

The Promise and Peril of Evidence-Based Guidelines – a US Physician’s Cautionary Tale

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Outline

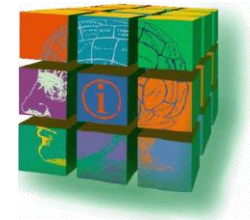
- The promise of evidence-based guidelines
- Problems not insurmountable
- Physicians do not follow guidelines
- Influence of vested interests on evidence creation
- Influence of vested interests on guideline development
- Better guidelines for guideline development: the Institute of Medicine



- Developed using the evidence-based medicine process should
 - Improve quality
 - Control costs
- “In the next decade, medical practice guidelines will be vigorously promoted as a means for improving the effectiveness of the U.S. health care system.” [1990]
- Audet AM et al. Ann Int Med 1990; 113: 709.

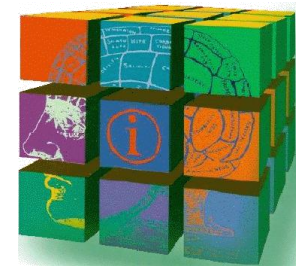


- **Medicine based on the systematic search for and systematic, critical review of the best available evidence**
- **The integration of best research evidence with clinical expertise and patient values**
- **The underlying goal is to maximize the likelihood of benefit and minimize the likelihood of harm for each patient, according to the patient's values**



The Evidence Based Medicine Process

- Pick important clinical problem that affects defined population
- Identify possible management options, and their possible outcomes
- Systematic search for the best possible evidence
- Critical review of each study
- Assess outcome probabilities (for each option)
- Assess values (utilities) of possible outcomes
- Combine probabilities and values to determine option with most favorable benefit vs harm, or highest expected utility



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- Physicians' misconceptions about EBM → teach them
- Capacity issues:
 - Lack of clinical evidence about important questions → do more studies
 - Lack of access to the data → the internet
- Physicians' are not used to thinking and making decisions according to EBM → teach them



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- Failure to use treatments whose benefits clearly outweigh harms
 - ASA, beta-blocker post MI
 - Angiotensin converting enzyme inhibitors (ACEI's) for CHF with systolic dysfunction
 - Flu and pneumonia vaccines
 - Antidepressants for depression
- Use of treatments whose benefits do not clearly outweigh harms
 - Calcium channel blockers for congestive heart failure (CHF) with systolic dysfunction



1995 – We started to teach a course...

- We assumed...
 - The evidence base would grow as more and better clinical research would be published about an increasing number of clinical problems
 - More evidence-based guidelines would appear
 - Clinicians would become more familiar and comfortable with evidence-based medicine
 - Clinical practice would become more evidence-based
- And based a course about persuading physicians to practice more in accord with evidence-based guidelines based on these assumptions



Things didn't turn out the way we expected...

- The evidence base grew, but
 - the quality of the research did not improve
 - many important clinical problems were not addressed, e.g., lack of comparative effectiveness research, that is, studies comparing credible alternatives
- More guidelines appeared, but most were not rigorously evidence-based
- Clinicians did not become more familiar and comfortable with evidence-based medicine
- Clinical practice was not more evidence-based
- Clinicians became less interested in cooperating with our studies, and more resistant of attempts to change their behavior



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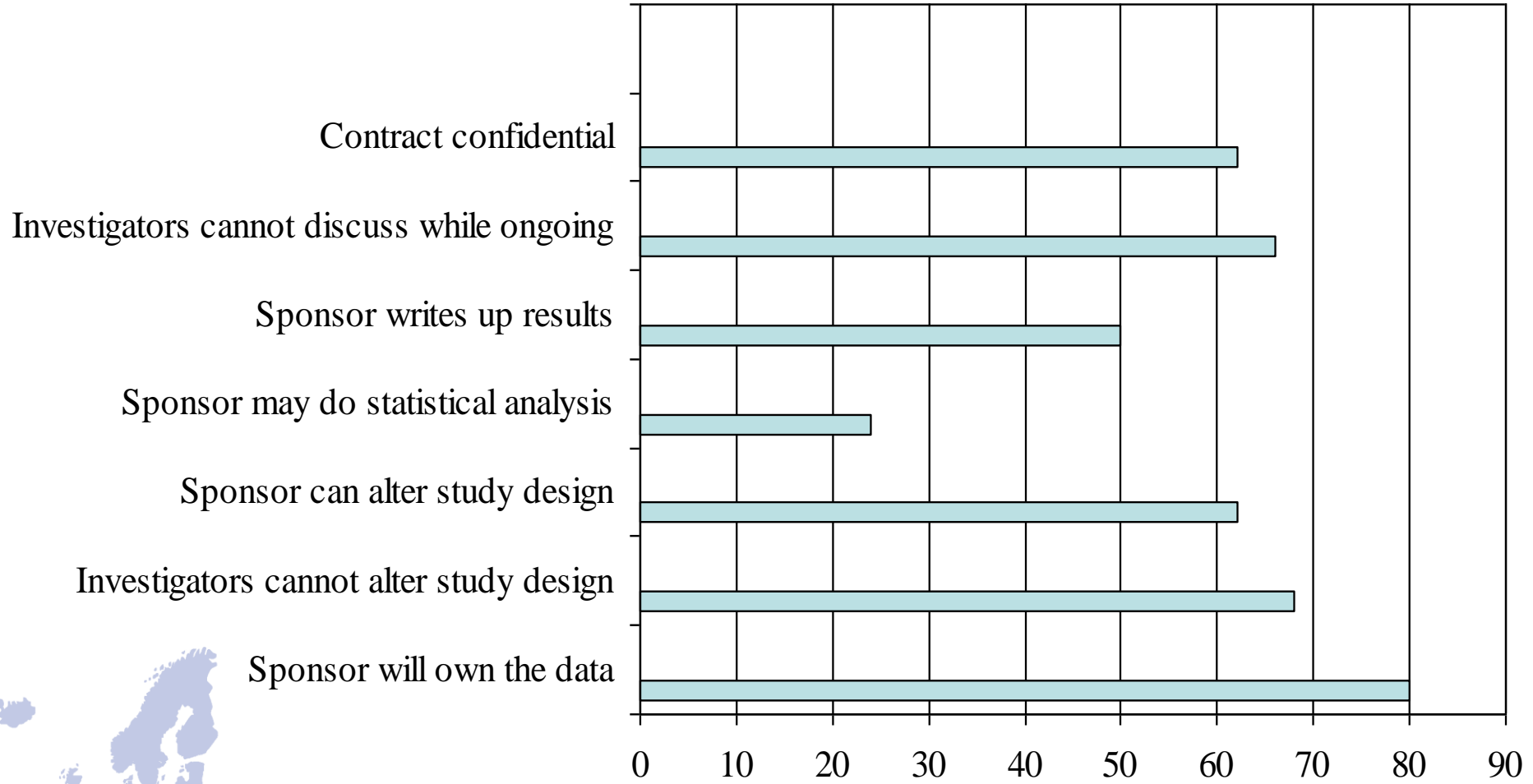
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- Clinical research, especially assessing tests or treatments, increasingly sponsored and controlled by organizations with vested interests in the results of the research turning out in a certain way
- Such organizations include:
 - Pharmaceutical companies, biotechnology companies, device companies, (insurance companies, government agencies)



Academic Research Administrators Finding Contract Provisions Acceptable



Mello MM. NEJM 2005; 152: 21

Bias in Commercially Sponsored Research?

- Multiple studies about how commercial sponsorship relates to results favoring the sponsors' products
- Two systematic reviews in 2003 showed commercial sponsorship predicted positive results
- Pooled odds ratios of sponsorship as predictor of positive results:
 - 3.60 (95% CI 2.63, 4.91)(1)
 - 4.05 (2.98, 5.51)(2)
- Bekelman JE et al. JAMA 2003; 289: 454. Lexchin J et al. BMJ 2003;326: 1167



- Reviewed 57 publications 2002-09
- 26 studies compared conclusions of drug trials according to sponsorship:
 - 23/26 “positive correlation between the financing of the study by pharmaceutical companies and/or conflicts of interest on the part of the authors and results or conclusions that were favorable to the sponsor”
 - 4/26 showed that the studies’ findings were “interpreted favorably towards the pharmaceutical concern that funded the study”
- Schott G et al. *Arztebl Int* 2010; 107: 279



- **Study Population**
 - Select a study population unlikely to have adverse outcomes, but unrepresentative of patients who might use the treatment
 - Keep the trial too small to detect adverse effects of treatment
- **Alternative Treatment**
 - Compare the treatment to one known to be inferior
 - Use a dosage of the comparison treatment that is too low (so it won't work), or too high (so it will have side effects)
- Smith R. PLoS Med 2006; 2: 364. Brophy JM. JAMA 2005; 294: 2633. Psaty BM et al. JAMA 2008; 209: 1813.



- **Measurement**

- Use multiple endpoints in the trial, but pick the ones that shows a favorable result
- Use composite endpoints related to possible benefits to increase the likelihood of finding a statistically significant effect
- Use individual endpoints related to possible harms to decrease the likelihood of finding a statistically significant effect
- Use intermediate outcomes (e.g., laboratory tests) rather than clinical outcomes

- **Analysis**

- Drop patients with unfavorable outcomes
- Do multi-center trials, but use only results from the centers with favorable outcomes for the product
- Do multiple sub-group analysis, but only publish those with favorable results
- Do “on-treatment” rather than intention-to-treat analysis of adverse events, thus omitting events that occur after treatment stops



Reporting Bias Affecting Clinical Studies

- (Any) Publication
- Time lag
- (Single or) Multiple Publication
- Location (within journals, or media)
- Citation
- Language
 - All can depend on nature and direction of results



- “Identified reporting bias in 40 indications comprising about 50 different interventions”
 - Mental / behavioral: depression, SSRIs, newer antidepressants, bipolar disorder (lamotrigine, gabapentin), schizophrenia (quetiapine), panic disorder (paroxetine)
 - Nervous system: Alzheimer’s disease (rofecoxib), acute pain (valdecoxib), migraine (gabapentin)
 - Circulatory: coronary heart disease (aprotonin), arrhythmia (class I anti-arrhythmics)
 - Digestive: irritable bowel syndrome (alosetron)
 - Genitourinary: incontinence (duloxetine)
 - Musculoskeletal: osteoarthritis (rofecoxib, celecoxib)
 - Skin: atopic dermatitis (evening primrose oil)
 - Endocrine and metabolic: diabetes (rosiglitazone), hypercholesterolemia (ezetimibe and simvastatin, cerivastatin), thyroid (levothyroxine), menopause (tibolone)
 - Neoplasms: ovarian cancer (combination chemotherapy), multiple myeloma (combination chemotherapy)
 - Blood: thalassemia major (iron-chelation agents)
 - Infections: influenza (oseltamivir), HIV/AIDS (anti-HIV agents)
 - Acute trauma: spinal cord injury (high-dose steroids), shock (albumin)
 - Vaccinations: HIV-2 vaccine, cancer vaccines
 - Other: nocturnal leg cramps (quinine)
- McGauran N et al. *Trials* 2010: 11:37



- 6% of faculty admitted delaying publication of undesirable results[1]
- Anonymous cases of articles withdrawn because results “ran counter to financial interests and strong beliefs.”[2]
- Other older famous cases
 - Betty Dong, UCSF, “thyroid storm”
 - David Kern, Brown, flock lung
 - Nancy Olivieri, U of Toronto, defirapone
- 1. Blumenthal D et al. JAMA 1997; 277: 1224. Bodenheimer T. NEJM 2000; 342: 1539.



Suppression of Research - II

- Celebrex (celecoxib, Pfizer) – 12-month CLASS trial data showing no benefits suppressed
- Vioxx (rofecoxib, Merck) – adverse cardiovascular event data from VIGOR suppressed
- Ventak Prism ICD (Guidant) – data on failures due to short circuits suppressed
- Famvir (famcyclovir, Novartis) – data possibly unfavorable to drug suppressed
- Traysylol (aprotinin, Bayer) – observational study showing increased adverse event rate suppressed
- Avandia (rosiglitazone, GlaxoSmithKline) – trials whose combined data suggested increased cardiovascular risk suppressed
- SSRIs – 31% of pharma supported registered trials, mainly negative, never published



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- Organizations with vested interests in promoting products or services may
 - Fund guideline development
 - Have financial relationships with organizations that develop guidelines
 - Have financial relationships with individuals involved in guideline development
- Could this be related to poor methodological quality of guideline development?



Conflicts of Interest in Guideline Development

- Studied 17 cardiovascular guidelines
- 56% of 498 individual involved in development had conflict of interest
 - 63% of guideline committee members
 - 81% of chairs/co-chairs/first authors
- Per guideline, range of proportions of conflicted participants: 13-85%
- Most participants in development of single guideline with COI due to relationships with a single company: 21 with relationships with Medtronic for device therapy guideline
- Mendelson TB et al. Arch Int Me 2011; 171: 577



Published Guidelines Not Based on EBM

- 279 guidelines published 1985-97: 43% adherence to evidence-based medicine principles(1)
- 27 cardiovascular prevention guidelines published 2003-10: 10/27 (37%) had rigor score <50%(2)
- 1. Shaneyfelt TM et al. JAMA 1999; 281: 1900. 2. Ferget BS et al. Arch Int Med 2010; 170: 27



- Recommendations from 16 cardiovascular guidelines new or revised after 2007:
 - 11% based on A level evidence (multiple controlled trials)
 - 41% B (single trial or observational studies)
 - 48% C (expert opinion)
- 41 infectious disease guidelines current as of 2010:
 - 15% based on level I (one or more controlled trials)
 - 35% II (observational studies)
 - 50% III (expert opinion)
- Tricoci P et al JAMA 2009; 301: 831. Lee DH. Arch Int Me 2011; 171: 18



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- Based on systematic review of the existing evidence
- Developed by knowledgeable, multidisciplinary panel of experts and representatives from key affected groups
- Consider important patient subgroups and patients preferences
- Based on explicit and transparent process that minimizes distortion, biases, and conflicts of interest
- Provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of recommendations
- Reconsidered and revised as appropriate when important new evidence warrants modifications of the recommendations



Summary

- Trustworthy, truly evidence-based guidelines if implemented potentially could increase quality and lower costs
- Physicians are currently reluctant to follow guidelines
- Most guidelines developed to date are not evidence-based, or are not based on good evidence
- Most guidelines developed to date may be influenced by conflicts of interest
- Better, more trustworthy guideline development may lead to more widespread implementation

