L'Italia non è un paese per vecchi …..

SOCIETA' SCIENTIFICA DI MEDICINA INTERNA
FADOI
FEDERAZIONE DELLE ASSOCIAZIONI DEI DIRIGENTI OSPEDALIERI INTERNISTI

XIII CONGRESSO NAZIONALE
Firenze, 4-7 maggio 2008

EBM o ……..
Evidence Biased Medicine
Dai trial clinici al mondo reale

Giovanni Gambassi

Outline

- EBM e LG
- Problemi di EBM e LG
- Diversa EBM
- Conseguenze
- Soluzioni possibili
- Futuro

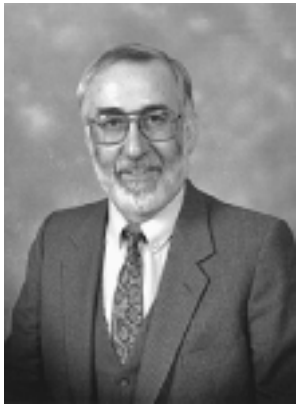
- **EBM e LG**


SERVE QUALCUNO CAPACE
DI DECIDERE CHI DEVE
DECIDERE COSA.
ACIAN.

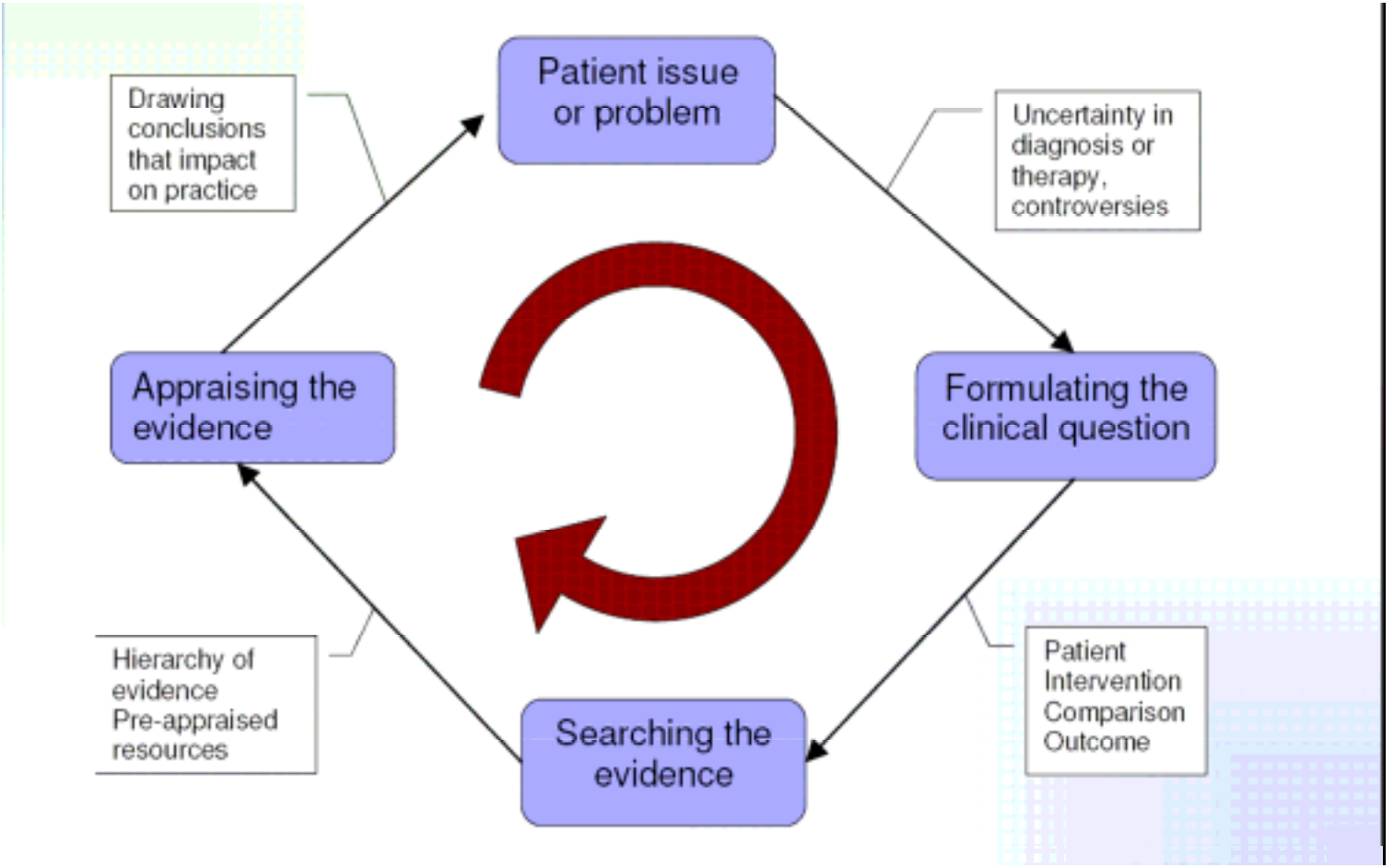
Eminence Based Medicine

Compiere lo stesso errore
con confidenza sempre crescente
un numero infinito di volte

- **Vehemence**
- **Eloquence**
- **Providence**
- **Nervousness**

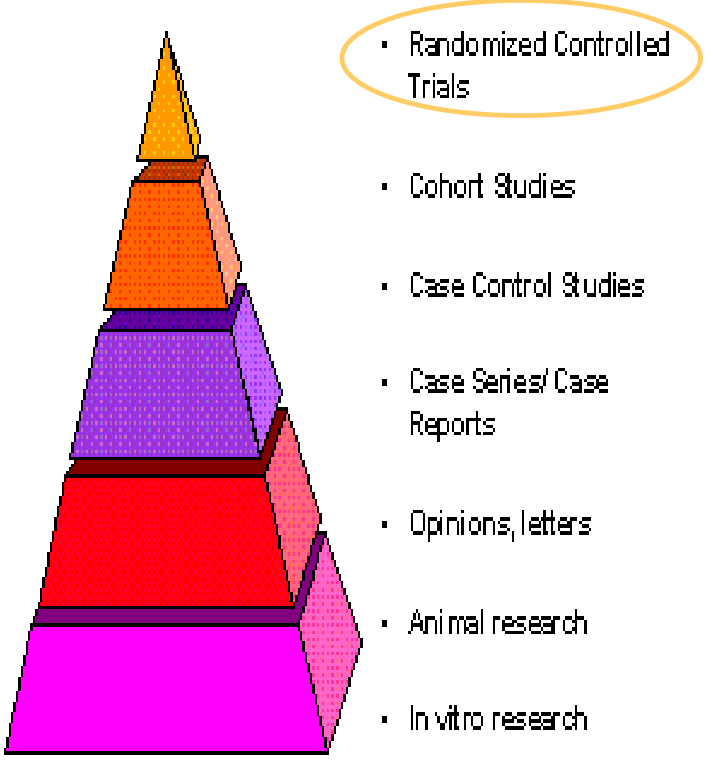


Evidence Based Medicine



The trial laude

- **120+ journals**
  50,000 articles
- **Is it valid?**
  (<5%)
- **Is it relevant?**
- < 0.5% selected



THE COCHRANE COLLABORATION®

ANALYSIS

BMJ | 26 APRIL 2008 | VOLUME 336

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Guidelines are inconsistent in how they rate the quality of evidence and the strength of recommendations. This article explores the advantages of the GRADE system, which is increasingly being adopted by organisations worldwide

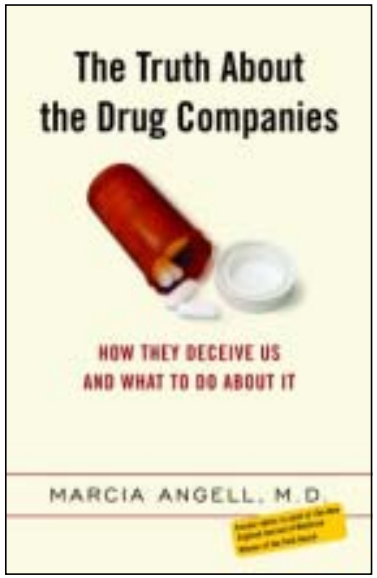
- Problemi EBM e LG

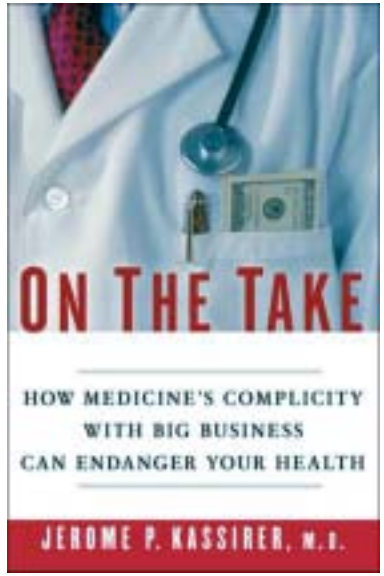
Problemi EBM

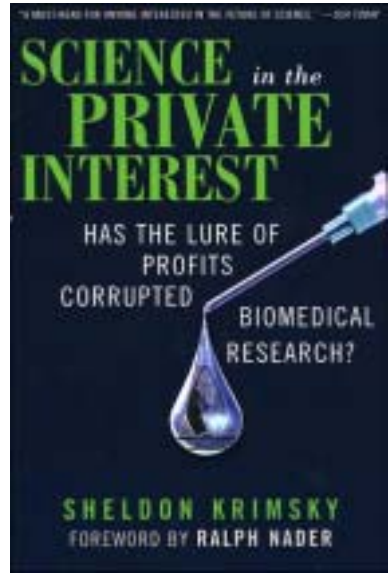
- EBM lacks its prerequisite, the medicine based evidence.
- NOT a RCT for any clinical query

There are estimates that as much as 80% of health care practice has yet to be validated by RCT

DeJong, Am J Med 1999







Molti bias

- 99% industry based
- data dredging & interpretation
- very likely to be positive
- publication bias

JAMA®

Online article and related content current as of May 5, 2008.

Impugning the Integrity of Medical Science: The Adverse Effects of Industry Influence

Catherine D. DeAngelis; Phil B. Fontanarosa

JAMA. 2008;299(15):1833-1835 (doi:10.1001/jama.299.15.1833)

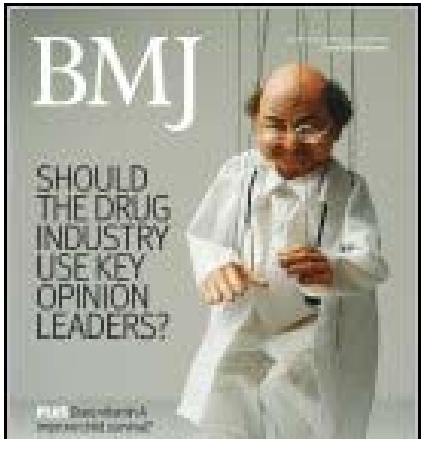
JAMA®

Online article and related content current as of June 12, 2008.

Guest Authorship and Ghostwriting in Publications Related to Rofecoxib: A Case Study of Industry Documents From Rofecoxib Litigation

Joseph S. Ross; Kevin P. Hill; David S. Egilman; et al.

JAMA. 2008;299(15):1800-1812 (doi:10.1001/jama.299.15.1800)



BMJ 2008;336 (21 June)

Key opinion leaders, your time is up

Fiona Godlee, *editor, BMJ*

Figure 2. Likelihood of Subsequent Safety-Related Problem for Drugs Approved in the Last 2 Months before the Review Deadline as Compared with All Other Drugs, 1993–2004.

Problemi LG

- Caratteristiche di un RCT (VALIDITY)

  - come è fatto (INTERNAL)
  - ciò che può e non può dare (EXTERNAL)

Strengths	Weaknesses
Randomized, controlled trial	
Study groups very similar before treatment	Costly, cumbersome
Conducted by well-established methodologic rules	Involve limited number of participants
Considered gold standard for assessing efficacy	Often underrepresent key patient groups
Can be registered to prevent selective reporting	Short duration
	Comparator (or placebo) often irrelevant
	May measure surrogate end points rather than clinical outcomes
	Protocol may not reflect typical care

Paziente ideale per EBM e LG

- Uomo
- Giovane-adulto
- Mono-patologia
- Non compromissioni funzionali
- Acute/subacute condition
- Relative short-term treatment/FU
- Effectiveness piuttosto che safety/tolerability
- Placebo-controlled
- Ottima compliance
- Mortality as outcome

- Diversa EBM


SE NE VEDONO DI TUTTI I COLORI.
TUTTA LA GAMMA DAL GRIGIO AL MARRONE.

Dal paziente ideale al mondo reale

- Uomo
- Giovane-adulto (45-60 aa)
- Mono-patologia
- Non compromissioni funzionali
- Acute/subacute condition
- Relative short-term treatment/FU
- Effectiveness
- Placebo-controlled
- Ottima compliance
- Mortality as outcome

- Donna
- (Molto) anziana (75+)
- 3+ patologie
- Disabile e deteriorata
- Condizioni croniche
- Lunghissimo follow-up
- Efficacia e sicurezza
- Irrilevanza del placebo
- Compliance modesta
- Outcome funzionali

Evidence biased medicine

- Elderly are systematically excluded from RCTs
- Even if included, RCTs show comparative efficacy of treatments, for an “average” randomized patient.
- EBM lacks its prerequisite, the medicine based evidence

Sir John Grimley Evans
University of Oxford

Il grande vecchio è davvero un buco nero per la farmacologia clinica?

Gambassi et al. **Giornale di Gerontologia** 1999;47:51-5

The exclusion of older cancer patients from clinical trials

Gambassi et al. **RAYS** 1999;24:26-31

Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals

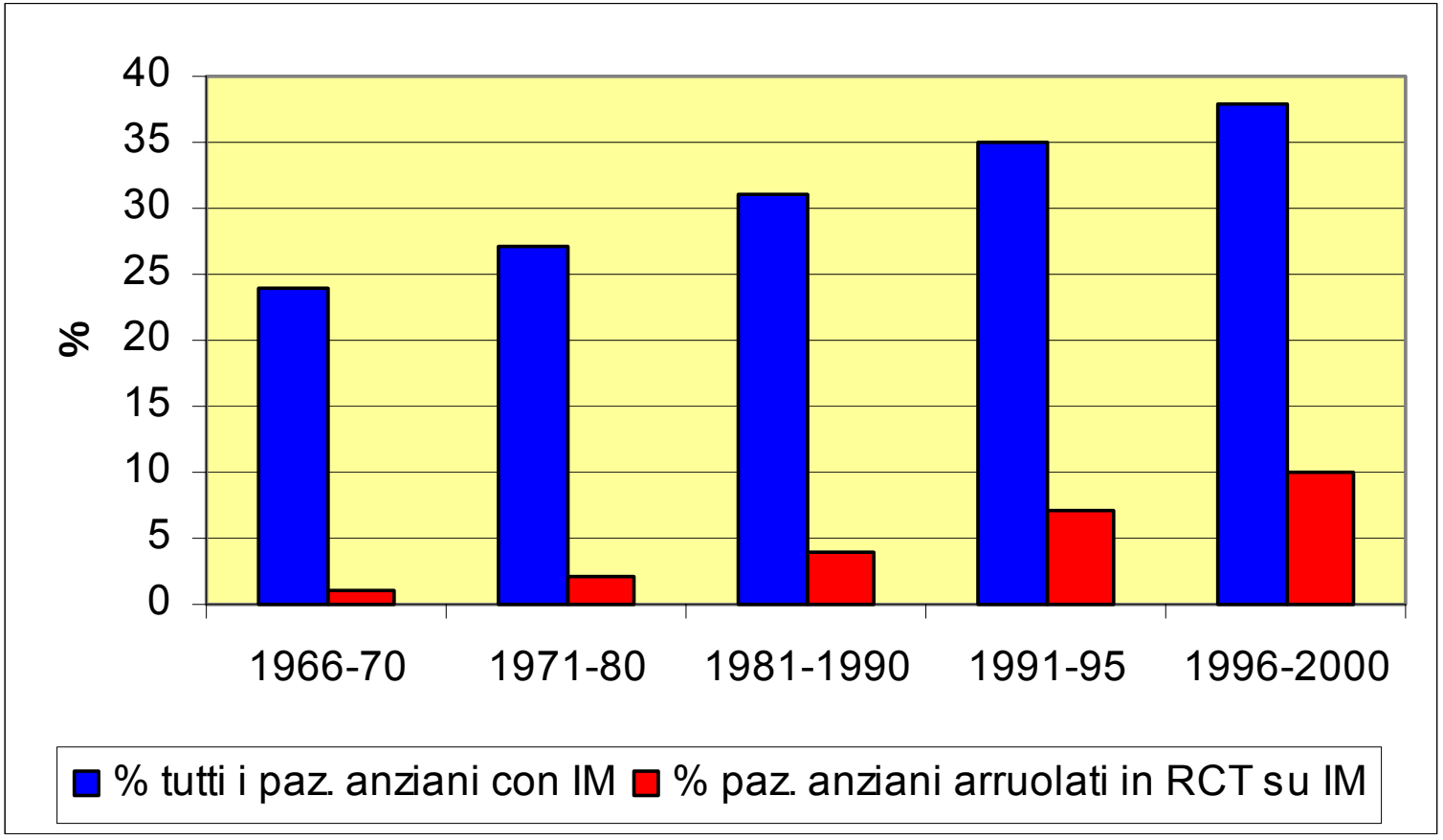
JAMA. 2007;297:1233-1240

- Patients were excluded due to

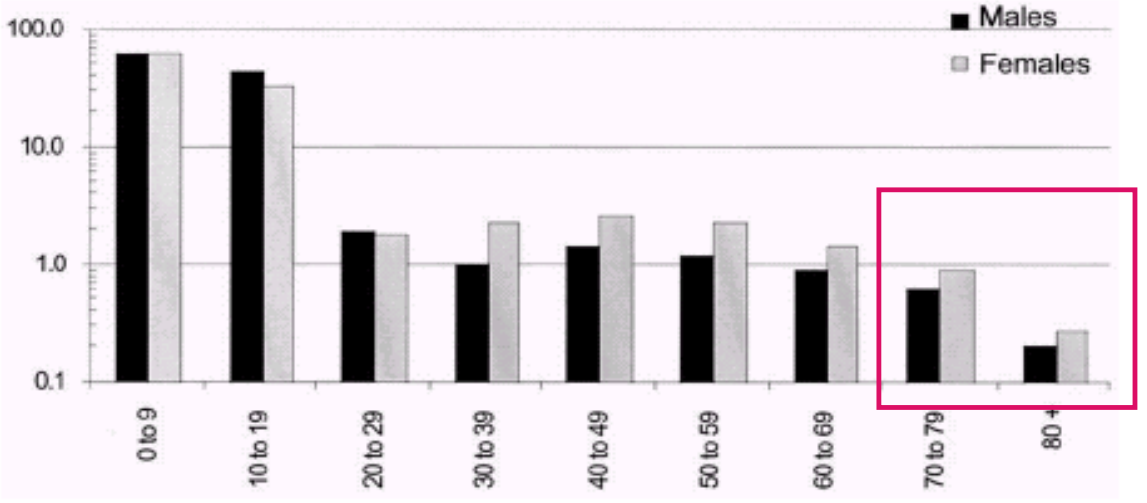
- age	72.1%
- female gender	47.0%
- comorbidities	81.3%
- polypharmacy	54.1%

- Trials with drug interventions were more likely to exclude individuals due to polypharmacy, comorbidities, age and female sex.

Proporzione di pazienti >75 anni in RCT su terapie dell'infarto miocardico, rispetto alla proporzione di anziani affetti nella popolazione generale (Lee PY, JAMA 2001)



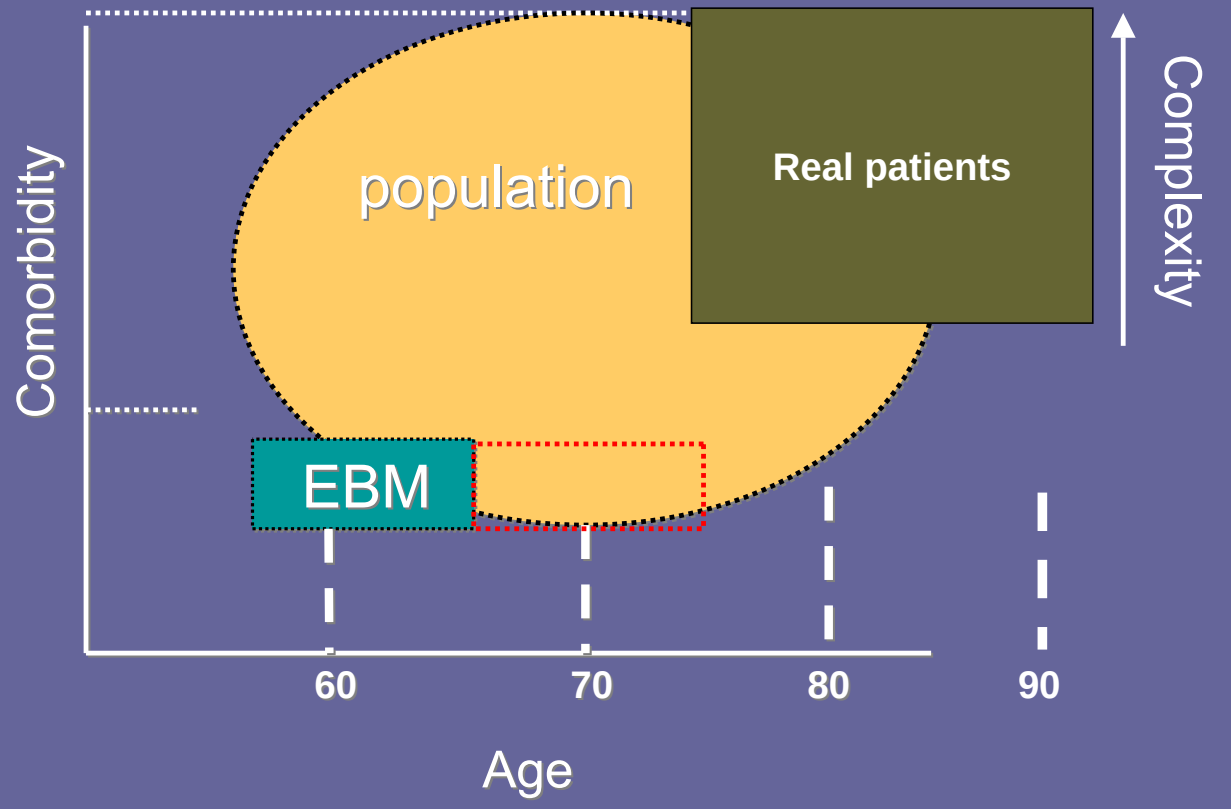
NCI Sponsored Trials



Essentially no data for patients 80+

J Clin Oncol 20:2109-2117, 2002

Evidence-B(i)ased Medicine



- Conseguenze

Multiple health problems in elderly people

The problem is that in health care the specialist medical view predominates. And, as a direct result, multiple diagnoses lead almost inevitably to polypharmacy as each condition is treated in perverse isolation from the others. Research findings are extrapolated from younger age groups and interpreted overoptimistically in the context of what inevitably are limited life expectancies. As a direct result, older people are taking an ever increasing number of prescribed drugs, but because of diminished physiological reserve they are also more susceptible to adverse drug reactions and interactions. Nevertheless, the all too easy accusation of age discrimination means that the limited time available for older people to derive clinical benefit is not seen as a legitimate reason for "underprescribing."

Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid Diseases

	Chronic Disease Addressed by Guideline				
	Diabetes Mellitus[14-32]	Hypertension[36]	Osteoarthritis[33-35]	Osteoporosis[48]	COPD[37,38]
Guideline addressed treatment for type of patient?	Older: yes Multiple comorbidities: yes Both: yes	Older: yes Multiple comorbidities: no Both: no	Older: yes Multiple comorbidities: yes Both: yes†	Older: no Multiple comorbidities: no Both: no	Older: no Multiple comorbidities: no Both: no
Quality of evidence discussed for type of patient?	Older: yes Multiple comorbidities: yes Quality of evidence poor, requires extrapolation for nutrition recommendations	Older: yes Multiple comorbidities: no Quality of evidence good for treating hypertension in older patients	Older: no Multiple comorbidities: no	Older: no Multiple comorbidities: no	Older: no Multiple comorbidities: no
Specific recommendations for patients with 1 comorbid condition?	Yes Diseases: hypercholesterolemia, hypertension, congestive heart failure, chronic kidney disease, cardiovascular disease, peripheral vascular disease, benign prostatic hypertrophy	Yes Diseases: coronary artery disease, diabetes mellitus, metabolic syndrome, sleep apnea, chronic kidney disease, gout, left ventricular hypertrophy, erectile dysfunction, peripheral	Yes Diseases/drugs: anticoagulants, glucocorticoids, peptic ulcer disease, chronic kidney disease, hypertension, congestive heart failure	No	No

JAMA, August 10, 2005—Vol 294, No. 6

Hypothetical 79 yrs old woman
12 meds, 19 doses/day, 5 times/day

N ENGL J MED 351;27 WWW.NEJM.ORG DECEMBER 30, 2004

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Potential Pitfalls of Disease-Specific Guidelines for Patients with Multiple Conditions

Mary E. Tinetti, M.D., Sidney T. Bogardus, Jr., M.D., and Joseph V. Agostini, M.D.

Comment

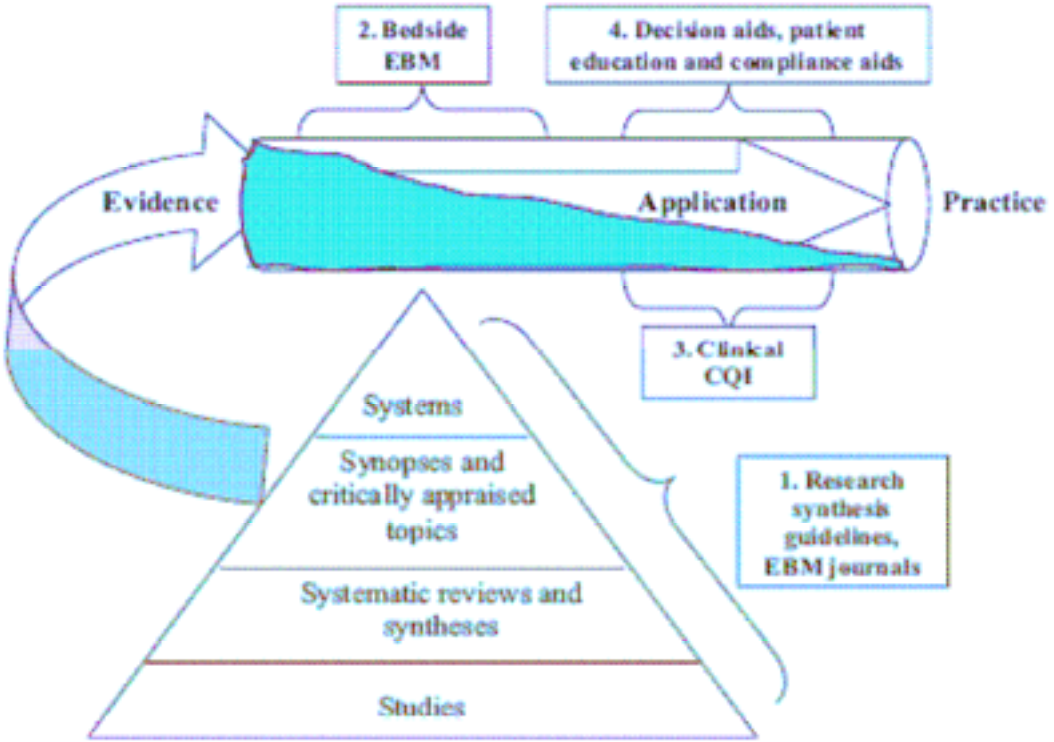
www.thelancet.com Vol 367 February 18, 2006

Comorbidity and guidelines: conflicting interests

SHATTUCK LECTURE

Clinical Research to Clinical Practice — Lost in Translation?

N Engl J Med 2003;349:868-74.



ARTICLE | *Ann Intern Med.* 2008;148:578-586. **Annals of Internal Medicine**

Effect of Unrelated Comorbid Conditions on Hypertension Management

Barbara J. Turner, MD, MSEd; Christopher S. Hollenbeak, PhD; Mark Weiner, MD; Thomas Ten Have, PhD; and Simon S.K. Tang, MPH

Table 1. **Unrelated and Related Comorbid Conditions Reported at Visits**

Variable	Patients, *n* (%)	Visits, *n* (%)
Total	15 459 (100)	70 557 (100)
Number of unrelated comorbid conditions*		
0	786 (5.1)	12 074 (17.1)
1	2035 (13.2)	16 655 (23.6)
2	2816 (18.2)	15 334 (21.7)
3	2827 (18.3)	11 472 (16.2)
4	2507 (16.2)	7097 (10.1)
5	1751 (11.3)	3909 (5.5)
6	1215 (7.9)	1900 (2.7)
≥7	1522 (9.8)	1803 (2.6)
Related comorbid conditions		
Single vascular disease†	2300 (14.9)	7998 (11.3)
Multiple vascular diseases†	873 (5.6)	1927 (2.7)
Diabetes	4943 (32.0)	31 533 (44.7)
Chronic renal insufficiency	999 (6.5)	6969 (9.9)

ARTICLE | *Ann Intern Med.* 2008;148:578-586. **Annals of Internal Medicine**

Effect of Unrelated Comorbid Conditions on Hypertension Management

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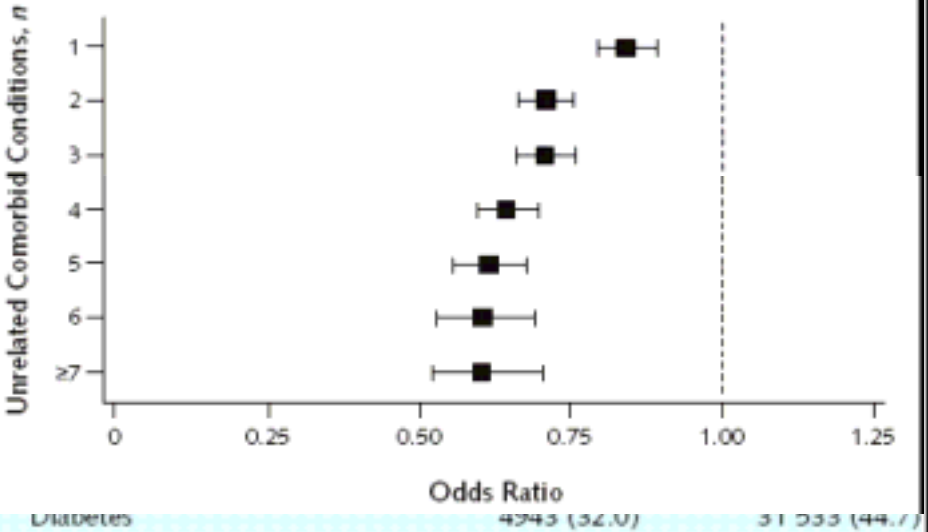
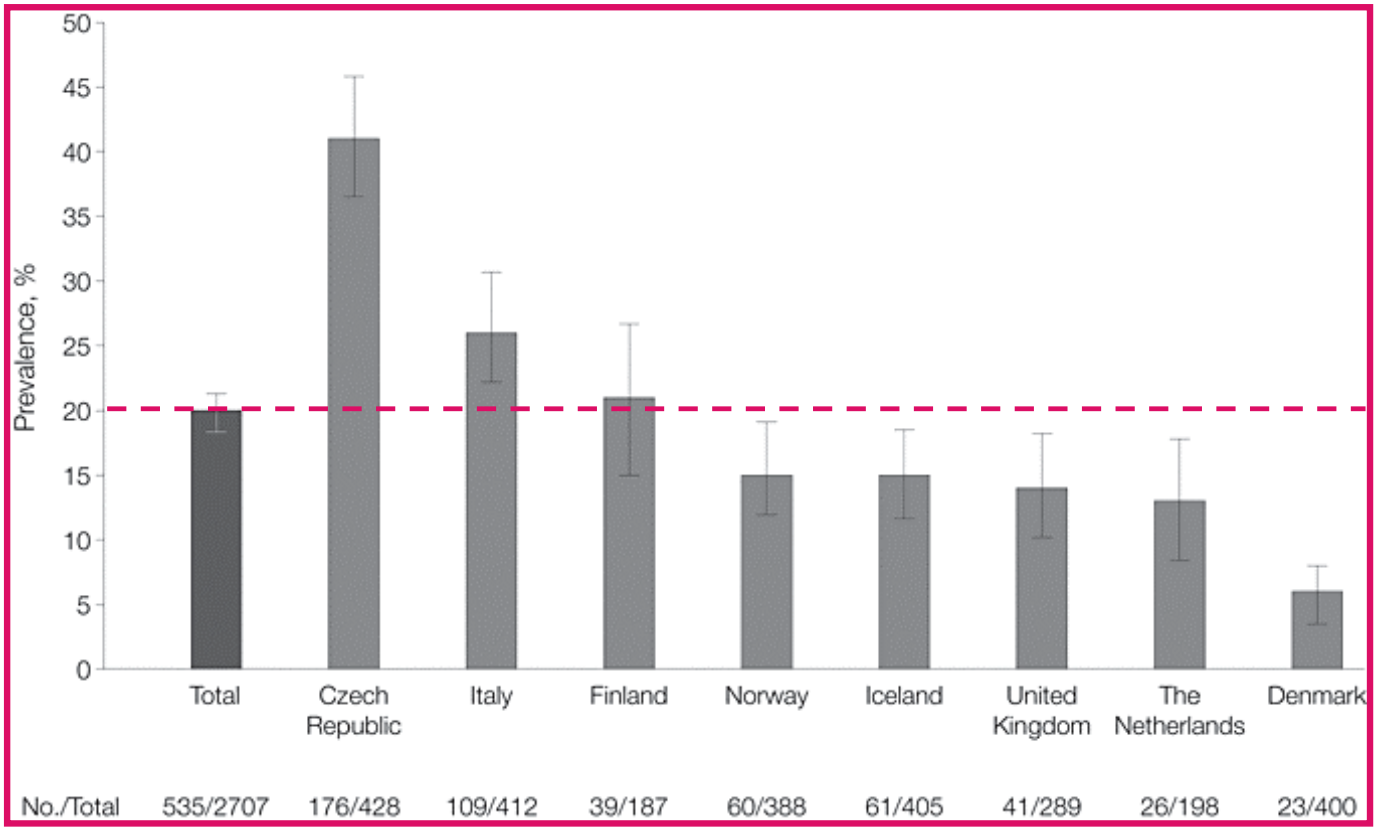
Table 1. **Unrelated and Related Comorbid Conditions Reported at Visits**

Figure 2. **Adjusted association of unrelated comorbid conditions with management of uncontrolled hypertension.**



Diabetes	4943 (32.0)	31 533 (44.7)
Chronic renal insufficiency	999 (6.5)	6969 (9.9)

Prevalence of Inappropriate Medications



Fialova, D. et al. JAMA 2005

JAMA

An "intensifying focus on safety and a diminished tolerance for side effects" by FDA have "dramatically lowered" the chances that experimental medications will reach the market and have led to a recent decrease in approvals of new treatments.

Last year, FDA approved 19 new medications -- the fewest in 24 years -- and announced about 75 new or revised "black box" warnings, twice the number announced in 2004. In addition, the number of approvable letters, which require pharmaceutical companies to submit additional clinical data before FDA will make a decision on whether to approve experimental medications, increased by 40% last year.

G Model
YPHRS-1935; No. of Pages 12
ARTICLE IN PRESS

Pharmacological Research xxx (2008) xxx–xxx

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Use of antipsychotics in elderly patients with dementia: Do atypical and conventional agents have a similar safety profile?

Gianluca Trifirò[a,b], Edoardo Spina[a,b,*], Giovanni Gambassi[c]

- Soluzioni possibili

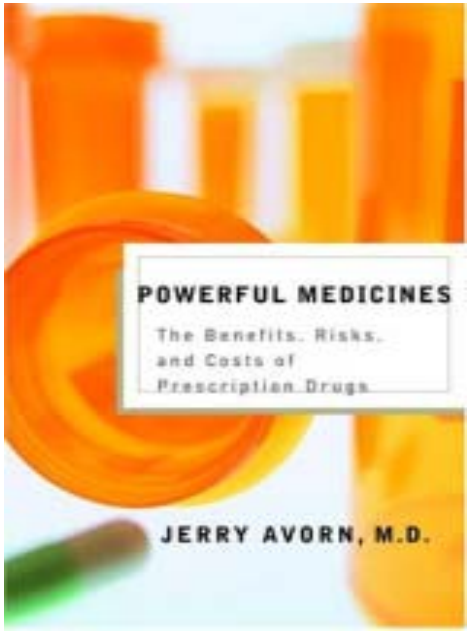
Illusorie

- Extrapolation
- Subgroup analyses
- RCT in the “real world” patients (HYVET)

Reali alternative

- Observational studies

Observational studies



Funai et al.

Distribution of study designs in four major US journals .....

Gynecol Obstet Invest 2001;51:8-1

Observational study

Can involve large numbers of typical patients in settings of routine care	Susceptible to confounding caused by underlying differences among patients treated with different drugs
Can focus on specific vulnerable populations	Confounding (especially due to patient selection and differences in compliance) can generate drug–outcome associations that are not truly causal
Can be performed relatively quickly and at modest cost	Methodologically difficult to do well
Can identify rare adverse events	Difficult to identify selective reporting of findings
Can follow patients over many years	Difficult to require registration
Can compare outcomes of several treatment alternatives	

ONLY CONNECT **Nicholas A Christakis**

Does this work for you?

To say a drug "works" is only half the story

Doctors say that a drug "works" if, in comparison with the control arm of a clinical trial, significantly more people in the treatment arm respond. Unfortunately, this is a naive oversimplification, and it breeds

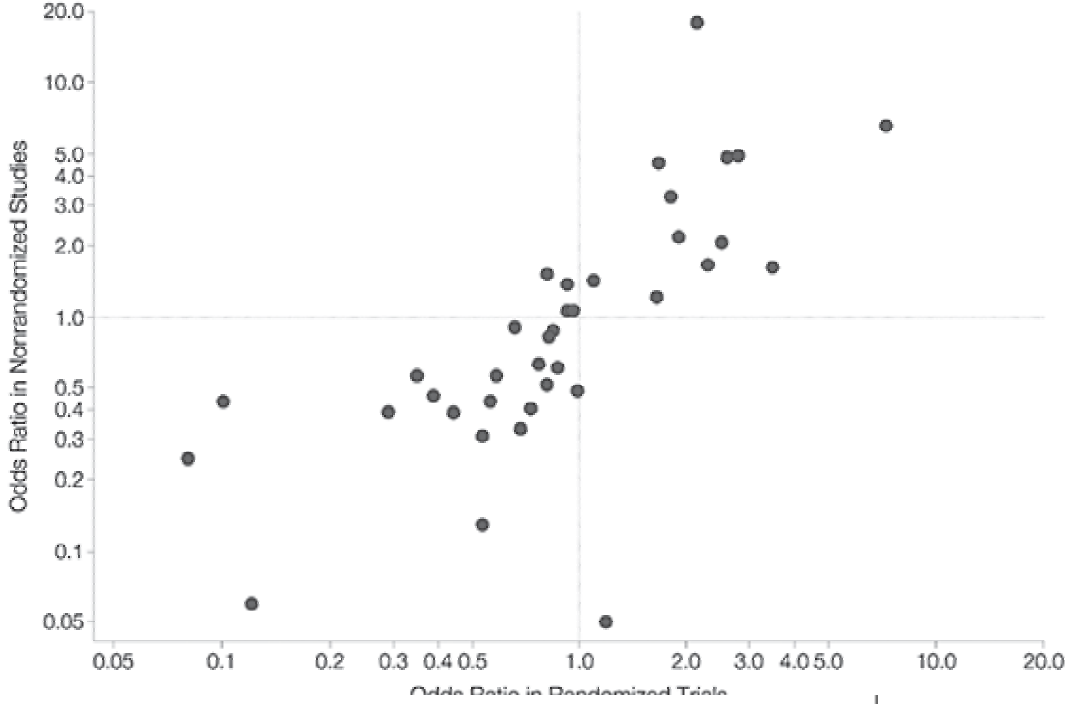
My point is not that drugs evaluated in randomised controlled trials are not terrific. They are. And the scientific evidence for their efficacy is impressive. Rather, the problem is that patients and doctors lose sight of what trials actually show and either have false expectations of drugs' effectiveness or are unaware that they should be vigilant about the possibility that the drug may have no effect whatsoever in any one person and hence fail to consider the need to switch or stop taking the drug.

variation. Because the original clinical trials showing that drugs work are rarely powered to look at variation in observable factors, post-marketing observational studies are needed to determine which patients, on average, do or do not respond.

JAMA®

Comparison of Evidence of Treatment Effects in Randomized and Nonrandomized Studies

Vol. 286, August 15, 2001



VIEWPOINT

When are observational studies as credible as randomised trials?

THE LANCET • Vol 363 • May 22, 2004 • www.thelancet.com

Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies

CMAJ · FEBRUARY 28, 2006 · 174(5)

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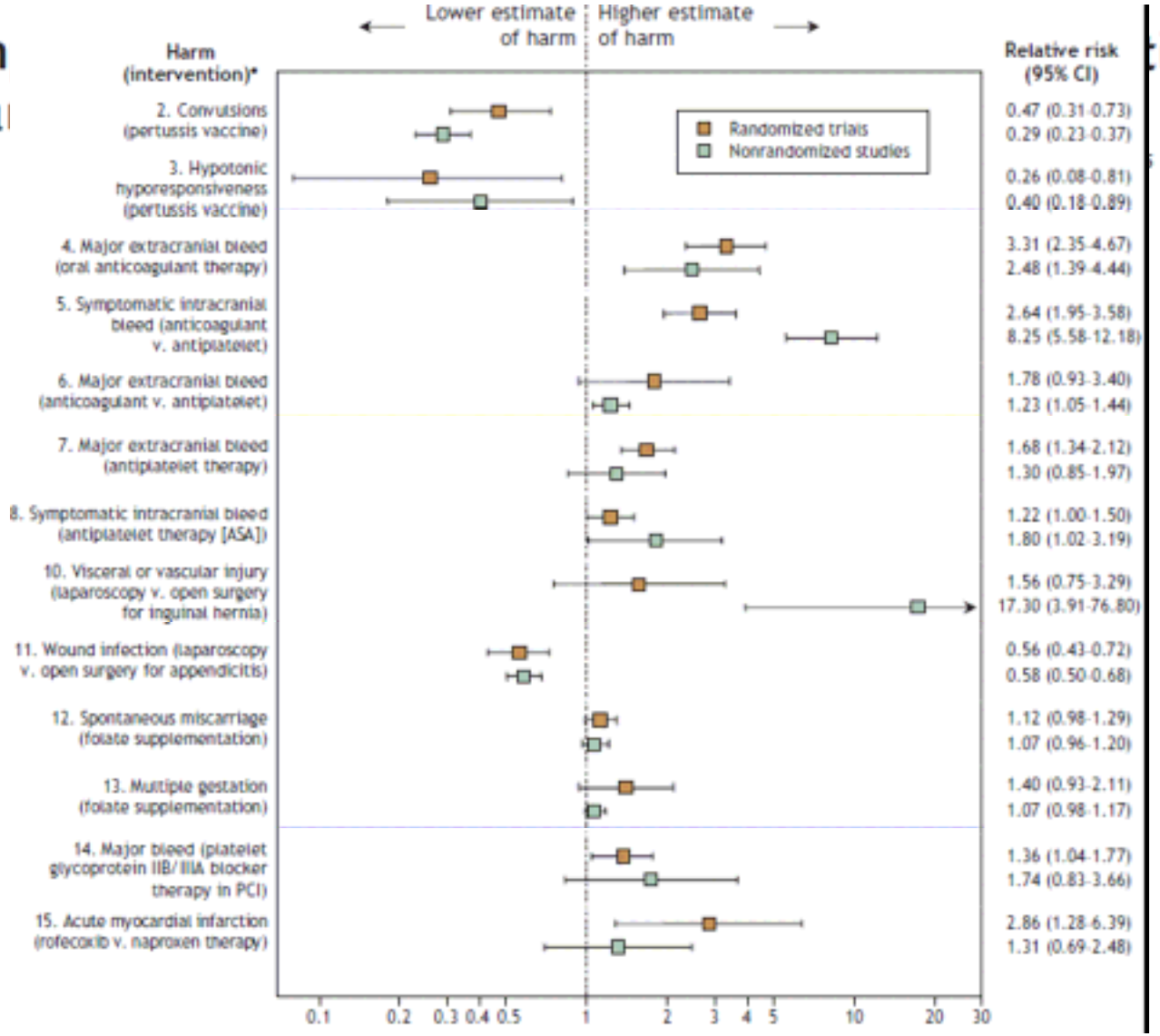
· 174(5)



JAMA®

Online article and related content
current as of November 27, 2008.

Benefits and Risks of Drug Treatments: How to Combine the Best Evidence on Benefits With the Best Data About Adverse Effects

Jan P. Vandenbroucke; Bruce M. Psaty

However, for a future that combines benefit and harms assessment, systematic reviews will need to incorporate and integrate the best information from both randomized trials and observational studies.

The greatest challenge ahead is that 2 disciplines should be combined: the world of systematic reviews that uses tight protocols to retrieve and pool evidence about benefits from randomized trials and the world of pharmacoepidemiology that uses observational epidemiology to identify harms and is often deeply preoccupied with the finer points of causal reasoning. The 2 fields are populated by different individuals who publish in different journals and use different textbooks and approaches. Epidemiology uses techniques such as confounder scores, propensity scores, or instrumental variable analysis that are unnecessary in the analysis of data from randomized controlled trials. Reviews about harms will often take the form of deliberations about likely biases and confounders and how these were met, or not, in various studies. That information is an essential part of the evidence base.

In Defense of Pharmacoepidemiology — Embracing the Yin and Yang of Drug Research

Jerry Avorn, M.D.

Pharmacoepidemiology is still in its adolescence, with all the characteristics that implies: expansive energy, huge potential, limited experience, a sense of infallibility, accident-proneness, and occasionally impaired judgment. Many of us who work in this area recognize the need to advance the discipline's methodologic sophistication to prevent the sort of glib conclusions that have bedeviled the field; that arcane work is making important strides.

We forget how difficult it was to establish the rules of the road for conducting randomized trials. In terms of design theory and pubic policy, drug-epidemiology research is now where randomized trials were in the 1950s. We have much to learn about methods, transparency, and protecting the public's interest. But that work can be done, and we often have no other way of gathering vital insights.

N ENGL J MED 357;22 WWW.NEJM.ORG NOVEMBER 29, 2007

In Defense of Pharmacoepidemiology — Embracing the Yin and Yang of Drug Research

Jerry Avorn, M.D.

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- Futuro

Improving the reporting of pragmatic trials: an extension of the CONSORT statement

	Explanatory attitude	Pragmatic attitude
Question	Efficacy—can the intervention work?	Effectiveness—does the intervention work when used in normal practice?
Setting	Well resourced, "ideal" setting	Normal practice
Participants	Highly selected. Poorly adherent participants and those with conditions which might dilute the effect are often excluded	Little or no selection beyond the clinical indication of interest
Intervention	Strictly enforced and adherence is monitored closely	Applied flexibly as it would be in normal practice
Outcomes	Often short term surrogates or process measures	Directly relevant to participants, funders, communities, and healthcare practitioners
Relevance to practice	Indirect—little effort made to match design of trial to decision making needs of those in usual setting in which intervention will be implemented	Direct—trial is designed to meet needs of those making decisions about treatment options in setting in which intervention will be implemented

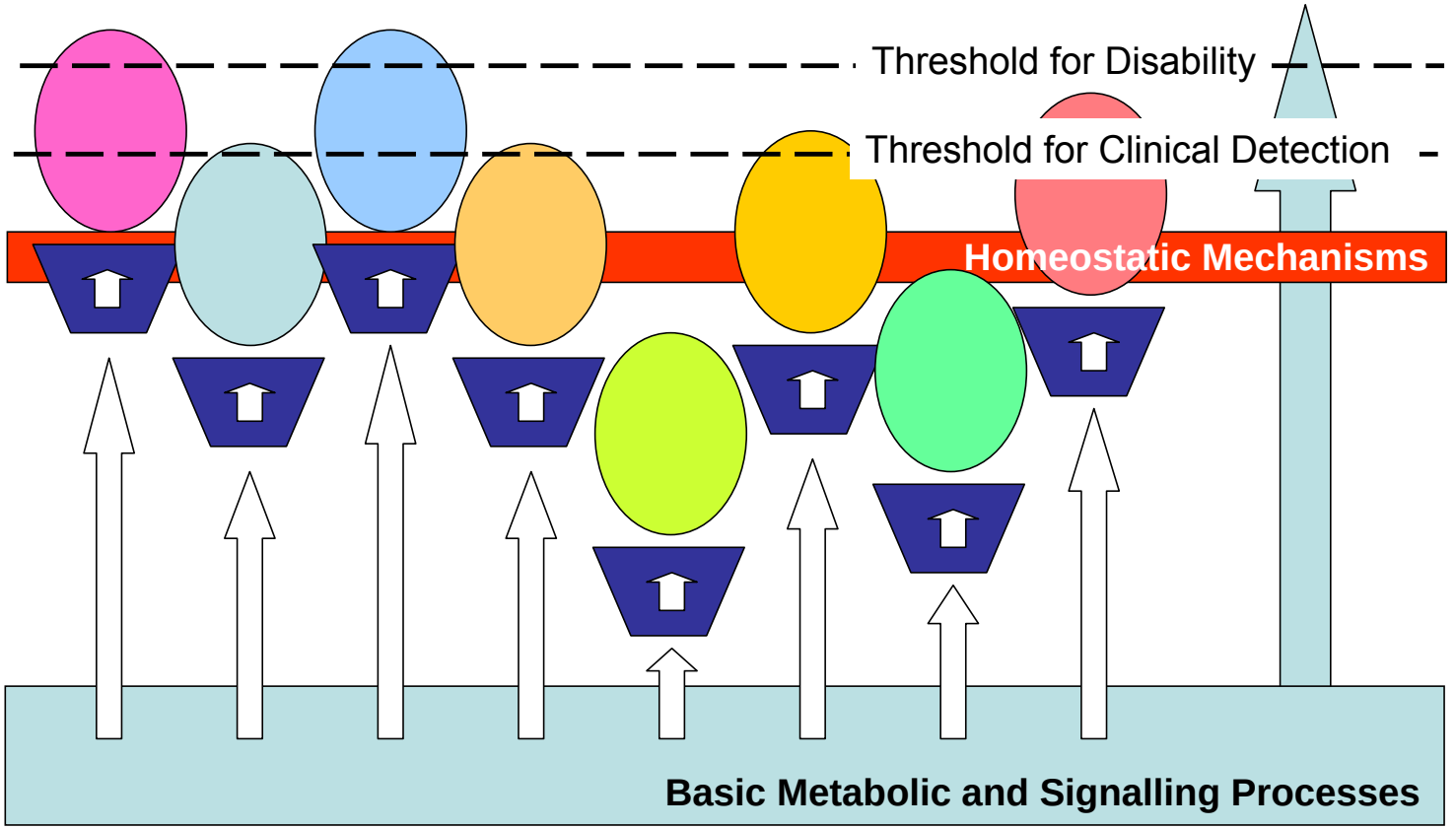
A systematic look at an old problem

Thomas B. L. Kirkwood

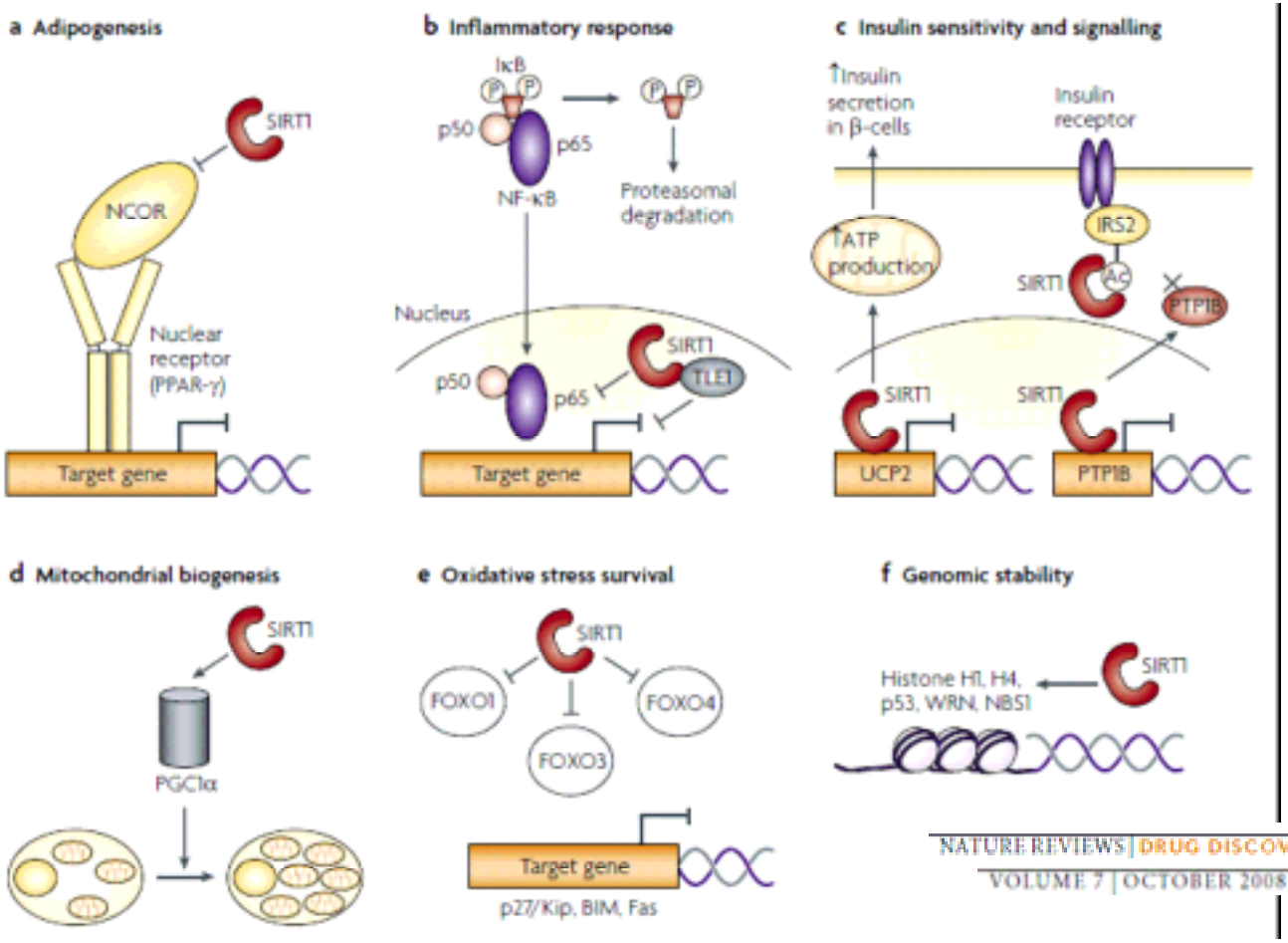
NATURE|Vol 451|7 February 2008

As life expectancy increases, a systems-biology approach is needed to ensure that we have a healthy old age.

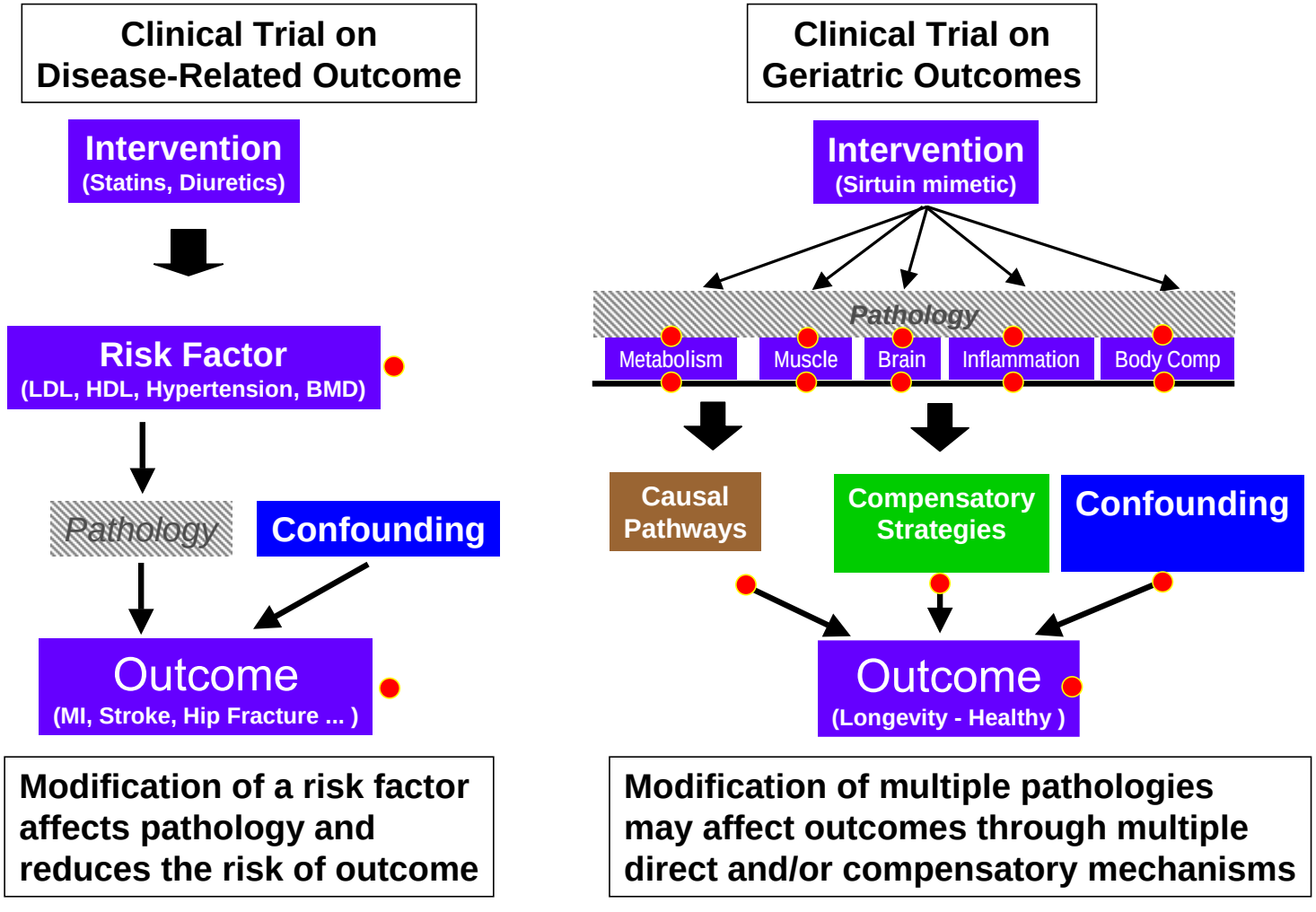
The Homeostatic Model



Sirtuins — novel therapeutic targets to treat age-associated diseases



NATURE REVIEWS | DRUG DISCOVERY
VOLUME 7 | OCTOBER 2008


Clinical Trial on Disease-Related Outcome
Intervention
(Statins, Diuretics)
Risk Factor
(LDL, HDL, Hypertension, BMD)
Pathology
Confounding
Outcome
(MI, Stroke, Hip Fracture ...)
Modification of a risk factor affects pathology and reduces the risk of outcome
Clinical Trial on Geriatric Outcomes
Intervention
(Sirtuin mimetic)
Pathology
Metabolism
Muscle
Brain
Inflammation
Body Comp
Causal Pathways
Compensatory Strategies
Confounding
Outcome
(Longevity - Healthy)
Modification of multiple pathologies may affect outcomes through multiple direct and/or compensatory mechanisms


HOPE
CHANGE
Endorses
Barack
Obama
for President of the
United States of America
"YES WE CAN"

Adding Value to Evidence-Based Clinical Guidelines

JAMA, August 10, 2005—Vol 294, No. 6

From the perspective of a patient, value is maximized by preferentially implementing clinical actions that have maximal clinical benefit to that individual. This is especially important for frail elderly patients with multiple chronic conditions, who may be unable or unwilling to tolerate, afford, or adhere to a large number of pharmacological and lifestyle interventions over long periods. Barton[3] compared the

COMMENTARY

JAMA, July 23/30, 2008—Vol 300, No. 4

The Next Step in Guideline Development

Incorporating Patient Preferences

CLINICAL INVESTIGATIONS

J Am Geriatr Soc 2008.

Views of Older Persons with Multiple Morbidities on Competing Outcomes and Clinical Decision-Making

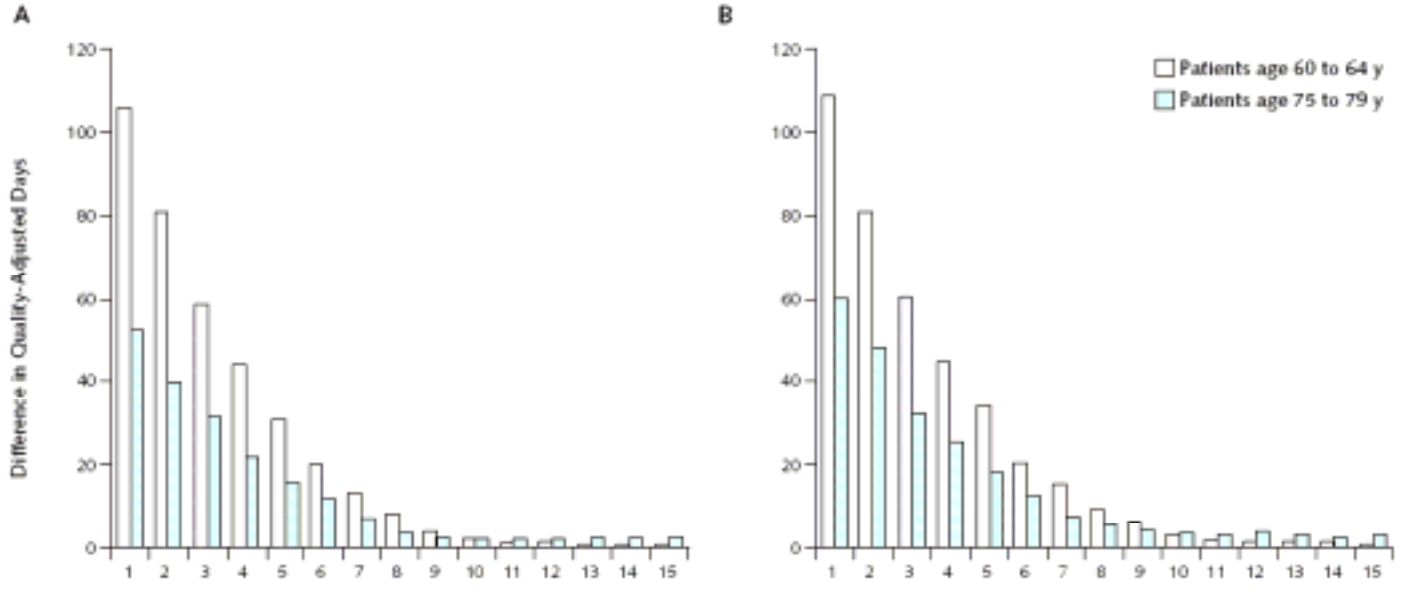
Terri R. Fried, MD,[*†] *Sarah McGraw, PhD,*[‡] *Joseph V. Agostini, MD,*[*†] *and Mary E. Tinetti, MD*[*]

CONCLUSION: Because of their experience with adverse medication effects, older persons with multiple morbidities can understand the concept of competing outcomes. The task of prioritizing global, cross-disease outcomes can help to clarify what is most important to seniors who are faced with complex healthcare decisions.

The Effect of Comorbid Illness and Functional Status on the Expected Benefits of Intensive Glucose Control in Older Patients with Type 2 Diabetes: A Decision Analysis

Ann Intern Med. 2008;149:11-19. 1 July 2008

Figure 2. Expected quality-of-life benefits of intensive glucose control for patients age 60 to 64 years and 75 to 79 years.



The art of medicine

Narrative evidence based medicine

We are coming to see that the three fundamental tensions upon which medicine finds itself—known/unknown, universal/particular, body/self—are reflected in the three circles of EBM. Clinical evidence examines the known and unknown. Clinical circumstances integrate the universal and particular. Patients' values speak to both body and self. By virtue of its capacity to recognise the tensions fully, narrative medicine can lend to evidence-based medicine the *methods* of respecting its three circles of attention. It is not through dearth of desire but dearth of methods that EBM has yet to achieve attention to all three circles. With narrative medicine's methods, EBM can indeed be true to all its promises.

Should geriatric medicine remain a specialty?

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True generalists are needed

Workforce reports across the world show increasing problems attracting trainees to geriatric medicine.[17 18] Faced with the rising tide of patients with comorbidities, disabilities, and frailty there has been a renewed impetus to increase the number of generalists in hospitals. The United States has created the hospitalist movement, and the Royal Australasian College of Physicians advocates for a return to generalism.[19 20] All of these staff require an understanding of geriatric principles, but singular geriatric training may no longer provide a doctor with the skills needed to manage older patients who require evidence based therapy for a wide range of conditions.

Advocacy, innovation, and teaching of health care for elderly people need enthusiastic supporters. However, specialised geriatric training may be neither necessary nor sufficient for such a role. Our challenge is to continue to incorporate the lessons of these pioneers in aged care into everyday clinical practice.

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