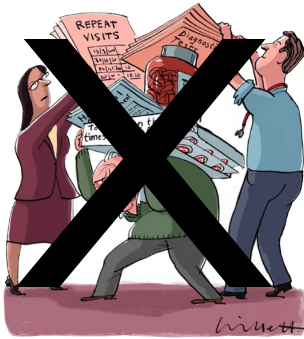
## Beware of “qualitative quantification”

Qualitative descriptor	EU assigned frequency	Mean frequency estimated by participants (n=200)
Very common	>10%	65% (24.2)
Common	1-10%	45% (22.3)
Uncommon	0.1-1%	18% (13.3)
Rare	0.01-0.1%	8% (7.5)
Very rare	<0.01%	4% (6.7)

Values are mean (SD).

Lancet 2002;359:853-54

## Minimally Disruptive Medicine



Establish burden of  
therapy

Encourage coordination  
in clinical practice

Acknowledge  
comorbidity in clinical  
evidence

Prioritize from the  
patient perspective

NEWER IS RARELY BETTER - WAIT 5 YEARS

SURROGATES CAN BREAK YOUR HEART

VERY HIGH IS BAD BUT AGGRESSIVE LOWERING RARELY  
SEEMS TO DO MUCH

COLLATERAL DAMAGE CAN COME FROM SHOOTING  
AT TARGETS

LEAVE PHYSIOLOGICAL MECHANISMS TO  
PHYSIOLOGISTS

START WITH VERY LOW DOSES

MEASUREMENT OBSESSION

RECONSIDER HOW YOU USE “RISKY” WORDS

9. HEALTHY SKEPTICISM AND BASIC CRITICAL  
APPRAISAL SKILLS ARE ESSENTIAL FOR  
STUDENTS/PRACTITIONERS