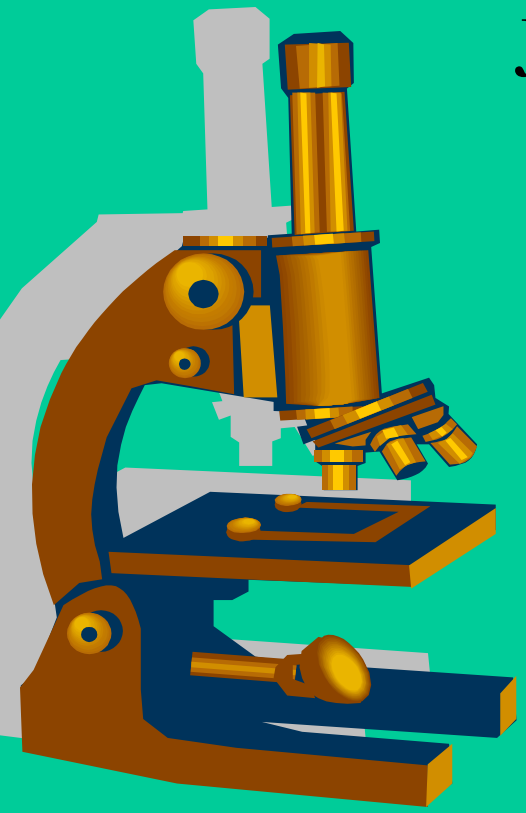
Evidence Based Medicine in Mental Health



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Dr. Ellison wishes to thank the ASCP for its support and Drs. David Osser and Stuart Carney for helpful input on this topic.

Question 1

Evidence Based Medicine emphasizes all but which of the following:

A. Use of current evidence
B. Use of best available evidence
C. Reliance on anecdotal experience
D. Integrating research evidence with individual patients' values
E. Practical application of statistical and epidemiological concepts

Question 2

Among the following, the least likely source for current evidence-based information is:

A. Last month's journals
B. Your 1995 textbook
C. Cochrane reviews
D. Medline
E. ACP Journal Club

Question 3

Which of the following represents the highest level in the evidence hierarchy?

A. Anecdotal letter to editor
B. Case series
C. Randomized controlled trial
D. Systematic review of RCTs
E. Epidemiologic study

Question 4

Effect size is measured by which of the following:

A. p-value
B. Number needed to treat (NNT)
C. Intention to treat analysis
D. Coreopsis parameters
E. Confidence interval

Question 5

Precision of results is measured by which of the following:

A. p-value
B. Number needed to treat (NNT)
C. Intention to treat analysis
D. Coreopsis parameters
E. Confidence interval

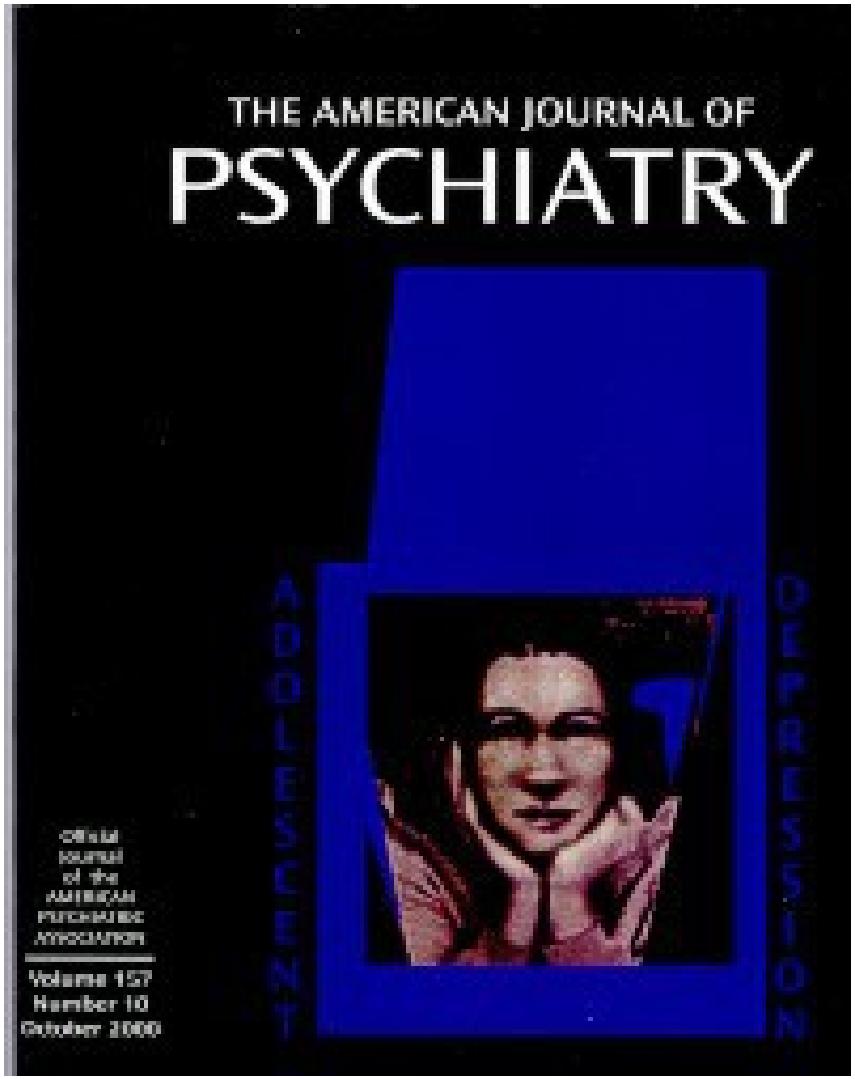
Major Teaching Points

- EBM provides clinicians with a strategy for coping with the overwhelming amount of data that floods all conscientious clinicians.
- EBM provides a systematic way for formulating clinical questions, structuring the search for information, and integrating the best available data with a patient's needs and values to arrive at optimal treatment decisions.
- Data bases, evaluation tools, and algorithms available over the internet can facilitate adoption of EBM methods and save valuable time while improving patient care.

Brief Outline

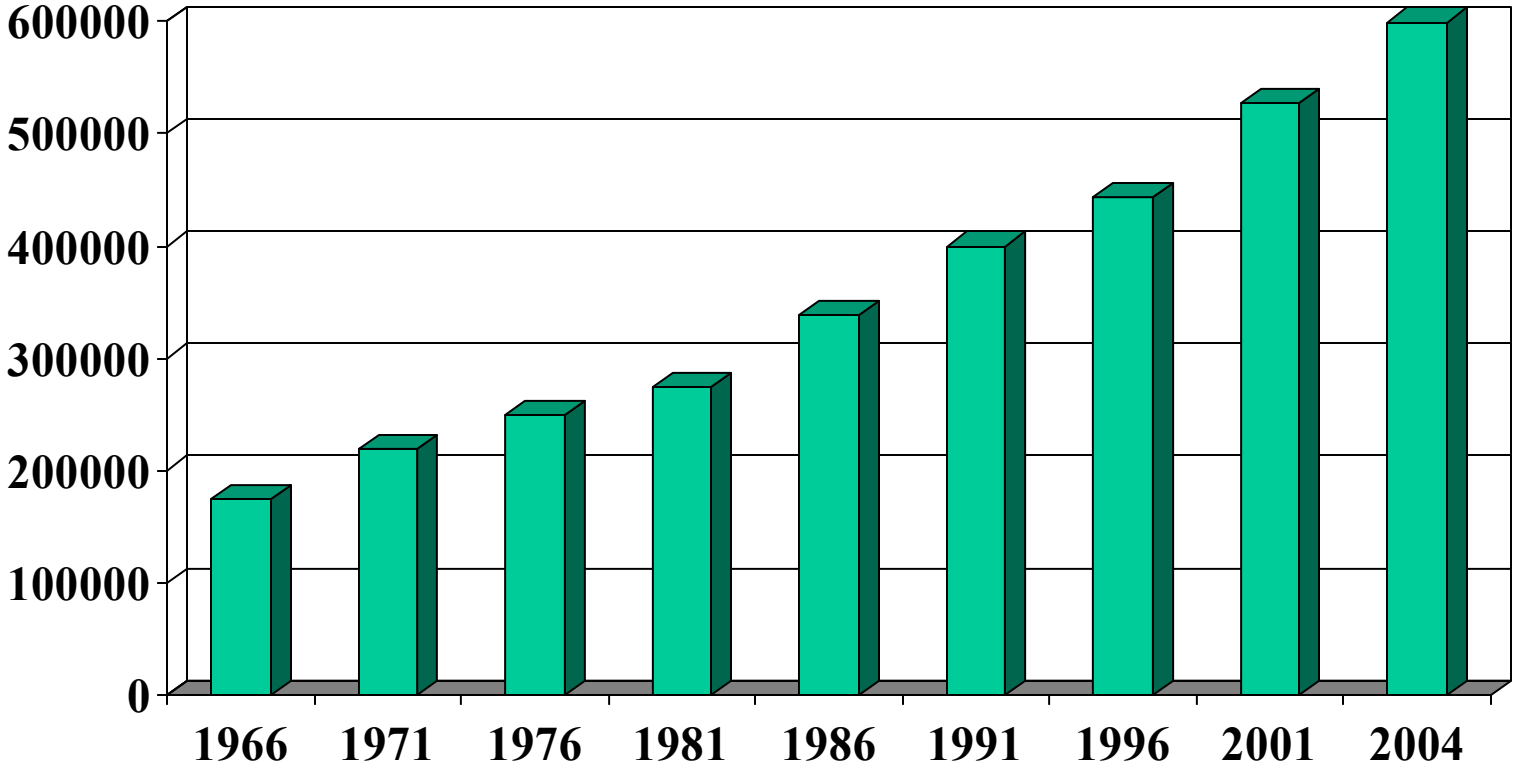
1. Why is the time ripe for EBM?
2. How is EBM implemented?
   a. Formulate question
   b. Search for answers
   c. Appraise the evidence
   d. Apply the results
   e. Assess the process
3. A “case example” applying EBM

Maintaining “Up to Date” and Rational Practices is Difficult!



The Medical Literature Is Growing Rapidly

38 Years of Medline:
Total Citations By Year of Publication*

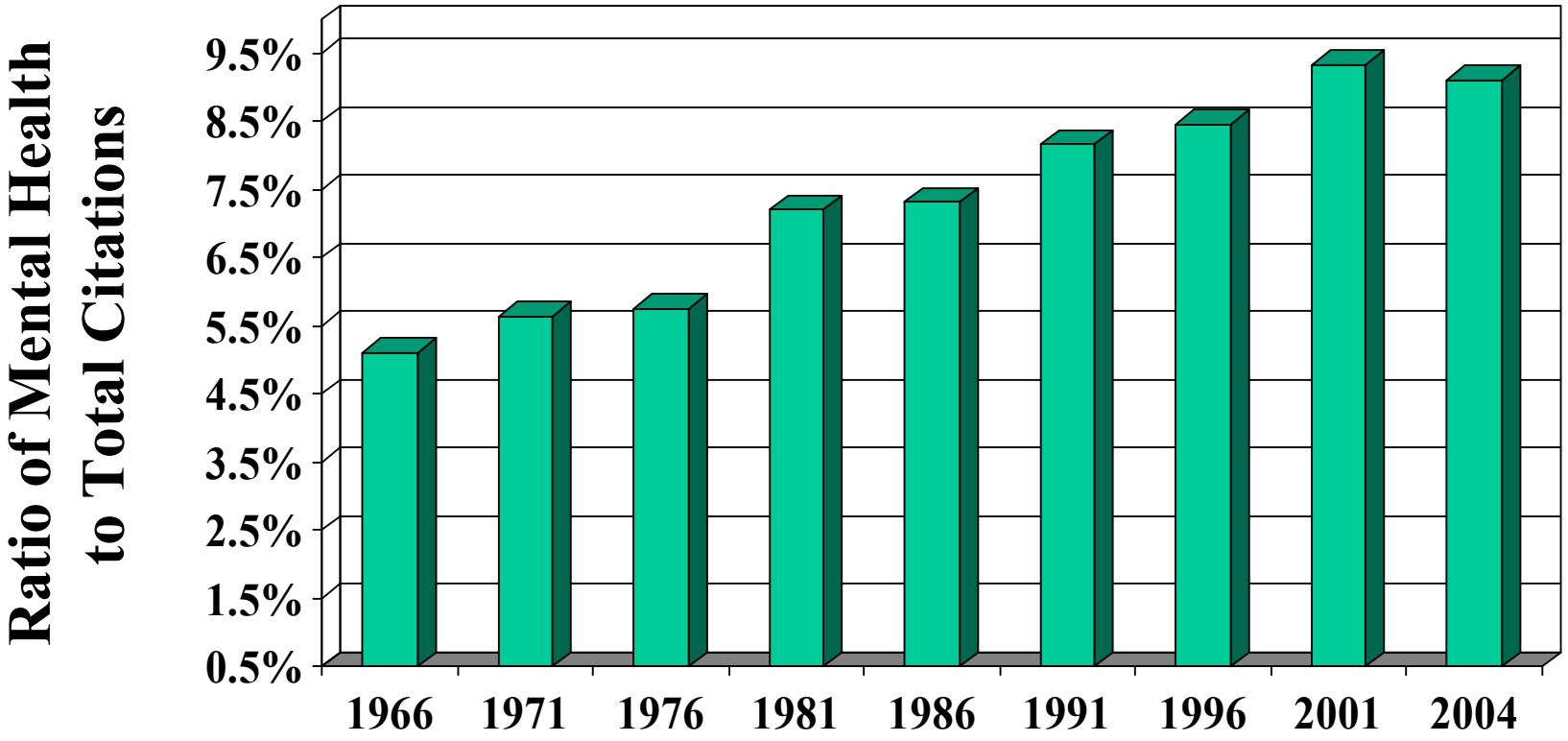


***Medline consulted 4/23/05**

The Mental Health Literature Grows Even Faster

38 Years of Medline:

Mental Health Publications Divided by All Publications Per Year*



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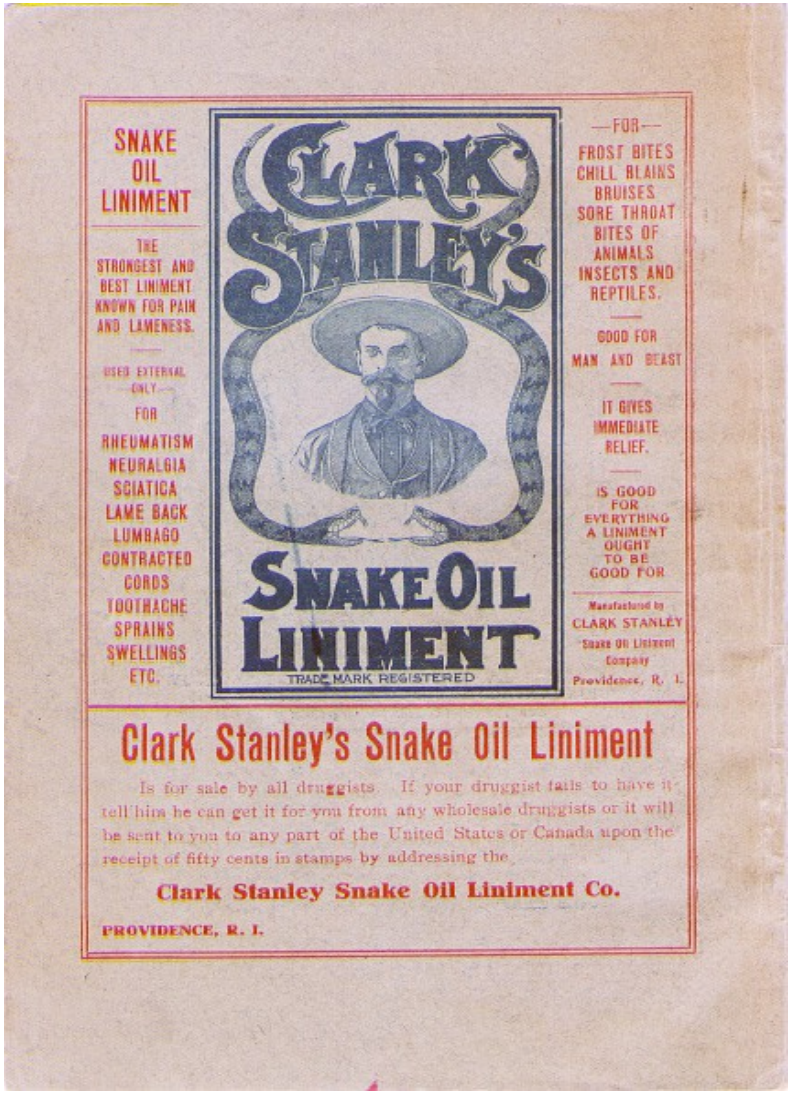
Evaluating the Quality of Data Requires Vigilance and an Organized Approach



Nobody Has Enough Time to Read It All!

Stage of Career	Range of median reading times (hr/wk)	% who reported NO reading in last week
Medical student	60 – 120	0
House officer	0 – 20	Up to 75%
Registrar	10 – 90	Up to 40%
Consultants	10 – 60	Up to 40%

from S. Carney 2004

Getting “Out of Date” Can Result In:

- Under-use of effective interventions
- Over-use of unproven interventions
- Unnecessary variations in practice
- Opinion-based vs evidence-based practice

After S. Carney 2004

Result of Information Overload and Busy Schedules: Limited Reliance on EBM

- Among admissions to an inpatient adult general psychiatry service:
  - All were evaluated for primary interventions[1]
  - Only 65% received interventions supported by evidence from randomized trials or systematic reviews.
- Among surveyed psychiatrists[2], majority believe:
  - SSRIs more effective than tricyclics and MAOIs even for severe depression
  - Depressed patient refractory to SSRI should take alternative new antidepressant vs TCA

1. Geddes et al 1996. Qual Health Care 5:215-7; 2. Studies cited in Dwight-Johnson et al 2003. Psychiatric Services 54;1076-8.

Where Does Professional Education Come From?

CME Is Available Through Professional Associations

Or In Other Venues Such as Industry-Sponsored Lectures

NewMeds, Inc.

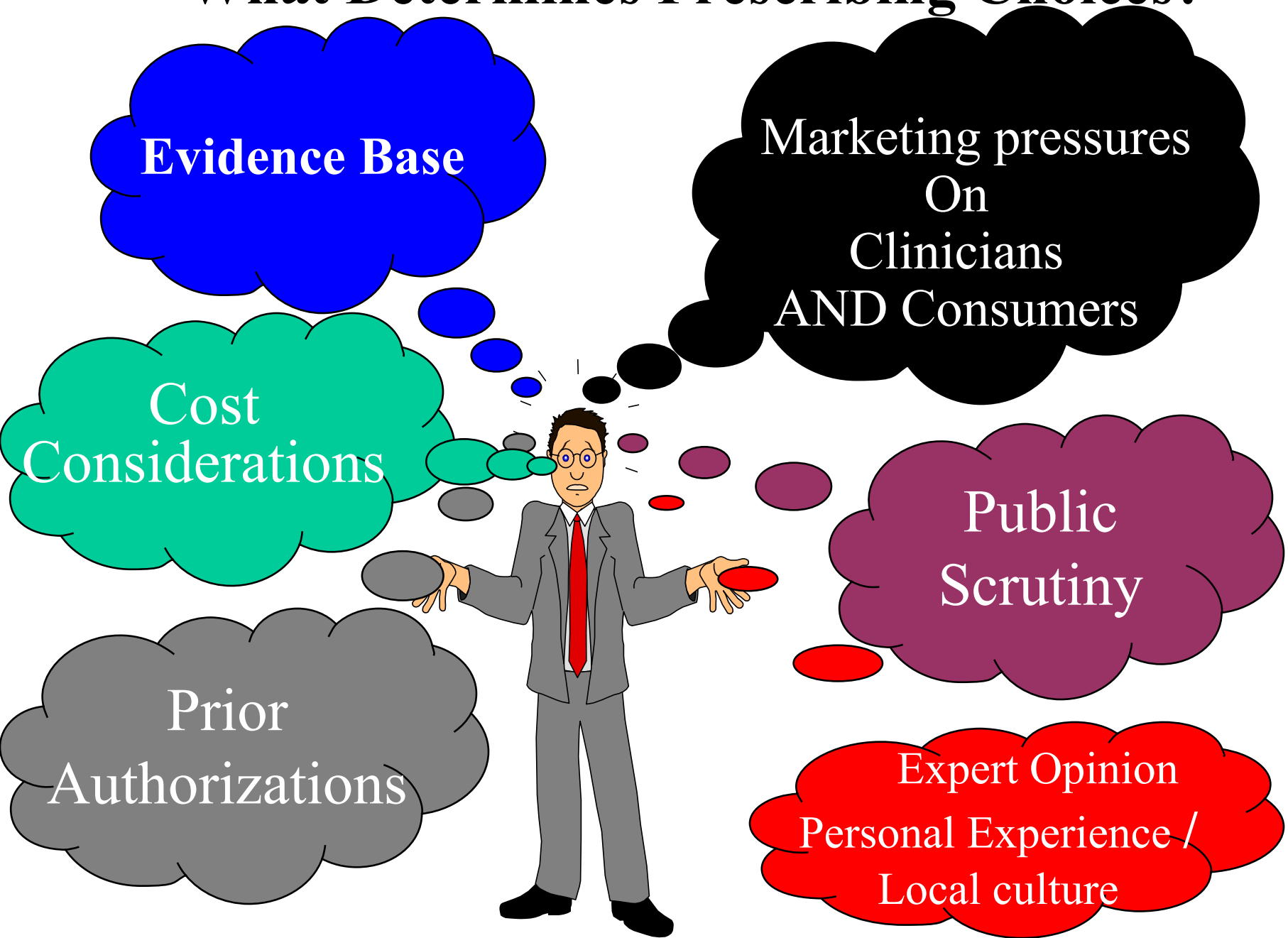
Or Sponsored Dinners

Practice Guidelines -- Can Be Useful But Sometimes Contain Biased Information

The Expert Consensus Guideline Series:

Pharmacotherapy of Depressive Disorders in Older Patients
Treatment of Behavioral Emergencies
Treatment of Depression in Women
Treatment of Attention-Deficit/Hyperactivity Disorder
Medication Treatment of Bipolar Disorder 2000
Treatment of Posttraumatic Stress Disorder
Treatment of Schizophrenia 1999
Agitation in Older Persons with Dementia
Treatment of Obsessive-Compulsive Disorder

What Determines Prescribing Choices?



Is EBM the Solution?

"Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decision about the care of individual patients"[1]

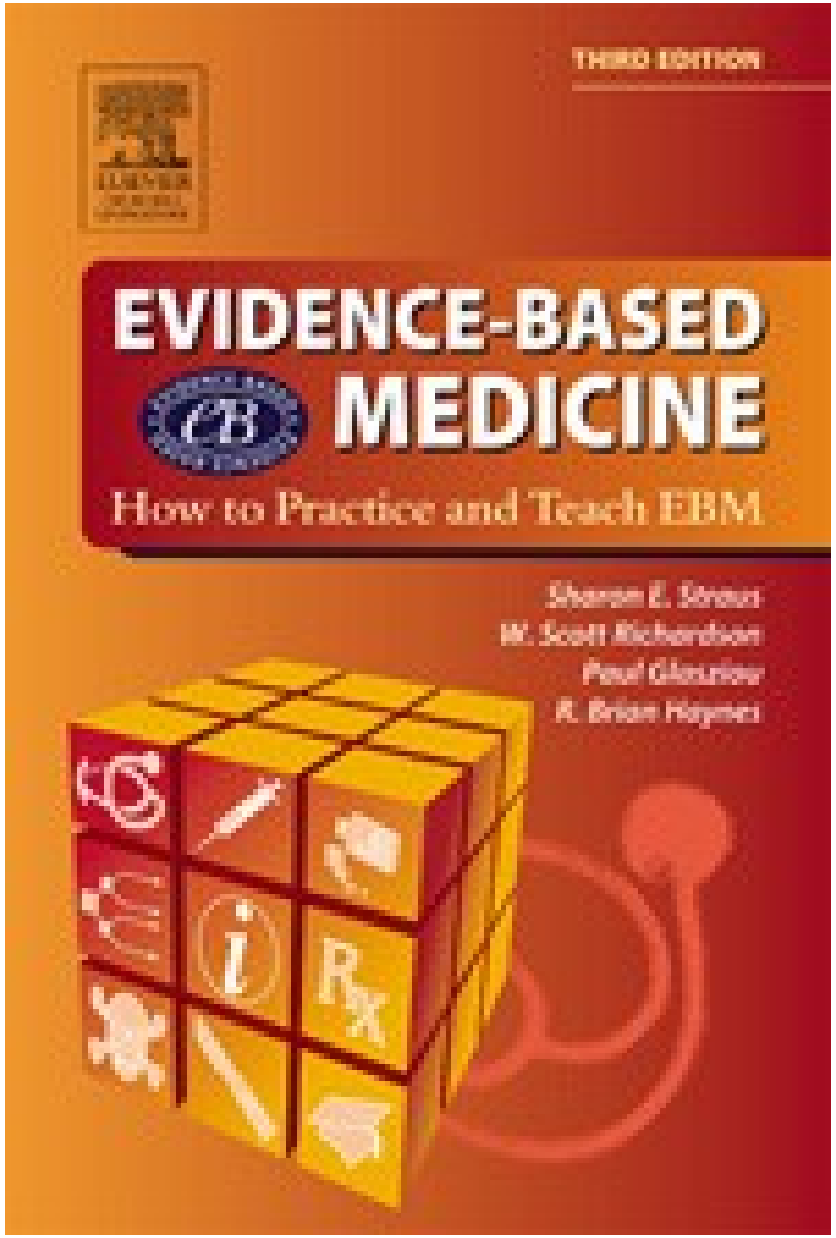
"...the integration of best research evidence with clinical expertise and patient values"[2]

1. Sackett et al. 1996; 2. Sackett et al. 2000

History of EBM

- Originated in the Dept of Clinical Epidemiology and Biostatistics, McMaster University in early 1990's
- Enthusiastic reception in UK
  - Embraced by National Health Service
  - Furthered by Cochrane Centre, BMJ Publishing
  - NICE (National Institute for Clinical Excellence)
- Gradual acceptance in US
  - AHRQ promotes EBM for clinicians
  - ACGME encourages incorporation into training

Gray GE, Pinson LA: Evidence-based medicine and psychiatric practice. Psychiatric Quarterly 2003;74:387-399.



Straus et al: Evidence-Based Medicine. 3rd ed. Elsevier, 2005

EBM in Mental Health?

- Promoted by:
  - Centre of EBMH at Oxford
  - “Evidence-Based Mental Health”
- Resistance:
  - New paradigm
  - New skills
  - Need to reconcile with honored values

How Is EBM Implemented?

1) Formulate Question Relevant to Areas of Interest

- Clinical findings
- Etiology
- Clinical manifestations
- Differential diagnosis
- Diagnostic tests
- Prognosis
- Therapy
- Prevention

Sackett et al. 2000

2) Search for Answers

- Match best study type to question
  - Dx: Cross-sectional study
  - Tx: RCT
  - Prognosis: Cohort study
  - Etiology: Cohort or case-control

Gray GE, Pinson LA: Evidence-based medicine and psychiatric practice. Psychiatric Quarterly 2003;74:387-399.

Use Best Available Evidence

- 1a: Systematic review of RCTs
- 1b: Individual RCT with narrow CI
- 2a,b: Cohort studies (review, individual)
- 2c: Outcomes research; epidemiologic studies
- 3a,b: Case-control (review, individual)
- 4: Case series
- 5: Expert opinion

Modified from Gray GE, Pinson LA: Evidence-based medicine and psychiatric practice. Psychiatric Quarterly 2003;74:387-399.

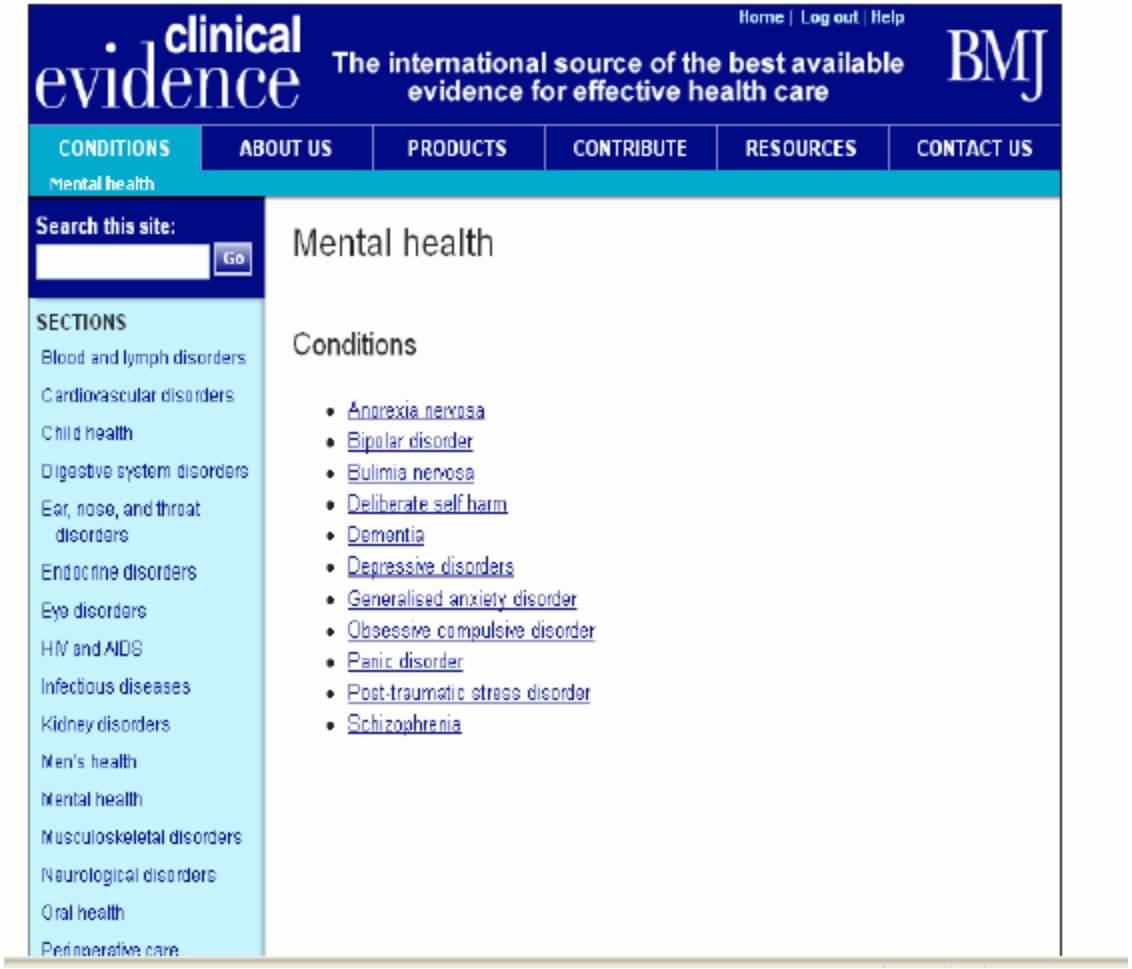
Find the Best Evidence

- Textbooks may be out of date
- Journals contain much that is irrelevant
- General databases may be cluttered with less useful sources
- EBM sources are increasingly available
  - EBMH Journal
  - Cochrane Reviews
    - Cochrane collaboration founded in 1992 for "preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions"
  - American College of Physicians (ACP) Journal Club

NICE (National Institute for Clinical Excellence)

- UK's independent organization responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.
- WWW.NICE.ORG.UK
- Evidence-based practice guidelines
- Focus on quality of evidence assessed through systematic reviews of RCTs rather than list of treatment alternatives

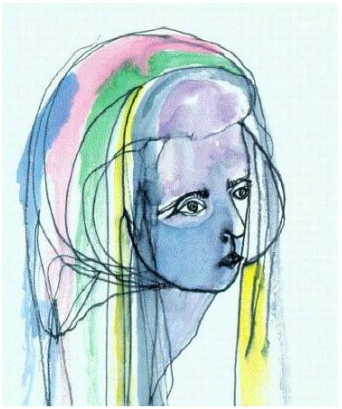
Online Resources:
Up to Date and Evidence Based



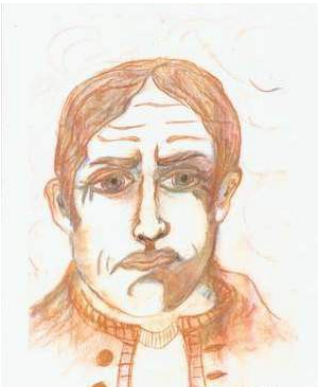
Algorithms

- Time-saving summary of pre-evaluated evidence resulting in systematic, valid approach to treatment
- Examples at Psychopharmacology Algorithm Project (http://www.mhc.com/Algorithms)

Treatment of Schizophrenia

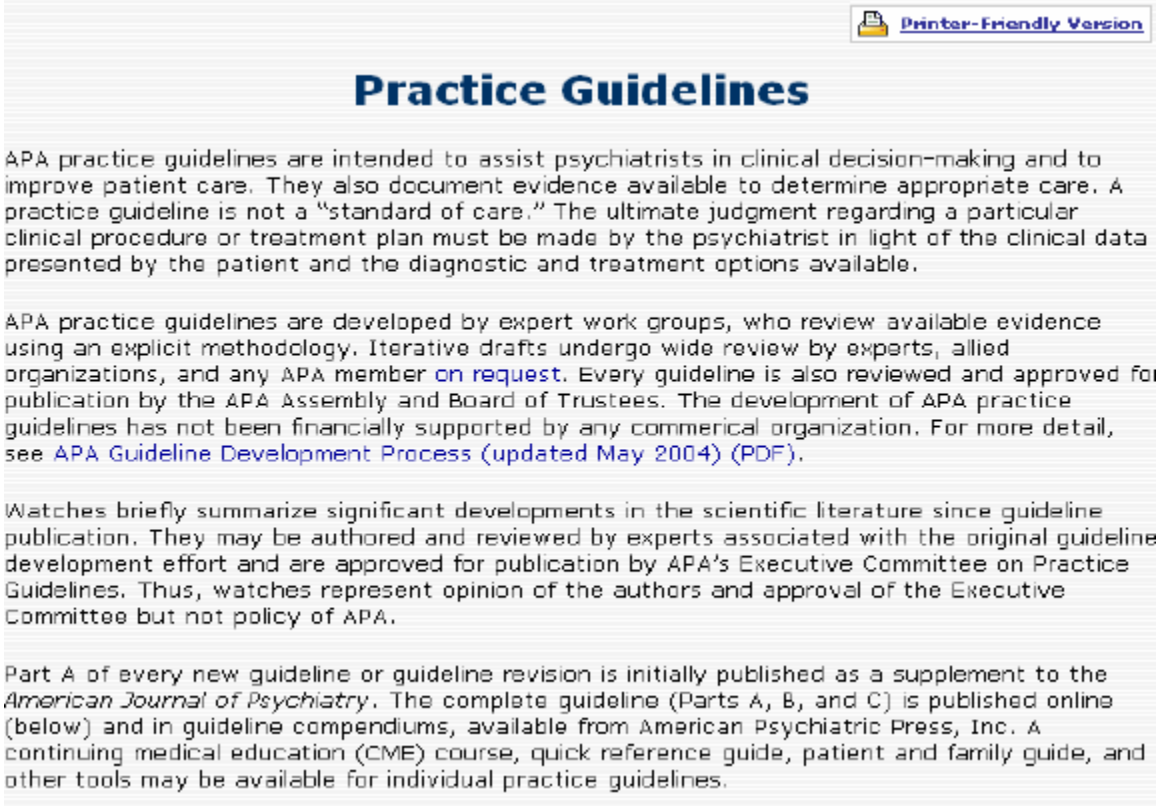


Treatment of Depression



Treatment of Anxiety in Patients with History of Chemical Abuse or Dependence

Secondary Resources: Practice Guidelines



Printer-Friendly Version

Practice Guidelines

APA practice guidelines are intended to assist psychiatrists in clinical decision-making and to improve patient care. They also document evidence available to determine appropriate care. A practice guideline is not a "standard of care." The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available.

APA practice guidelines are developed by expert work groups, who review available evidence using an explicit methodology. Iterative drafts undergo wide review by experts, allied organizations, and any APA member on request. Every guideline is also reviewed and approved for publication by the APA Assembly and Board of Trustees. The development of APA practice guidelines has not been financially supported by any commerical organization. For more detail, see APA Guideline Development Process (updated May 2004) (PDF).

Watches briefly summarize significant developments in the scientific literature since guideline publication. They may be authored and reviewed by experts associated with the original guideline development effort and are approved for publication by APA's Executive Committee on Practice Guidelines. Thus, watches represent opinion of the authors and approval of the Executive Committee but not policy of APA.

Part A of every new guideline or guideline revision is initially published as a supplement to the *American Journal of Psychiatry*. The complete guideline (Parts A, B, and C) is published online (below) and in guideline compendiums, available from American Psychiatric Press, Inc. A continuing medical education (CME) course, quick reference guide, patient and family guide, and other tools may be available for individual practice guidelines.

3) Appraise the Evidence: Methods

- Concealed randomization?
- Double blind?
- All subjects accounted for and analyzed in groups?
  - 80% follow up necessary for valid results
  - ITT analysis
- Were groups comparable?
- Aside from experimental treatment, treated equally?

Gray 2002

3) Appraise the Evidence: Statistical Significance of Results, or "What is the Value of P-Value?"

- Probability that a particular outcome occurred by chance
- Most frequently chosen is 0.05
- Multiple statistical tests without correction affect true probabilities
- Significant p value does not clarify effect size or number of subjects likely to respond to intervention.

3) Appraise the Evidence: Effect Size: Calculating NNT

- CER (Control Event Rate)
- EER (Experimental Event Rate)
- AAR (Absolute Risk Reduction: CER-EER)
- NNT = 1/ARR

Gray 2002

3) Appraise the Evidence
Precision of Results:
Calculating CI of ARR

$$CI = 1.96*\{[CER*(1-CER)/Nc]+[EER*(1-EER)]/Ne\}^{1/2}$$

4) Apply the Results

- How applicable?
  - Is my patient like those studied?
  - Is treatment consistent with my patient's values and preferences?
  - Is treatment feasible in my practice setting?

5) Assess the Process

How Involved in EBM Should You Get?

- **"Doer"** uses EBM methods to formulate and answer questions, assess evidence
- **"User"** consults pre-appraised resources
- **"Replicator"** follows
    - Recommendations of EBM leaders
    - Evidence-based guidelines

Example:

Should My Patient With Alzheimer's Disease Take Vitamin E?

A Keats Good Health Guide

MEDICINE FOR THE 21ST CENTURY®

$3.95

Vitamin E Updated

New roles for the vitamin that preserves the health and integrity of body cells

Len Mervyn, Ph.D.

GOOD HEALTH GUIDES: Published regularly to give you the newest and best-available information on health topics of major importance, written by leading physicians and other health practitioners, researchers and expert reporters.

Oxidative Damage Theory: Rationale for Vitamin E Use in AD

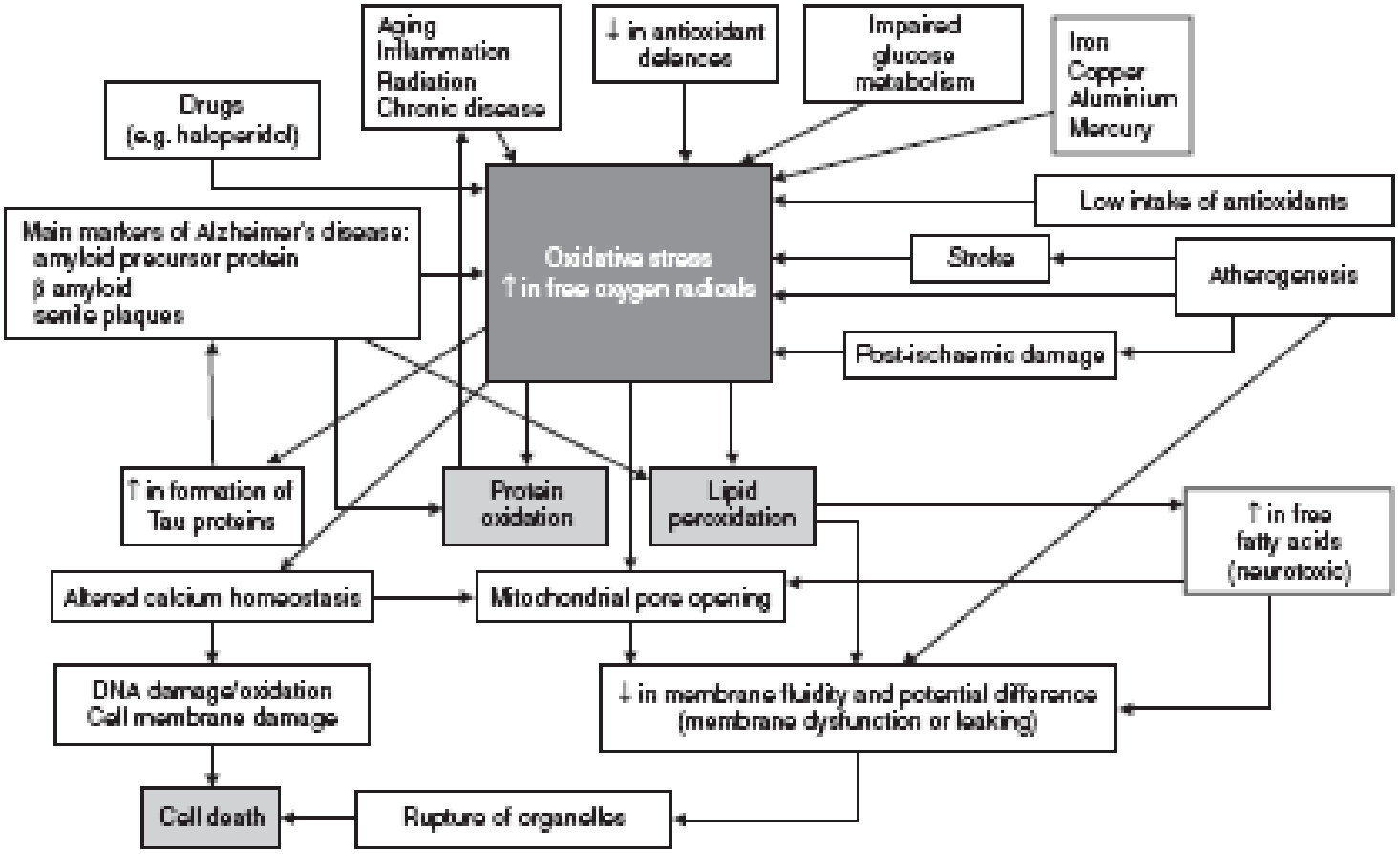


Fig. 2. Model demonstrating the cyclical nature of oxidative stress in Alzheimer's disease. ↑ indicates increase; ↓ indicates decrease.

Berman E, Brodaty H: Tocopherol (Vitamin E) in Alzheimer's Disease and other neurodegenerative disorders. CNS Drugs 2004;18:807-25.

AAN Practice Recommendations: Pharmacologic Treatment of AD

- Vitamin E(1000 IU PO BID) should be considered in an attempt to slow progression of AD (Guideline).

Doody RS, Stevens JC, Beck DC, et al: Practice parameter: Management of dementia (an evidence-based review). Neurology 2001;56:1154-1166

1) Formulate Question (PICO)

"Should my patient with mild Alzheimer's Disease take Vitamin E as recommended by AAN (1000 IU by mouth twice daily) to slow progression of the disease"?

2) Search for Answers

- Match best study type to question
  - Dx: Cross-sectional study
  - Tx: RCT
  - Prognosis: Cohort study
  - Etiology: Cohort or case-control

Find the Best Evidence

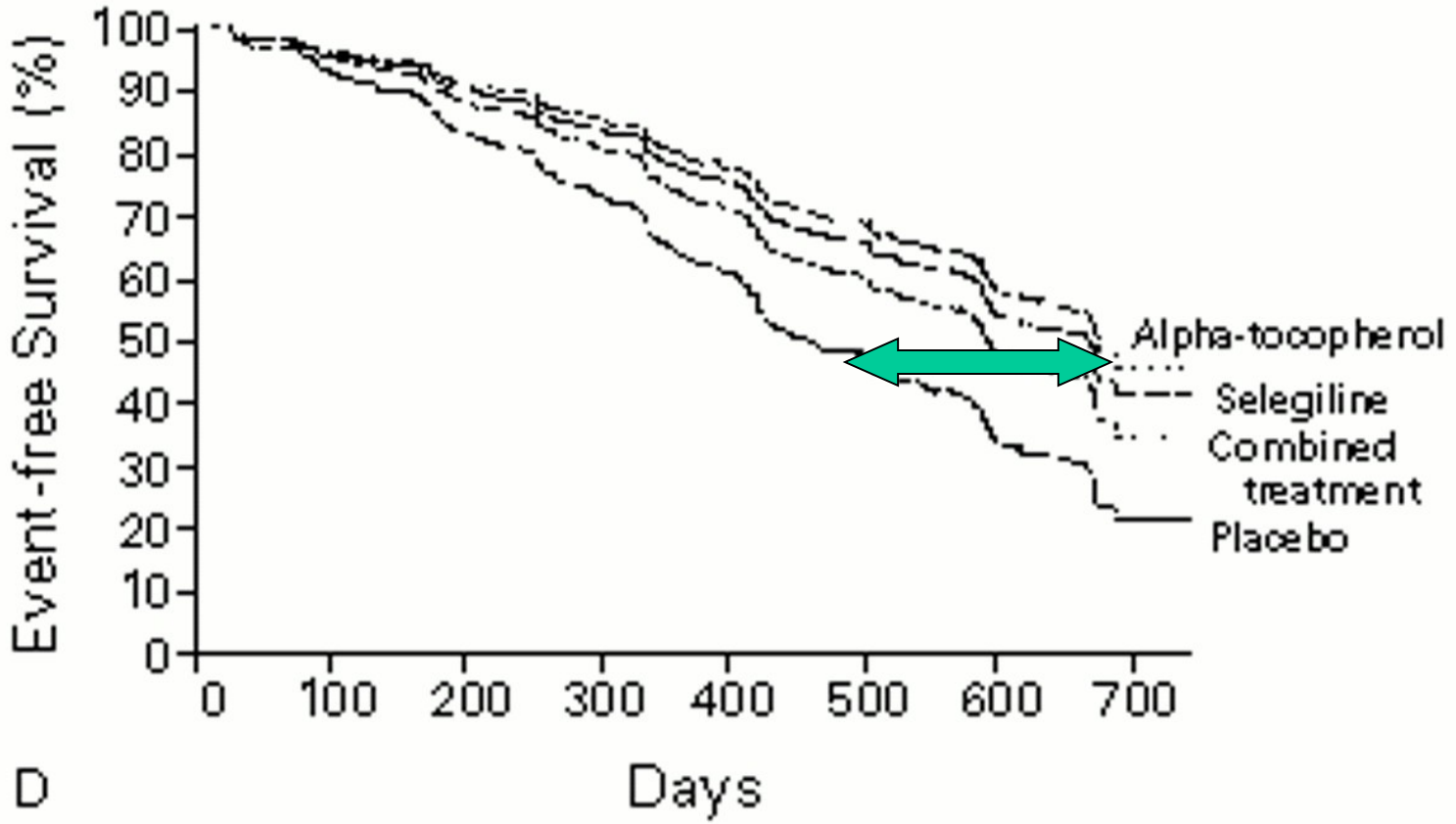
- Medline search reveals…1 relevant RCT*:
  - Multicenter RCT, 2 year follow up
  - N = 341 (mean age 73, 65% women)
  - 85 treated with alpha tocopherol vs 84 placebo
- Dx: AD of moderate severity (residing at home, no other CNS disease and no other psychoactive medications)
- Intervention: α tocopherol 1000 IU bid vs placebo
- Outcomes:
  - Primary: Death, Institutionalization, Loss of ≥2 of 3 basic ADLs, or reach CDR 3
  - Secondary: Cognition, ADLs, behavior, extrapyramidal signs

*Sano M, Ernesto C, Thomas RG, et al: A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's Disease. NEJM 1997;336:1216-1222.

3) Appraise the Evidence

- Methods
  - Concealed randomization? Difficult to assess from publication
  - Double blind? Yes
  - 80% of subjects accounted for and analyzed in groups? Yes
  - ITT analysis? Yes
  - Were groups comparable? No
    - Vit E cohort had lower baseline MMSE, so results were adjusted prior to analysis
  - Aside from experimental treatment, treated equally? Yes

Vitamin E, Selegiline, or Both for Alzheimer's Disease



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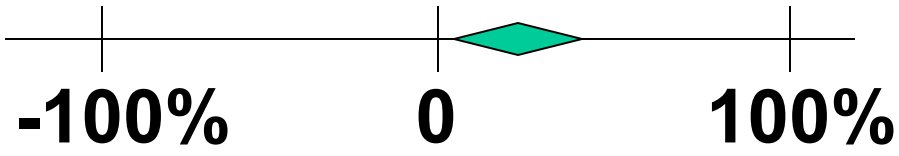
Sano M, Ernesto C, Thomas RG, et al: A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's Disease. N*EJM 1997;336:1216-1222.M*

3) Appraise the Evidence

- Results
  - How large was the treatment effect (NNT)?
    - Control Event Rate 0.69
    - Experimental Event Rate 0.53
    - Absolute Risk Reduction (CER-EER) 0.16
    - NNT (1/ARR) 6

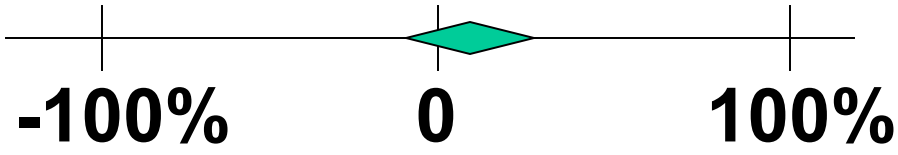
3) Appraise the Evidence

- Results
  - How precise is the result?
    - CI = **$1.96*\{[CER*(1-CER)/Nc]+[EER*(1-EER)]/Ne\}^{1/2}$**
    - = $1.96*\{(0.69*0.31/84)+(0.53*0.47/85)\}^{1/2}$
    - =0.1450
  - ARR = 0.16±0.14 = 2% - 30%



3) Appraise the Evidence

- Sensitivity Analysis (Worst Case Scenario)
  - Assume all placebo dropouts did not reach primary outcome
  - Assume all treatment dropouts did meet primary outcome
  - Recalculated NNT = 14
  - Recalculated ARR = 7%±14% = -7% to 21%



Another Possibly Relevant Study: Vitamin E / Donepezil for MCI

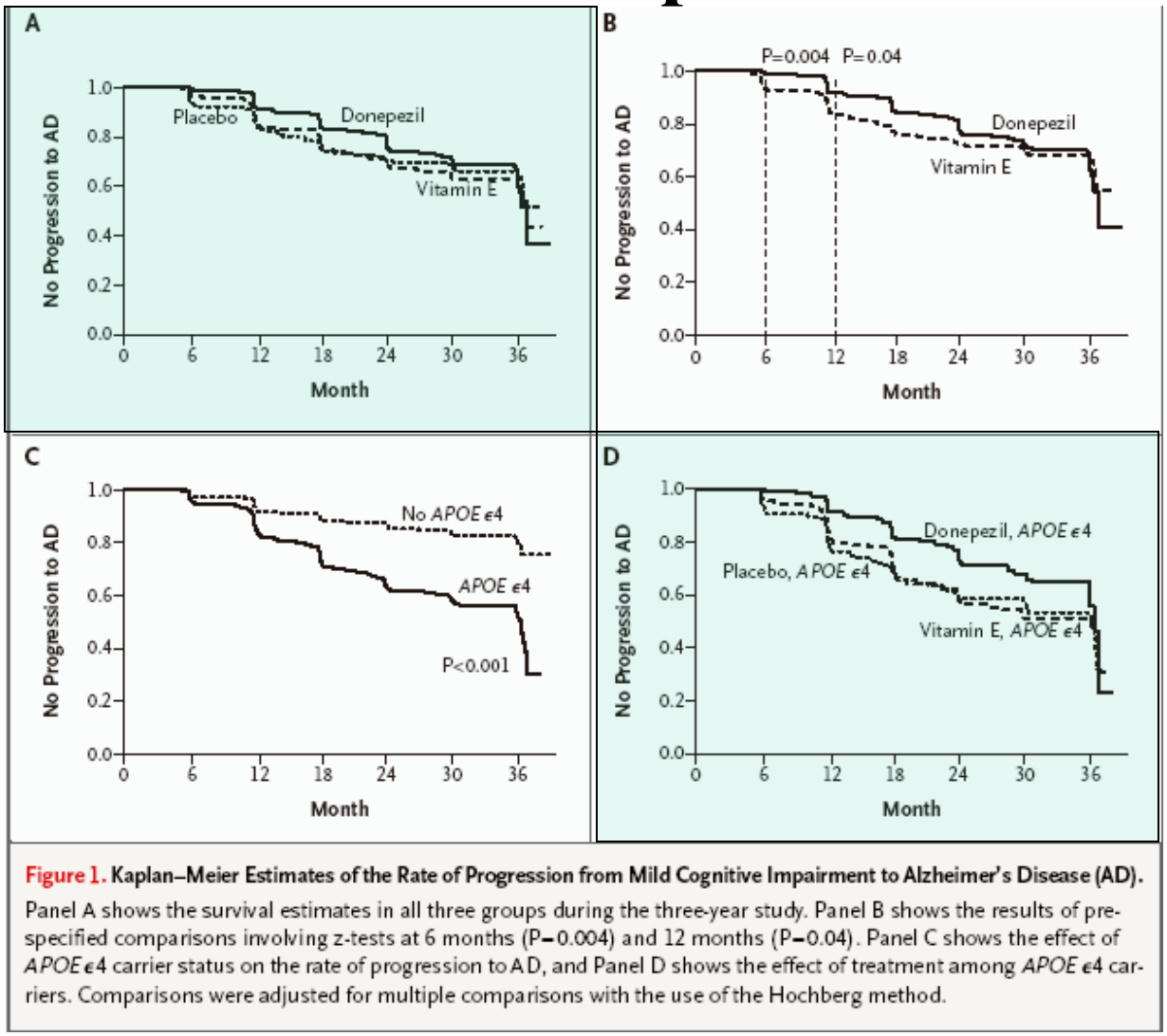


Figure 1. Kaplan–Meier Estimates of the Rate of Progression from Mild Cognitive Impairment to Alzheimer's Disease (AD).

Panel A shows the survival estimates in all three groups during the three-year study. Panel B shows the results of prespecified comparisons involving z-tests at 6 months (P=0.004) and 12 months (P=0.04). Panel C shows the effect of *APOE* ϵ4 carrier status on the rate of progression to AD, and Panel D shows the effect of treatment among *APOE* ϵ4 carriers. Comparisons were adjusted for multiple comparisons with the use of the Hochberg method.

Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. NEJM 2005

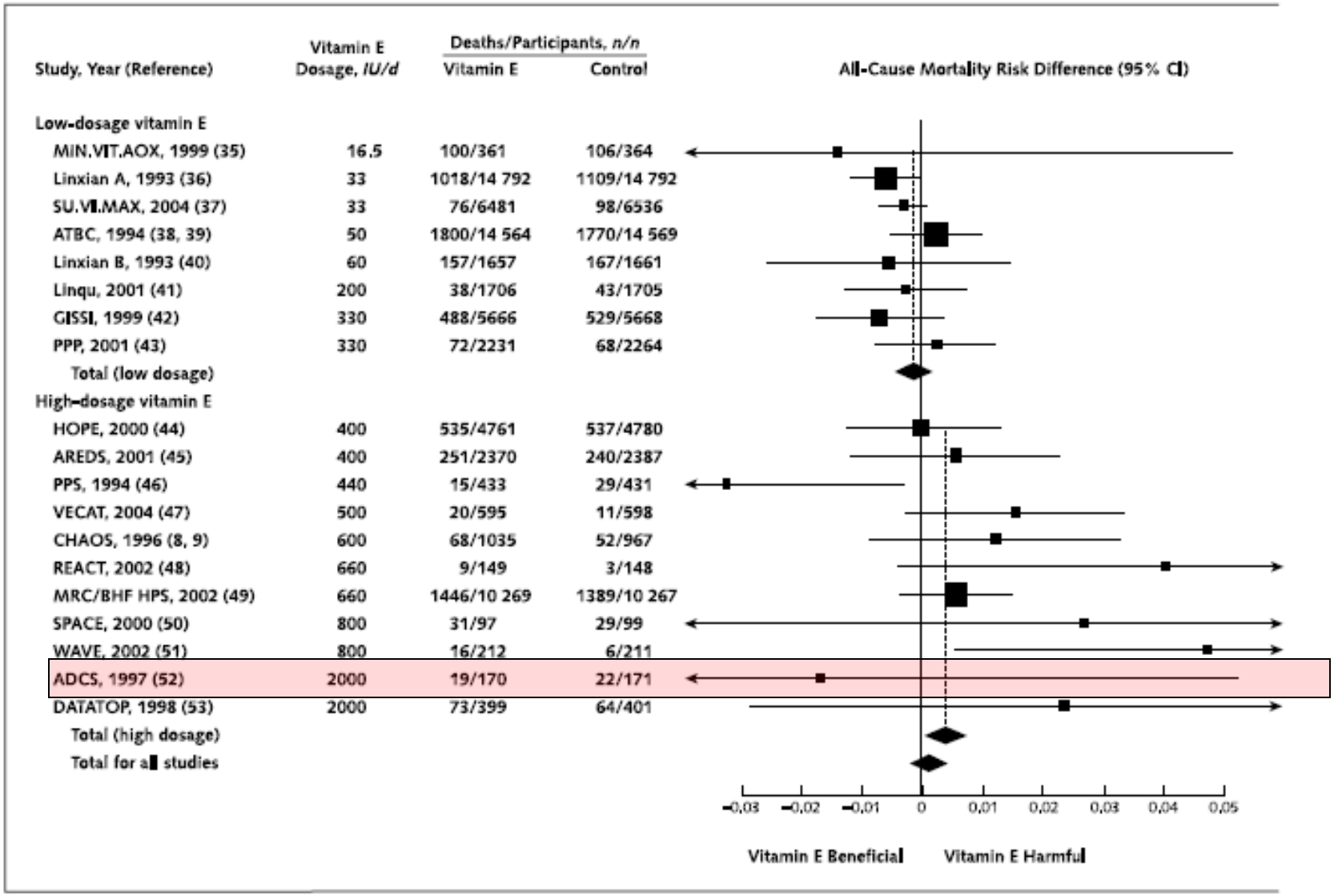
4) Apply the Results

- Is my patient like those studied?
  - Stage of AD
    - Mild vs moderate?
    - Other CNS diseases?
    - Other meds?
- Is treatment consistent with my patient's values and preferences?
- Is treatment feasible in my practice setting?

Also Consider Potential for Harm

- NNH similar to NNT
- Assesses risk for discontinuation or AE
- For the Sano et al. study, falls occurred in 14% of Vitamin E subjects vs. 5% of placebo subjects
- CER-EER=ARR=9%
- OR = 3; NNH=1/0.09 =11
- Drug interaction considerations

High-Dose Vitamin E and Mortality



Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al: Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005;142(1):37-46.

How Does This Apply to My Patient?

- Against Vit E Use
  - This patient's illness may be at a different stage than that of subjects in Sano's studyh who were benefited (e.g. this patient has significant comorbid medical illnesses that may place her in a higher mortality risk category and has concurrent medications that may interact [statin])
  - Risk of increasing this patient's falls may outweigh modest benefits
  - Compliance with a bid dosing may be problematic and/or interfere with compliance with current regimen
- For Vit E Use
  - Limited therapies available for AD
  - Sano provides best single source of data re AD, though inconsistent with some other E studies
  - Cost, AE probably low
  - Patient may want to take

BOTTOM LINE:

For this patient, high dose Vitamin E may be of limited potential benefit and its benefits may be outweighed by potential disadvantages.

Conclusions

- EBM is an important new paradigm
- It is applicable to mental health
- It can help us
  - Explain and justify our treatment decisions
  - Increase clinical effectiveness
  - Appraise the value of treatment interventions
  - Manage information overload

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B. Use of best available evidence
C. Reliance on anecdotal experience
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C. Cochrane reviews
D. Medline
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