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
Evidence-Based Guidelines

- 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]

Evidence Based Medicine

- 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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(Not Insurmountable) Barriers to Evidence-Based Guidelines

- 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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Doctors Don’t Follow Guidelines

- 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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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)

- Contract confidential
- Investigators cannot discuss while ongoing
- Sponsor writes up results
- Sponsor may do statistical analysis
- Sponsor can alter study design
- Investigators cannot alter study design
- Sponsor will own the data

Mello MM. NEJM 2005; 152: 21
• 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)

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”

Tactics to Increase Likelihood of Favorable Results

- **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)

Tactics to Increase Likelihood of Favorable Results - II

• **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
Review of Reporting Bias

• “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 (aprotinin), arrhythmia (class I anti-arrhythmics)
  – Digestive: irritable bowel syndrome (alosetron)
  – Genitourinary: incontinence (duloxetine)
  – Musculoskeletal: osteoarthritis (refocoxib, celecoxib)
  – Skin: atopic dermatitis (evening primrose oil)
  – Endocrine and metabolic: diabetes (rosiglitazone), hypercholesterolemia (ezetimibe and simvastatin, ceruivastatin), 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
Suppression of Research

- 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

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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Influence of Vested Interests on Guideline Development

- 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
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)

Published Guidelines Based More on Opinions Than Evidence

- 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)

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IOM - “Clinical Practice Guidelines We Can Trust”

- 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