ASCP Model Psychopharmacology Curriculum

Show Me the Evidence!

Understanding the Philosophy of Evidence-Based Medicine and Interpreting Clinical Trials

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Objectives

1. To be able to outline the steps involved in practicing Evidence-Based Medicine (EBM)
2. To be able to quantify clinical significance using Number Needed to Treat (NNT)
3. To be able to apply EBM and NNT to clinical practice

Major Teaching Points

- EBM provides clinicians with a strategy for coping with the overwhelming amount of data that floods all 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.

Pre-Test 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

Pre-Test 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

Pre-Test 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

Pre-Test 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

Pre-Test 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

Outline

I. EBM helps us interpret data from clinical trials and match appropriate treatments to individual patients:

A. Defining EBM: Core features, philosophy, and steps:

1. Formulate question
2. Search for answers– sources, quality, algorithms, guidelines
3. Appraise the evidence – understanding quality of evidence
4. Apply the results – assessing applicability of "evidence" to specific patients' needs and preferences
5. Assess the outcome

II. EBM helps us quantitatively appraise risks vs benefits of treatments

1. Absolute and relative risk
2. p-value and statistical significance vs effect size and clinical significance
3. Calculating and using NNT

IV. Examples of EBM applied to clinical questions

Interpreting Clinical Trials

- What is the problem?
- What is EBM?
- More about benefit, risk, and how NNT can help us understand this
- Applying EBM and NNT
- Summary

Interpreting Clinical Trials

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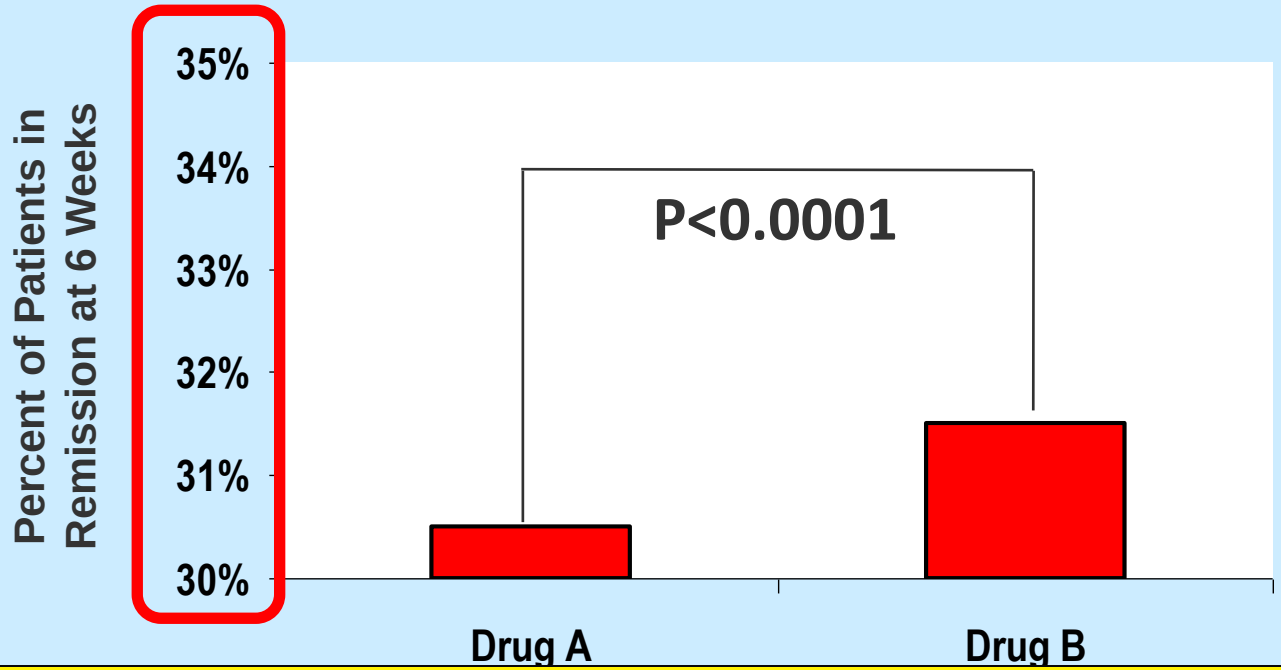
The difference in remission for a major depressive episode at 6 weeks for Drug A versus Drug B is highly statistically significant, but clinically irrelevant



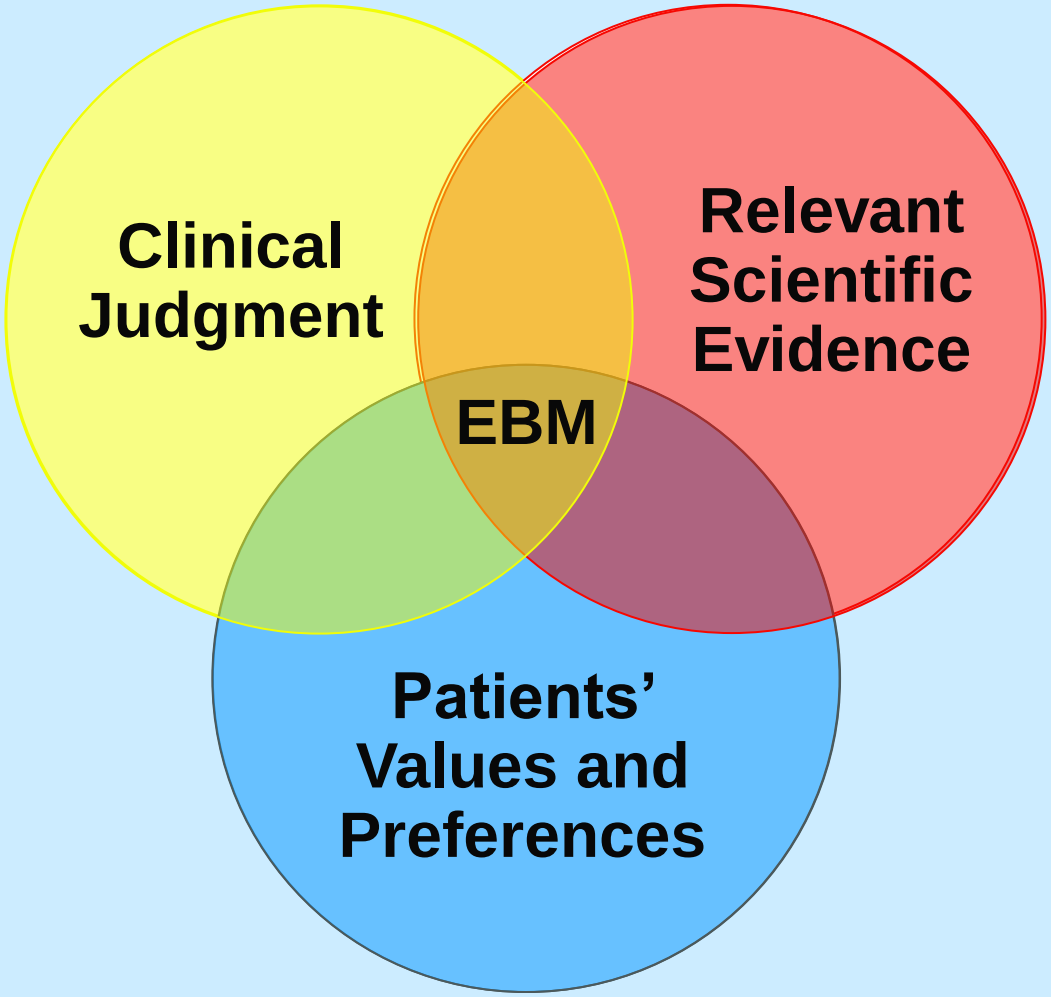
How irrelevant is this? Can we quantify this?

Citrome L Acta Psych Scand. 2008;117:412-419.

Interpreting Clinical Trials

- What is the problem?
- **What is EBM?**
- More about benefit, risk, and how NNT can help us understand this
- Applying NNT to real study results
- Summary

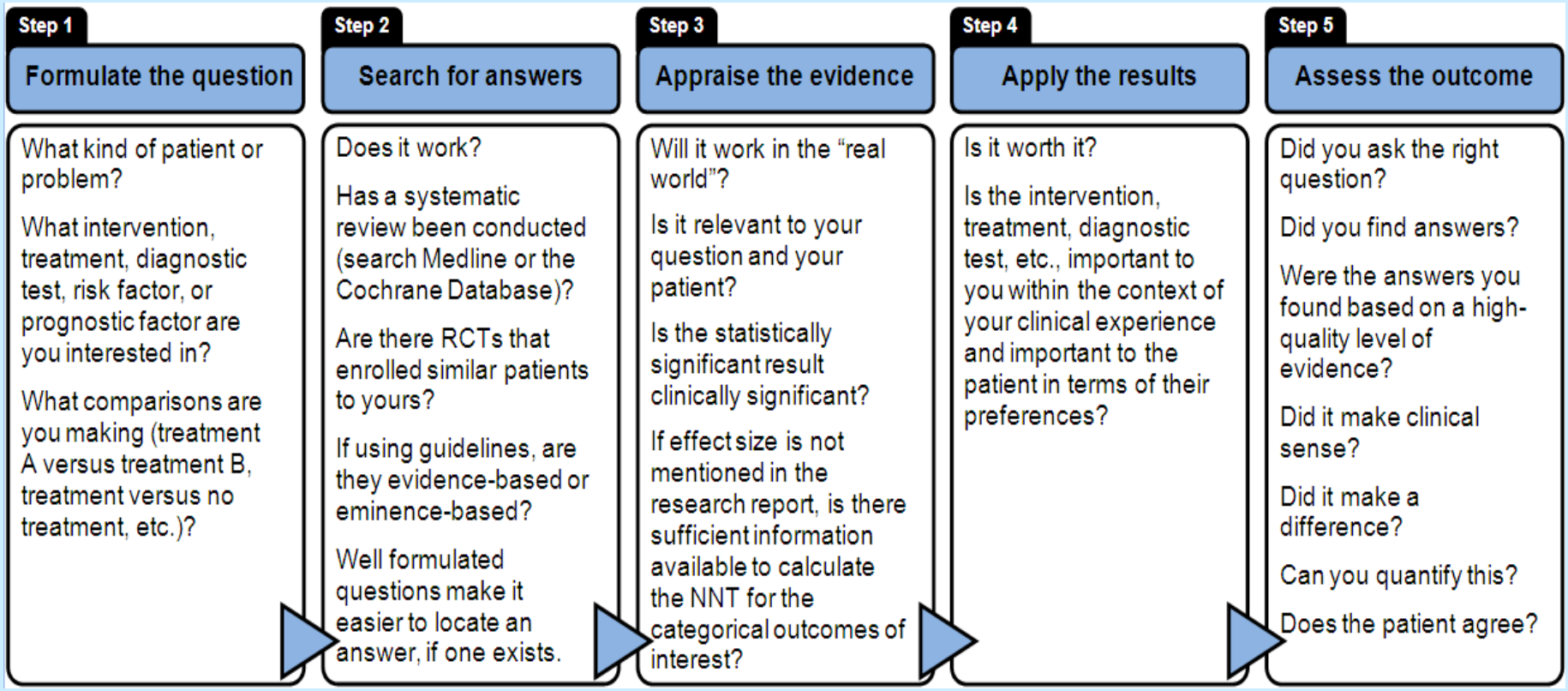
What Is Evidence-Based Medicine?



EBM—Core Features

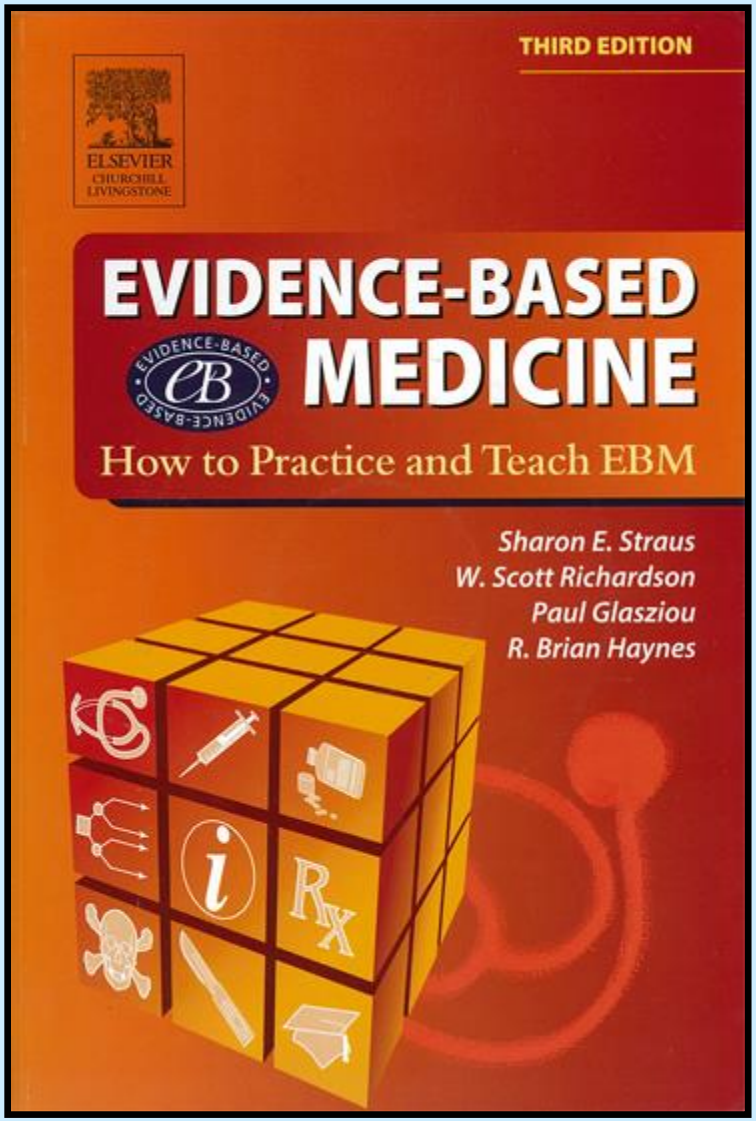
- EBM is about process
- EBM is a philosophy
- EBM is a set of tools
- EBM is NOT “cookbook medicine”

The EA* 5 Step Program

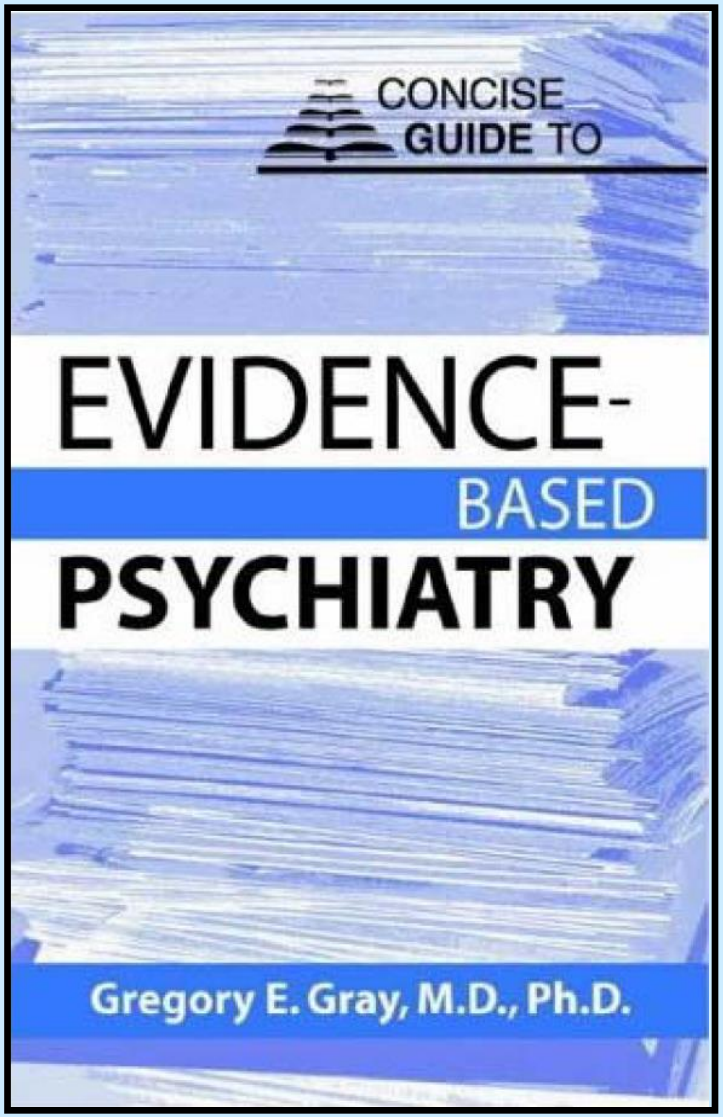


*** Evidence-based medicine Anonymous**

Citrome L, Ketter TA. *Int J Clin Pract*. 2009;63:353-359.

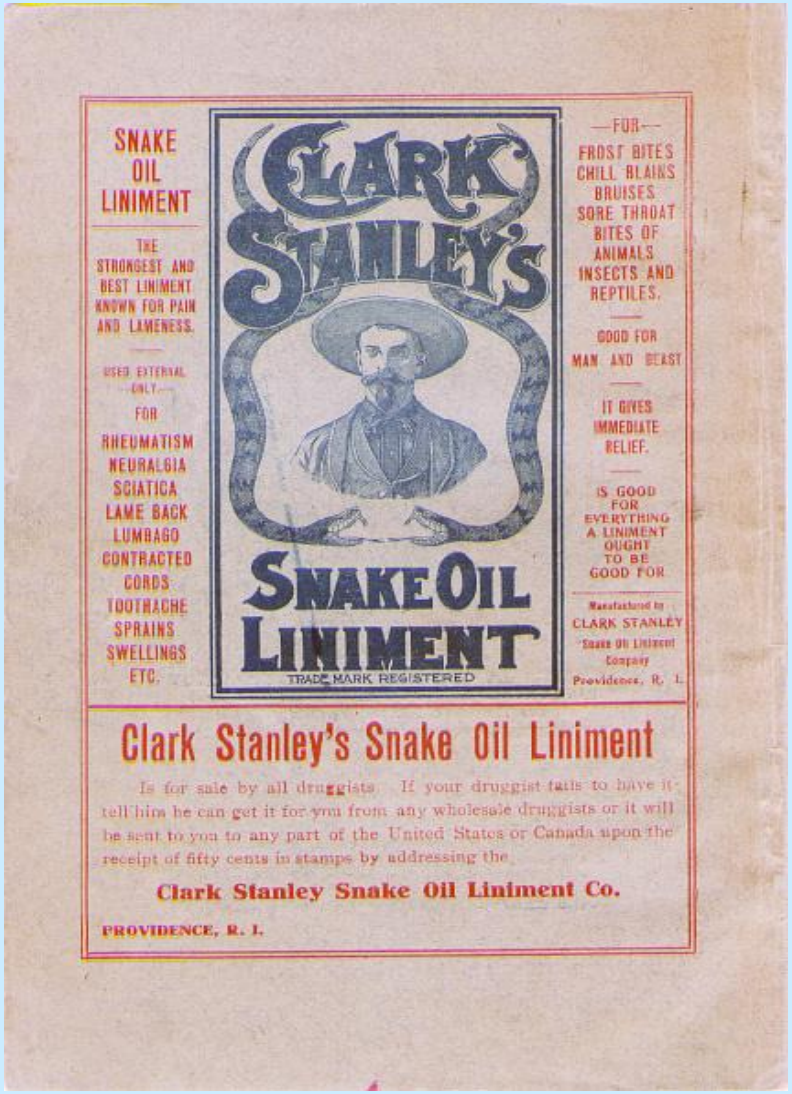


Straus et al: Evidence-Based Medicine. 3rd ed. Elsevier, 2005



Gray: Concise Guide to Evidence-Based Psychiatry. 1st ed. APPI, 2004

Evaluating the Quality of Data Requires Vigilance and an Organized Approach



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Evidence Changes Over Time!
Getting "Out of Date" Can Result In:

- Under-use of effective interventions
- Over-use of unproven interventions
- Unnecessary variations in practice
- Eminence-based vs evidence-based practice
- Reliance on LPIT (Last Patient I Treated)

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Need to Learn a Process to Evaluate the Evidence That is Presented in

- Journal articles
- CME offered by professional organizations
- Industry sponsored lectures
- Practice guidelines

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The Philosophy of EBM to the Rescue!

"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. BMJ 1996;312:71-72
2. Sackett et al. Evidence-based medicine: how to practice and teach EBM. 2nd Ed. London, Churchill-Livingstone, 2000

The Five Steps to EBM

(1) formulate the question
(2) search for answers
(3) appraise the evidence
(4) apply the results
(5) assess the outcome

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1) Formulate Question Relevant to Areas of Interest

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

Sackett et al. Evidence-based medicine: how to practice and teach EBM. 2nd Ed. London, Churchill-Livingstone, 2000

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2) Search for Answers

- Does it work? Efficacy studies (RCTs) can tell us if an intervention is better than placebo.
- Will it work? Effectiveness studies are usually more generalizable.
- Is it worth it? Benefits vs harms? Cost?

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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.

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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

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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

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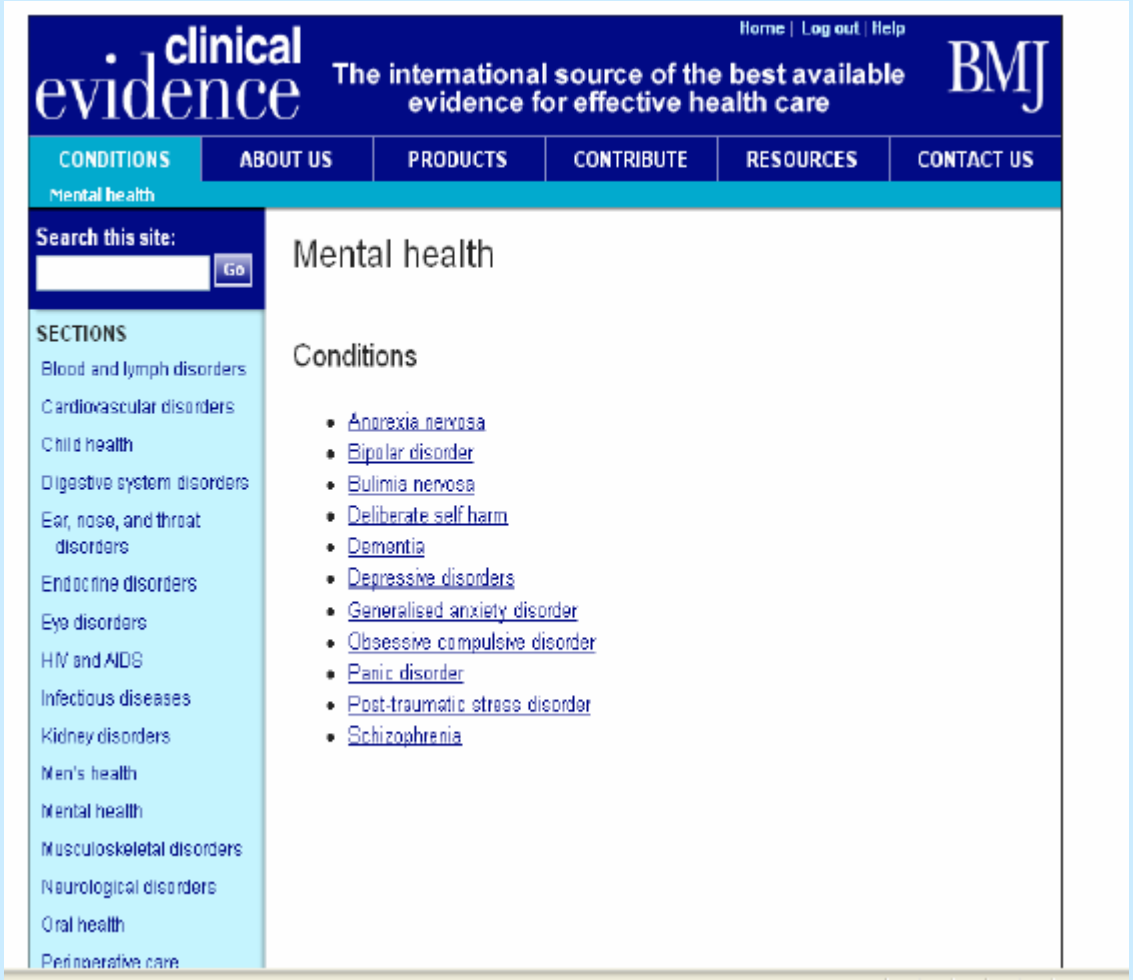
Online Resources:
Up to Date and Evidence Based



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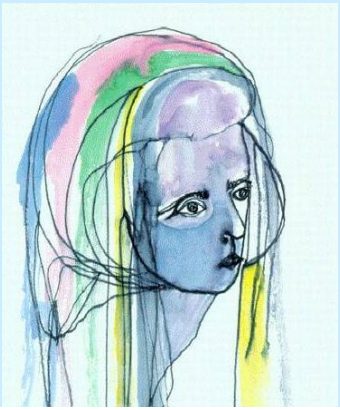
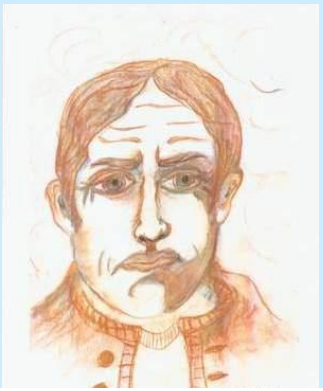
Algorithms

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

Treatment of Schizophrenia



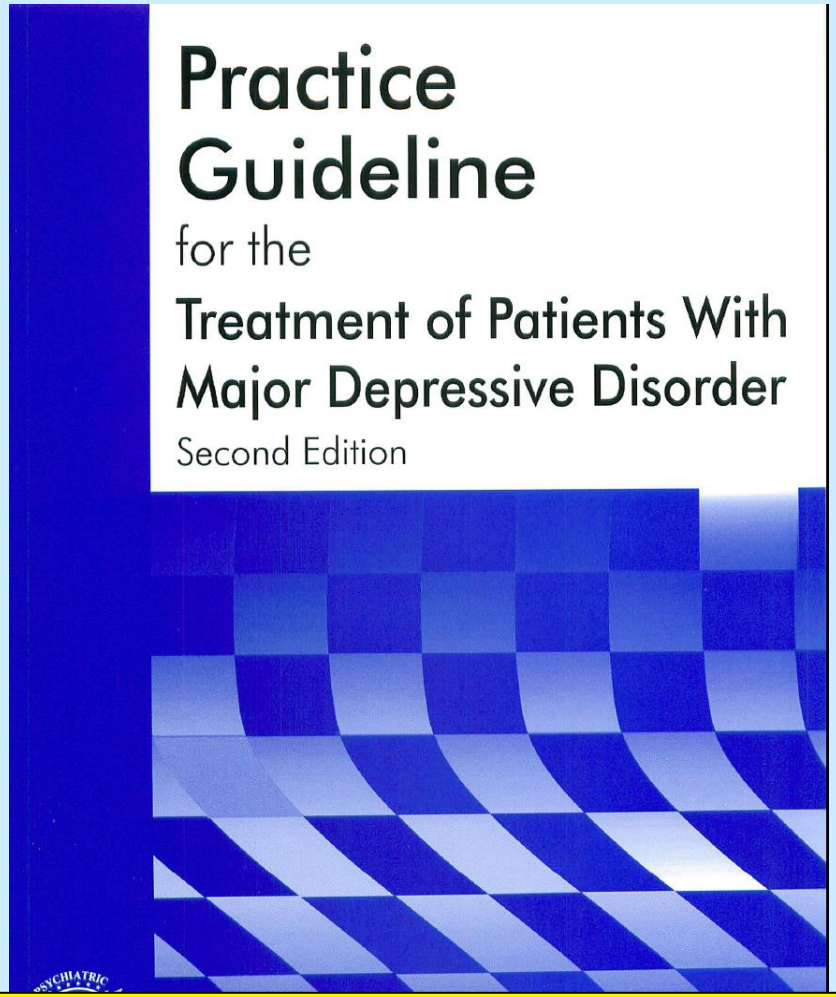
Treatment of Depression



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

Caution: Not all algorithms are evidence-based. There are many eminence-based algorithms out there!

Secondary Resources: Practice Guidelines



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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?
- Are the results statistically *and* clinically significant?

Straus SE, et al. Evidence-Based Medicine: How to Practice and Teach EBM; 2005

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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

- Is it working?

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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

Interpreting Clinical Trials

- What is the problem?
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- **More about benefit, risk, and how NNT can help us understand this**
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Evidence-Based Medicine is About Benefit and Risk: Key Concepts

- Absolute and relative risk
- *P*-value and statistical significance
- Effect size and clinical significance

Contrasting Absolute and Relative Risk

Prospective Results from the Women's Health Initiative

BBC NEWS

Aspirin cuts breast cancer risk

A new piece of US research backs the idea that aspirin protects against certain types of breast cancer.

It found women who used aspirin or similar painkillers at least once per week for six months reduced their risk of breast cancer by 20%.

http://news.bbc.co.uk/go/pr/fr/-/2/hi/health/3748697.stm

Contrasting Absolute and Relative Risk

Prospective Results from the Women's Health Initiative

Healthy Skepticism | *Part of an occasional series*

Overstating Aspirin's Role In Breast Cancer Prevention

How Medical Research Was Misinterpreted to Suggest Scientists Know More Than They Do

By Lisa M. Schwartz, Steven Woloshin and H. Gilbert Welch
Special to The Washington Post

Medical research often becomes news. But sometimes the news is made to appear more definitive and dramatic than the research warrants. This series dissects health news to highlight some common study interpretation problems we see as physician researchers and show how the research community, medical journals and the media can do better.

Preventing breast cancer is arguably one of the most important priorities for women's health. So when the Journal of the American Medical Association published research a year ago suggesting that aspirin might lower breast cancer risk, it was understandably big news. The story received extensive coverage in top U.S. newspapers, including The Washington Post, the Wall Street Journal, the New York Times and USA Today, and the major television networks. The headlines were compelling: "Aspirin May Avert Breast Cancer" (The Post), "Aspirin Is Seen as Preventing Breast Tumors" (the Times).

In each story, the media highlighted the change in risk associated with aspirin — noting prominently something to the effect that aspirin users had a "20 percent lower risk" compared with nonusers. The implied message in many of the stories was that women should consider taking aspirin to avoid breast cancer.

But the media message probably misled readers about both the size and certainty of the benefit of aspirin in preventing breast cancer. That's because the reporting left key questions unanswered:

See ASPIRIN, *Page F4*

"In each story, the media highlighted the change in risk associated with aspirin -- noting prominently something to the effect that aspirin users had a "20 percent lower risk" compared with nonusers."

"The implied message in many of the stories was that women should consider taking aspirin to avoid breast cancer."

Schwartz LM et al. The Washington Post Tuesday, May 10, 2005.

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Contrasting Absolute and Relative Risk

Prospective Results from the Women's Health Initiative

- **Absolute risk**
  - **The risk of developing breast cancer for postmenopausal women who do not take aspirin on a regular basis is 955/194, 884 person-years, or 0.49%**
- **Relative risk**
  - **Taking an aspirin a day for at least 5 years reduces risk by 20% to 99/24,398 person-years, or 0.41%; this is a relative risk reduction of 20%**
- **The absolute risk reduction is only 0.08% versus a relative risk reduction of 20%**

Harris RE et al. Cancer Research 2003;63:6096-6101.

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Contrasting Absolute and Relative Risk

Prospective Results from the Women's Health Initiative

"Another way to present these results would be to say that a woman's chance of being free from breast cancer over the next five years was 98.4 percent if she used aspirin and 98 percent if she did not.

"Seeing the actual risks leaves a very different impression than a statement like 'aspirin lowers breast cancer risk by 20 percent.' "

Schwartz LM et al. The Washington Post Tuesday, May 10, 2005.

Concepts Related To Benefit / Risk: P Value

- This gives an indication of how strong the likelihood that any difference is NOT due to chance
- The smaller the p value, the more convinced you are that something is going on that is not just random
- This does not state anything about the size or the importance of the nonrandom effect
- P value is not the same as effect size

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Concepts Related To Benefit / Risk: Effect Size - Number Needed To Treat

- NNT is one measure of effect size
- It is independent of p value and does not say anything about the likelihood of the difference between treatments being due to chance alone
- Helps you judge the clinical significance of a statistically significant result

Number Needed To Treat

- How many patients would you need to treat with Drug A instead of Drug B before you would see one extra responder, or one adverse outcome?

The smaller the NNT, the larger the differences between the two drugs, i.e. larger numbers mean more patients needed to treat to see the difference in effect

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Calculating NNT is Easy

What is the NNT for an outcome for Drug A versus Drug B?

f_A = frequency of outcome for Drug A
f_B = frequency of outcome for Drug B
Attributable Risk (AR) = $f_A - f_B$
NNT= 1/AR

By convention, when not presenting fractions, we round up the NNT to the next *higher* whole number

For example, Drug A results in remission 50% of the time, but Drug B results in remission 20% of the time.

NNT = 1/[0.50-0.20] = 1/0.30 = 3.33 → Round up to 4

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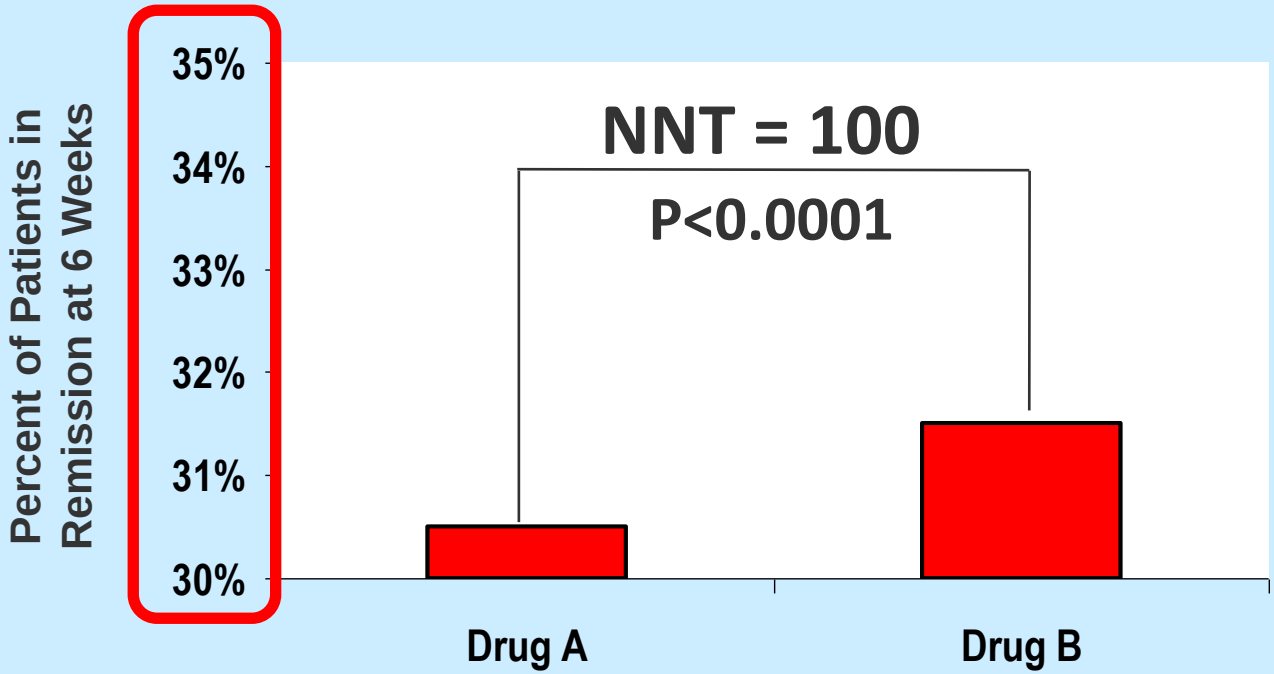
The difference in remission for a major depressive episode at 6 weeks for Drug A versus Drug B is highly statistically significant, but clinically irrelevant

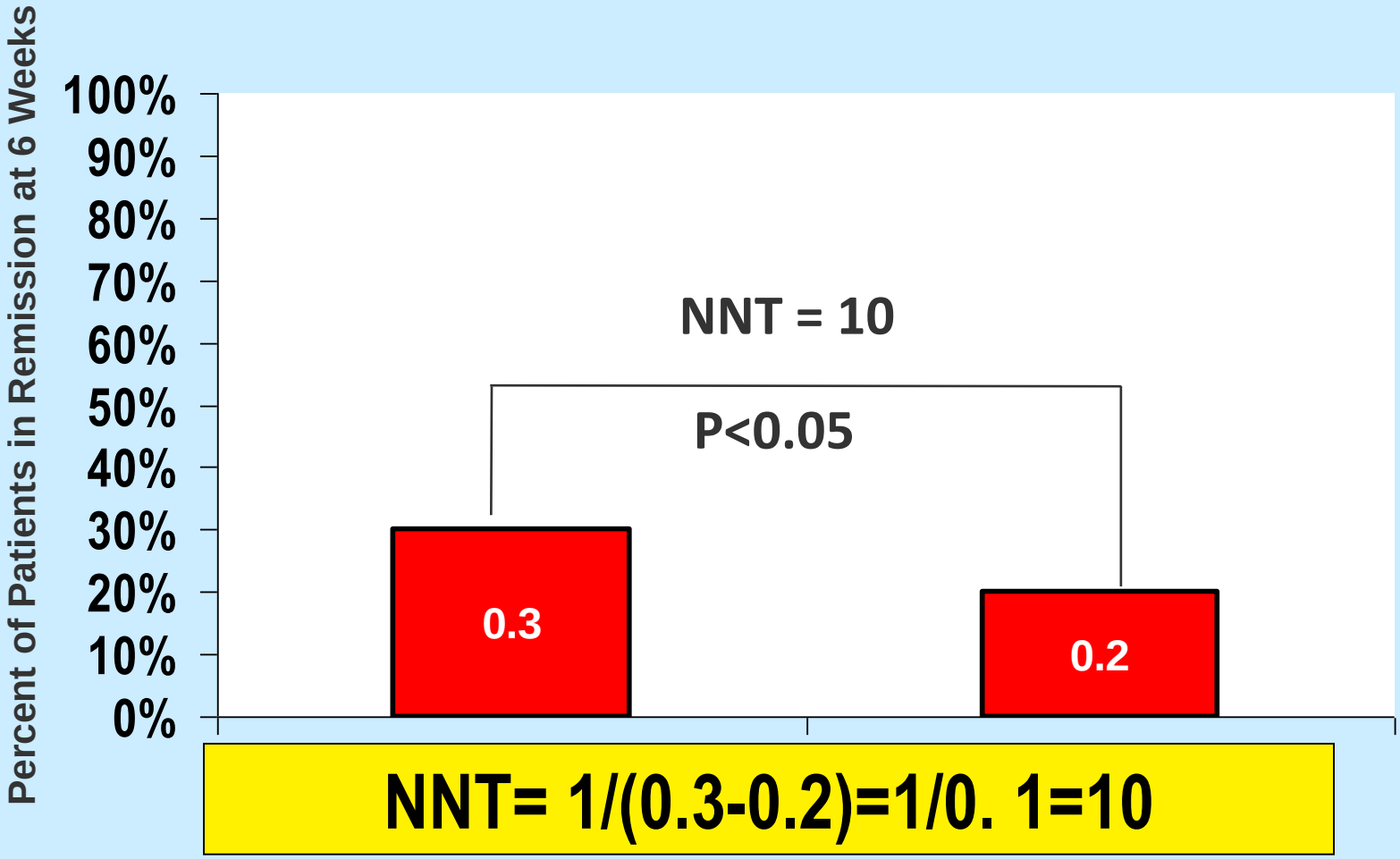


NNT= 1/(0.315-0.305)=1/0.01=100

Citrome L Acta Psych Scand. 2008;117:412-419.

Relative versus absolute differences:

Is Drug A (30% remission) is "50% better" than Drug B (20% remission)?



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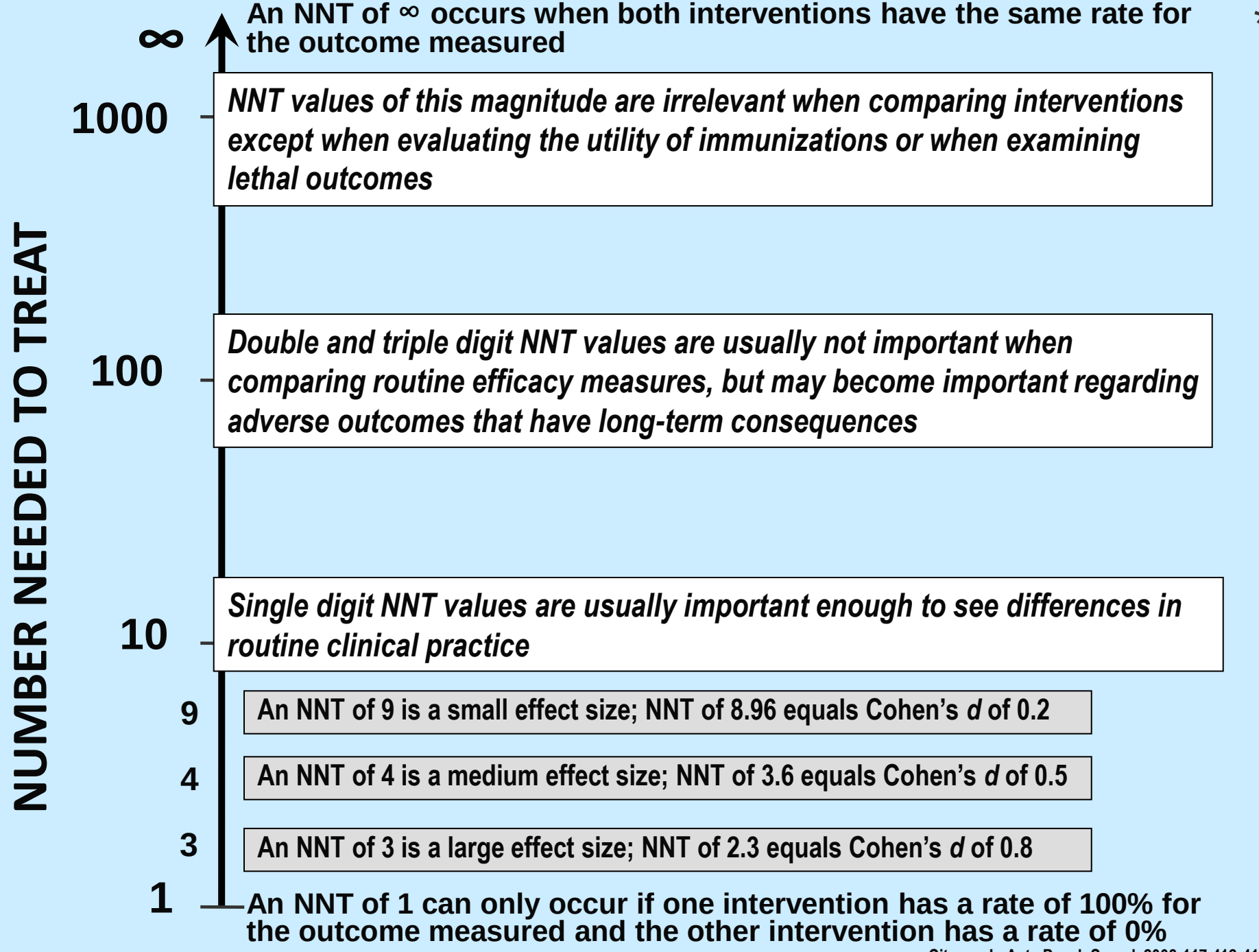
What Is NNH?

- NNH is Number Needed to Harm
- We would use NNH when referring to an outcome we are trying to avoid, or to refer to a disadvantage for Drug A versus Drug B
- In calculating NNT, if it is a negative number, we can call it a NNH



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What Is A Clinically Important NNT?

- A large NNT of 100 or more means that there is little difference between choosing Drug A or Drug B for the outcome measured
- A small NNT of 2 would be a hugely important difference
- Some NNTs may be clinically important, even if they are relatively large, for example when the outcome is death

Examples of NNT for Medical Conditions

Condition	Intervention	Prevented Event	NNT
Diabetes[1]	Insulin	Neuropathy	15
Acute myocardial infarction (MI)[2]	Streptokinase and aspirin	Death in 5 weeks	20
Prematurely born baby[3]	Prenatal corticoid	Respiratory distress syndrome or prematurity	11
Diastolic blood pressure 115-120[4]	Antihypertensive drugs for 5 years	Death, stroke, or MI	3
Diastolic blood pressure 90-109[4]	Antihypertensive drugs for 5 years	Death, stroke, or MI	141

NNT also depends on individual baseline risk

1. Centre for Evidence-Based Medicine. Available at: http://www.cebm.net/index.aspx?o=1044. Accessed Dec 17, 2007.
2. Second International Study of Infarct Survival Collaborative Group. *Lancet.* 1988;2(8607):349-360.
3. Crowley PA. *Am J Obstet Gynecol.* 1995;173(1):322-335.
4. A'Court C. *BMJ.* 2002;324(7350):1375.

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Examples of NNT for Psychiatric Conditions

Disorder	Treatment Comparison	Outcome Measure	NNT
Major depression	Antidepressant vs placebo	50% Reduction in Ham-D	3
Acute mania	Valproate or lithium vs placebo	50% Reduction in SADS-M	5
Bipolar disorder	Lithium vs placebo	Relapse	3
Schizophrenia	Antipsychotic vs placebo	40% Reduction in BPRS or "much improved" CGI scale	2-5
Panic disorder	SSRI vs placebo	Panic free	3-6
Social phobia	Paroxetine vs placebo	"Much improved" CGI scale	3
Obsessive-compulsive disorder	SSRI vs placebo	35% Reduction in Y-BOCS	4-5
Bulimia nervosa	Antidepressants vs placebo	Remission	9

Pinson L et al. Psychiatric Services 2003;54:145-146.

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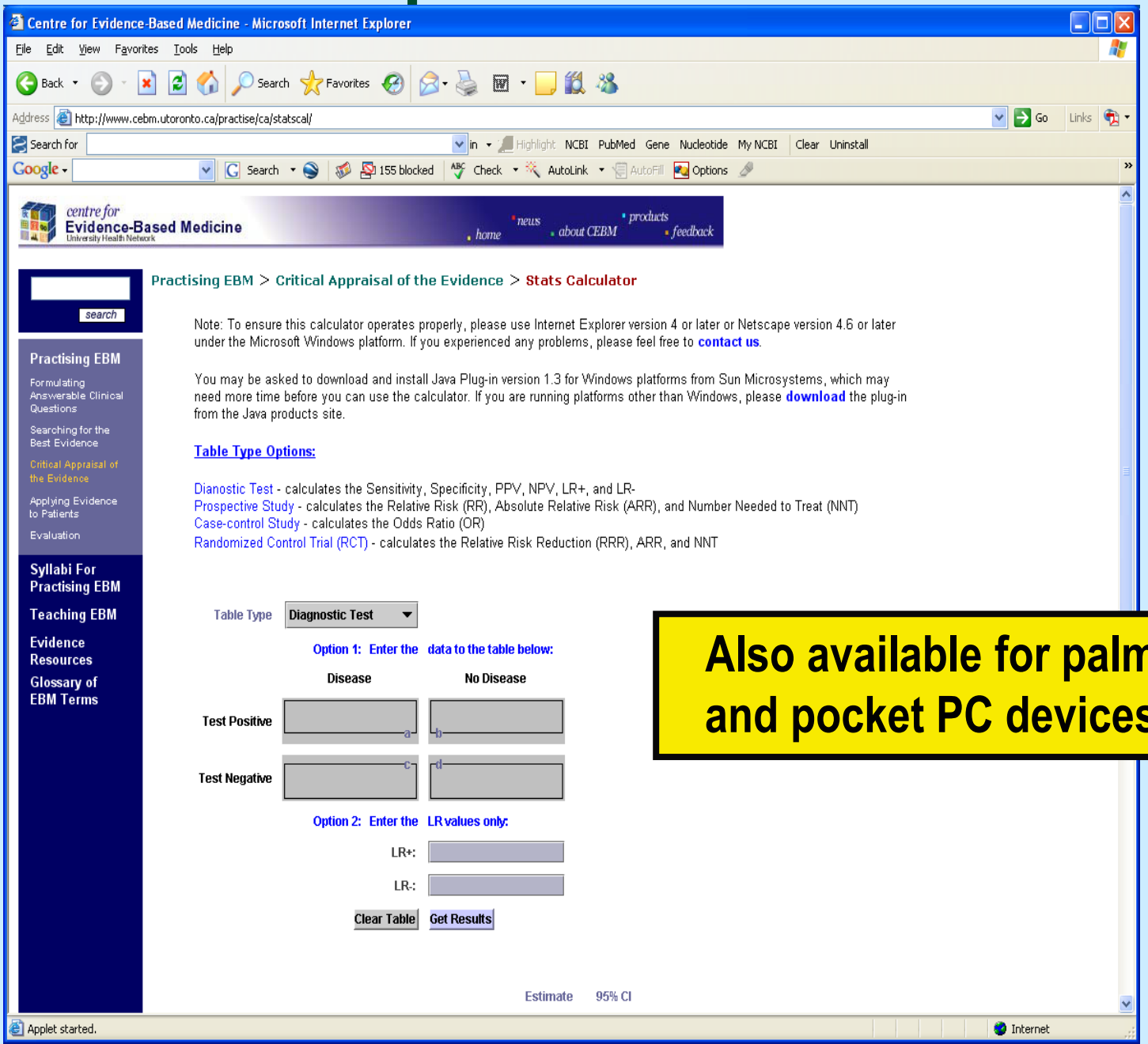
P Values vs NNT

P VALUE	NNT
Indicates Statistical Significance	Indicates Clinical Significance
Independent of Effect Size	Independent of P Value

Can We Express Statistical and Clinical Significance Together?

- We can do this for NNT by also giving the "Confidence Interval" or CI
  - What is the range of values of NNT within which "the truth" probably lies?
  - If this range includes "infinity" it means it can take an infinite number of patients to see a difference, i.e. there is no difference
  - CI tells us about the precision of our estimate of NNT
- You can calculate it with a simple formula, or use an on-line calculator

RESOURCES: http://www.cebm.utoronto.ca/



Also available for palm and pocket PC devices

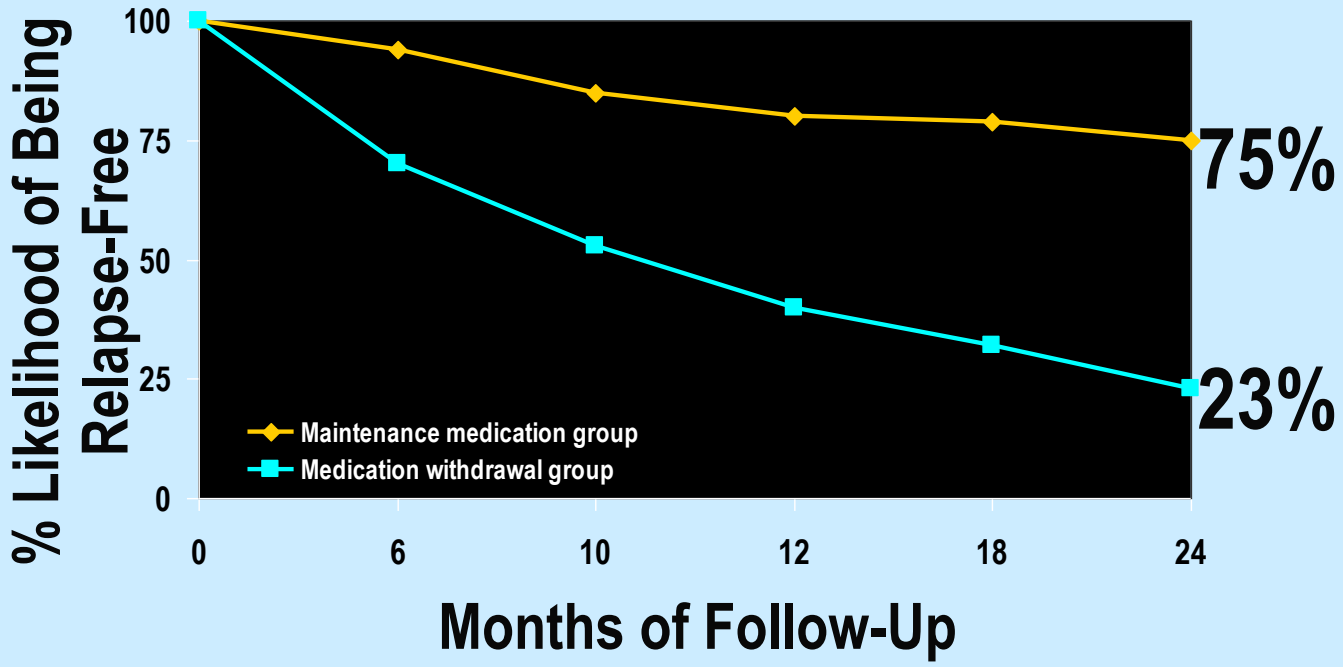
Limitations Of Using NNT / NNH

- It is most valid to calculate from a randomized controlled trial with identical conditions for all drugs under study
- Results are only calculable for binary or dichotomous events that are either present or absent, and do not apply to continuous variables such as the value of a blood test
- However, values with clinically significant thresholds, such as weight gain > 7% can be expressed as an NNT because then they are binary

QUESTION

What is the NNT?

Relapse in Schizophrenia: Medication versus No Medication



A. 1

B. 2

C. 3

D. .52

Adapted from DeQuardo JR et al. Journal of Psychiatry Research 1998;32:229-242.

QUESTION

What is the NNT?

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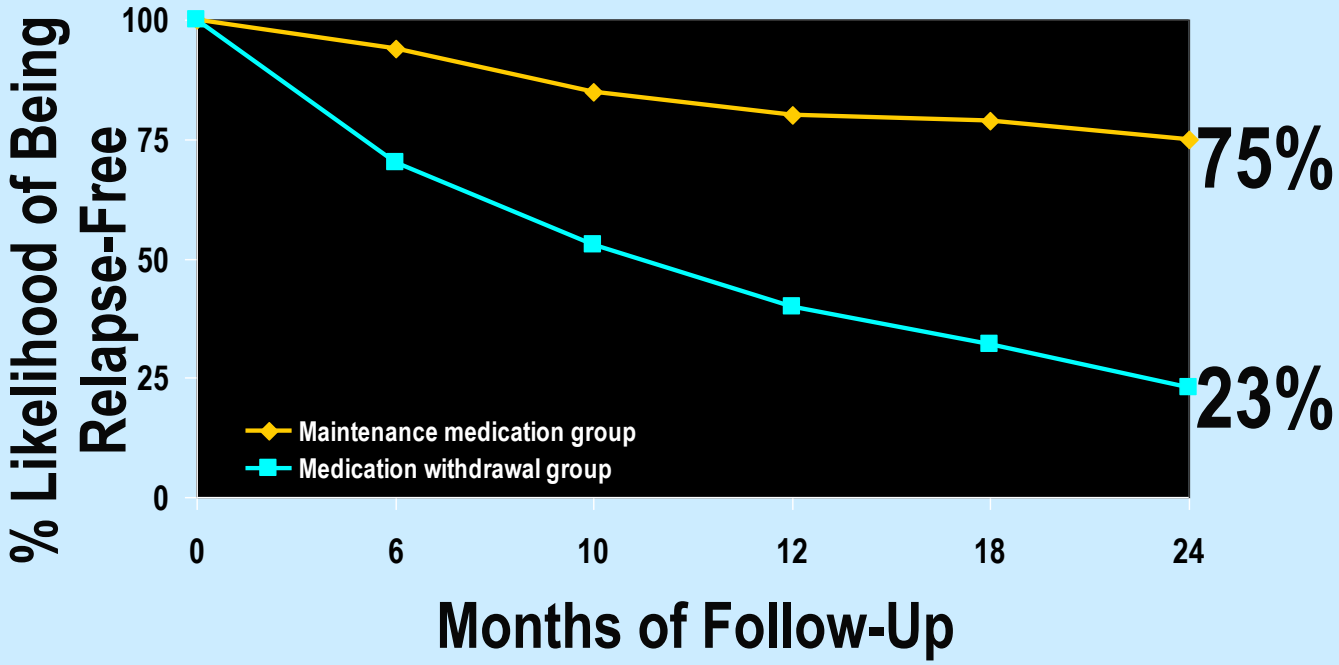
Relapse in Schizophrenia: Medication versus No Medication



A. 1

B. 2

C. 3

D. .52

NNT = 1/(.75-.23)=1/.52=1.92, round up to 2

Adapted from DeQuardo JR et al. Journal of Psychiatry Research 1998;32:229-242.

There Are Other Measures of Effect Size

Effect size	Range of possible values (weakest, i.e. no difference, to strongest)	Typical example of a small effect	Typical example of a large effect
Relative measures			
Relative risk	1 to ∞	2	4
Odds ratio	1 to ∞	2	4
Hazard ratio	1 to ∞	2	4
Relative risk increase	1 to ∞	<100%	300%
Absolute measures			
Attributable risk	0 to 100%	<10%	33%-50%
Number needed to treat	∞ to 1	≥10	2-3
Cohen's *d*	0 to ∞	0.2	0.8
Area under the curve	0.50 to 1.00 or 0.50 to 0	0.56	0.71
Success rate difference	0 to 1	0.11	0.43

Citrome L. ***Acta Psychiatr Scand*** **(in press)**

See also: Kraemer HC, Kupfer DJ. ***Biol Psychiatry*** 2005;59:990-996.

Interpreting Clinical Trials

- What is the problem?
- What is EBM?
- More about benefit, risk, and how NNT can help us understand this
- **Applying EBM and NNT**
- Summary

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Example:

Should I use intramuscular haloperidol or an intramuscular second-generation antipsychotic to treat agitation in my patient with schizophrenia?

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1) Formulate Question (PICO)

"Should my patient with agitation associated with schizophrenia take IM ziprasidone, olanzapine, or aripiprazole, instead of haloperidol?"

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2) Search for Answers

- RCTs can demonstrate efficacy
- Medline search reveals several RCTs - registration studies that the manufacturers use to obtain FDA approval
- A quantitative review matched the PICO:
  - Patient: Schizophrenia and agitation
  - Intervention: Antipsychotic IM
  - Control: Haloperidol
  - Outcome:
    - Improvement on a specific agitation scale
    - Avoidance of EPS

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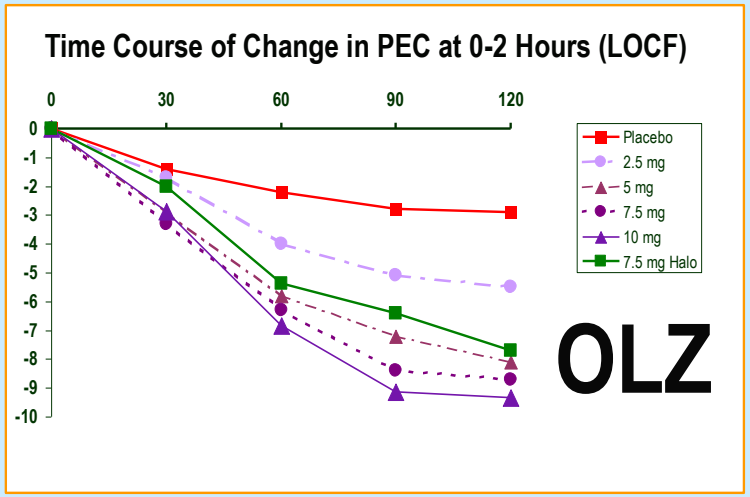
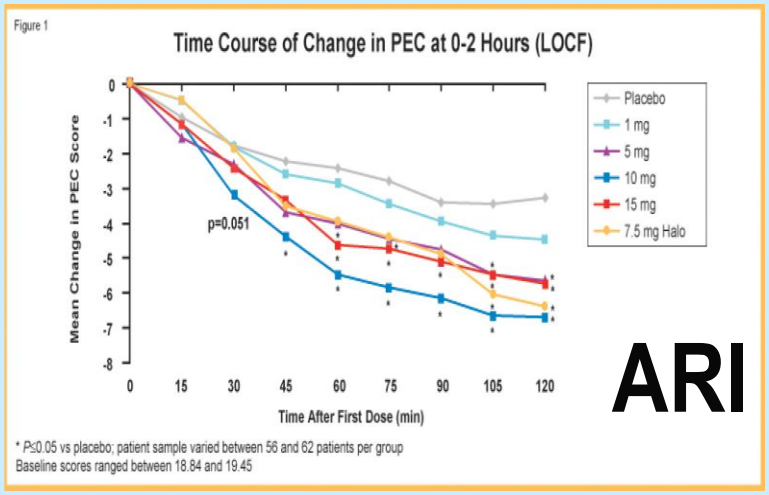
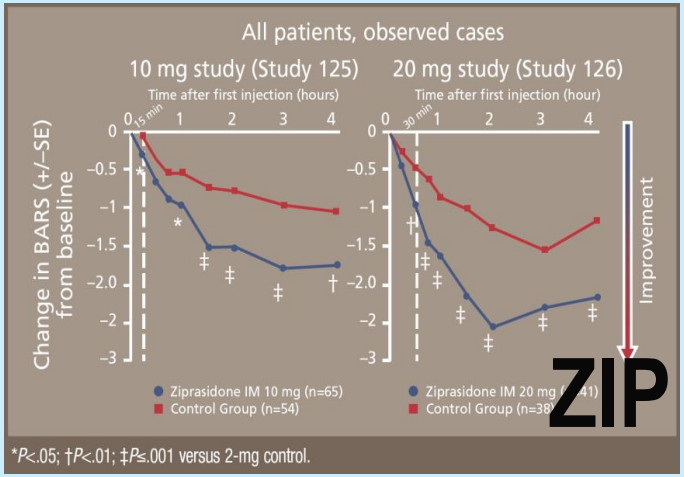
Using Intramuscular Agents for Agitation







Breier A et al. Arch Gen Psychiatry 2002;59:441-448; Modell S et al. Poster P02.428 presented at the 24th CINP Congress, Paris, France, June 20-24, 2004; Lesem MD et al. Journal Clinical Psychiatry 2001;62:12-18;Daniel DG et al. Psychopharmacology (Berl) 2001;155:128-134.

Using Intramuscular Agents for Agitation

Medication	Study	Disease	Definition of Response	Results versus placebo (or placebo-equivalent)
Olanzapine 10 mg	Breier, 2002	Schizophrenia	40% reduction or more on PANSS-EC 2 hours after the first injection	80% vs 20%
	Wright, 2001	Schizophrenia		73% vs 33%
	Meehan, 2001	Bipolar Mania		81% vs 44%
Aripiprazole 9.75 mg	Tran-Johnson, 2007	Schizophrenia		54% vs 36%
	Andrezina, 2006	Schizophrenia		55% vs 36%
	Zimbroff, 2007	Bipolar Mania		69% vs 37%
Ziprasidone 10-20 mg	Lesem, 2001	Schizophrenia	At least 2 point reduction on BARS 2 hours after the first injection	57% vs 30%
	Daniel, 2001	Schizophrenia		90% vs 34%

Citrome L. J Clin Psychiatry 2007;68:1876-1885.

*

3) Appraise the Evidence

- **Methods**
  - **Concealed randomization? Yes**
  - **Double blind? Yes**
  - **Were groups comparable? Yes**
    - **Aside from experimental treatment, treated equally? Yes**

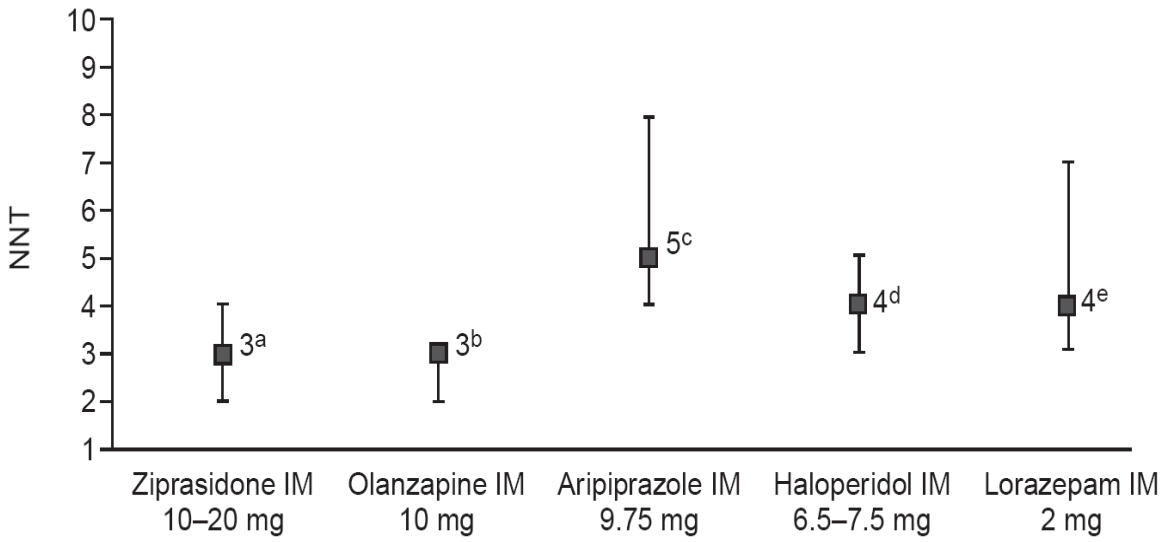
*

Using Intramuscular Agents for Agitation
What is the NNT versus Placebo?

Medication	Study	Disease	Results versus placebo (or placebo-equivalent)	NNT?
Olanzapine 10 mg	Breier, 2002	Schizophrenia	80% vs 20%	
	Wright, 2001	Schizophrenia	73% vs 33%	
	Meehan, 2001	Bipolar Mania	81% vs 44%	
Aripiprazole 9.75 mg	Tran-Johnson, 2007	Schizophrenia	54% vs 36%	
	Andrezina, 2006	Schizophrenia	55% vs 36%	
	Zimbroff, 2007	Bipolar Mania	69% vs 37%	
Ziprasidone 10-20 mg	Lesem, 2001	Schizophrenia	57% vs 30%	
	Daniel, 2001	Schizophrenia	90% vs 34%	

Citrome L. J Clin Psychiatry 2007;68:1876-1885.

Figure 1. Response and Number Needed to Treat for Ziprasidone, Olanzapine, and Aripiprazole at the Doses Recommended by the Manufacturer, and Comparators



[a]Response for ziprasidone defined as at least a 2-point reduction in Behavioral Activity Rating Scale 2 hours after the first injection.[8,9] NNT = 3, 95% CI = 2 to 4.

[b]Response for olanzapine was defined as a 40% or more reduction on the Positive and Negative Syndrome Scale-Excited Component 2 hours after the first injection.[10–15] NNT = 3, 95% CI = 2 to 3.

[c]Response for aripiprazole was defined as a 40% or more reduction on the Positive and Negative Syndrome Scale-Excited Component 2 hours after the first injection.[18–20] NNT = 5, 95% CI = 4 to 8.

[d]Response for haloperidol was defined as a 40% or more reduction on the Positive and Negative Syndrome Scale-Excited Component 2 hours after the first injection.[10–13,18,19] NNT = 4, 95% CI = 3 to 5.

[e]Response for lorazepam was defined as a 40% or more reduction on the Positive and Negative Syndrome Scale-Excited Component 2 hours after the first injection.[14,15,20] NNT = 4, 95% CI = 3 to 7.

Abbreviations: IM = intramuscular, NNT = number needed to treat.

How large was the treatment effect (NNT)?

How precise is the result (CI)?

Citrome L. J Clin Psychiatry 2007;68:1876-1885.

*

Using Intramuscular Agents for Agitation
What is the NNH for EPS in Schizophrenia?

Medication	Study	Adverse Event (as reported)	NNH vs Placebo	NNH vs HAL
Olanzapine	Breier, 2002*	Acute dystonia	∞	-20 (ns)
		Parkinsonism	142 (ns)	-7
		Akathisia	86 (ns)	-15 (ns)
		Requiring anticholinergic	Not reported	-15 (ns)
	Wright, 2001	Acute dystonia	∞	-14
		Extrapyramidal syndrome	-92 (ns)	-21
		Requiring anticholinergic	115 (ns)	-7
Aripiprazole	Tran-Johnson, 2007*	Acute dystonia	116 (ns)	-17 (ns)
		Akathisia	47	-12
	Andrezina, 2006	Extrapyramidal symptoms	-167 (ns)	-10

Citrome L. J Clin Psychiatry 2007;68:1876-1885.

* Data from all doses of the medication were pooled from these multiple dose studies

Using Intramuscular Agents for Agitation
What is the NNH for Other Adverse Events?

Table 3. Treatment-Emergent Adverse Events Reported in Product Labeling

Second-Generation Antipsychotic	Adverse Event	NNH Versus Placebo	95% Confidence Interval[d]
Ziprasidone[a]	Somnolence	22	NS* (–27 to –∞ and 8 to ∞)
	Nausea	18	NS* (–74 to –∞ and 8 to ∞)
	Dizziness	37	NS* (–35 to –∞ and 12 to ∞)
	Headache	15	8 to 703
Olanzapine[b]	Somnolence	34	NS* (–179 to –∞ and 16 to ∞)
	Dizziness	50	NS* (–108 to –∞ and 21 to ∞)
	Hypotension	50	30 to 154
	Asthenia	100	NS* (–93 to –∞ and 33 to ∞)
Aripiprazole[c]	Headache	20	11 to 170
	Nausea	17	11 to 38
	Dizziness	34	NS* (–137 to –∞ and 15 to ∞)
	Somnolence	34	NS* (–238 to –∞ and 16 to ∞)

*NS = not statistically significant at $p < .05$.
[a]Data from Pfizer,[5] Table 5, calculated by combining data regarding ziprasidone 10 mg and 20 mg, and comparing this with the placebo-equivalent dose of ziprasidone 2 mg.
[b]Data from Eli Lilly,[6] Table 3.
[c]Data from Bristol-Myers Squibb,[7] Table 3.
[d]When not statistically significant, the 95% confidence interval represents both positive and negative numbers. (See text.)
Abbreviation: NNH = number needed to harm.

Citrome L. J Clin Psychiatry 2007;68:1876-1885.

*

4) Apply the Results

- Is my patient like those studied?
  - More agitated?
  - Abusing street drugs and/or alcohol?
  - Medically compromised?
  - Receiving multiple medications?
- Is treatment consistent with my patient's values and preferences?
- Is treatment feasible in my practice setting?
  - Formulary?
  - Cost?

How Does This Apply to My Patient?

- FOR SGA IM
  - Response to SGA IM comparable or perhaps better than to HAL IM
  - Risk of EPS certainly lower for OLZ or ARI compared to HAL IM; ZIP IM was not directly compared with HAL IM
  - Adherence and therapeutic alliance would be enhanced by avoiding possibility of acute dystonia or akathisia

- AGAINST SGA IM
  - Patient has alcohol dependence; the evidence cited did not include such patients
  - Acquisition cost is higher

BOTTOM LINE:

For this patient, SGA IM has a greater benefit than harm compared with HAL IM

Example:

Which antipsychotic should I prescribe for my patient with schizophrenia?

1) Formulate Question (PICO)

"Should I switch to olanzapine, quetiapine, risperidone, ziprasidone, or clozapine?"

2) Search for Answers

- Large effectiveness trials may provide guidance
- Medline search reveals a large effectiveness trial that was randomized, mostly double-blind, and that compared multiple antipsychotics
    - Patient: Schizophrenia, not first episode, not refractory, can have comorbid medical conditions, can have comorbid alcohol or substance use disorder
    - Intervention: Oral antipsychotic
    - Control: Other oral antipsychotic
    - Outcome:
        - Time on medication; all-cause discontinuation
        - Multiple tolerability outcomes

CATIE

An effectiveness study that tested switches

CATIE Trial Design

1894 screened

1493 randomized

1460 after one site excluded

1432 received Rx

Phase 1*

Double-blind, random treatment assignment

R → OLANZAPINE
R → QUETIAPINE
R → RISPERIDONE
R → ZIPRASIDONE
R → PERPHENAZINE

UP TO 18 Months

Phase 2

Participants who discontinue Phase 1 choose either the clozapine or the ziprasidone randomization pathways

R → CLOZAPINE (open-label)
R → OLANZAPINE, QUETIAPINE or RISPERIDONE

R → ZIPRASIDONE
R → OLANZAPINE, QUETIAPINE or RISPERIDONE

No one assigned to same drug as in Phase 1

CLINICIANS CHOOSE PATHWAY

Phase 3

Participants who discontinue Phase 2 choose one of the following open-label treatments

- ARIPIPRAZOLE
- CLOZAPINE
- FLUPHENAZINE DECANOATE
- OLANZAPINE
- PERPHENAZINE
- QUETIAPINE
- RISPERIDONE
- ZIPRASIDONE
- 2 of the antipsychotics above

*Phase 1A: participants with TD (N=231) do not get randomized to perphenazine; phase 1B: participants who fail perphenazine will be randomized to an atypical (olanzapine, quetiapine, or risperidone) before eligibility for phase 2.

Stroup TS et al. Schizophrenia Bulletin 2003;29:15-31; http://www.catie.unc.edu/schizophrenia

CATIE Trial Design

Of the 74% that discontinued Phase 1, approximately half entered Phase 2

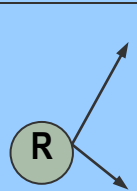
99 in Efficacy Pathway
(90 included in the effectiveness analysis)

444* in Tolerability Pathway
(333 included in the effectiveness analysis)

*some were actually eligible for the Efficacy Pathway but did not want to be possibly randomized to clozapine

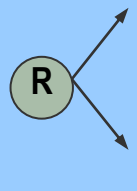
Phase 2

Participants who discontinue Phase 1 choose either the clozapine or the ziprasidone randomization pathways



CLOZAPINE
(open-label)

OLANZAPINE, QUETIAPINE or RISPERIDONE



ZIPRASIDONE

OLANZAPINE, QUETIAPINE or RISPERIDONE

No one assigned to same drug as in Phase 1; minimum 6 months offered to patients if desired

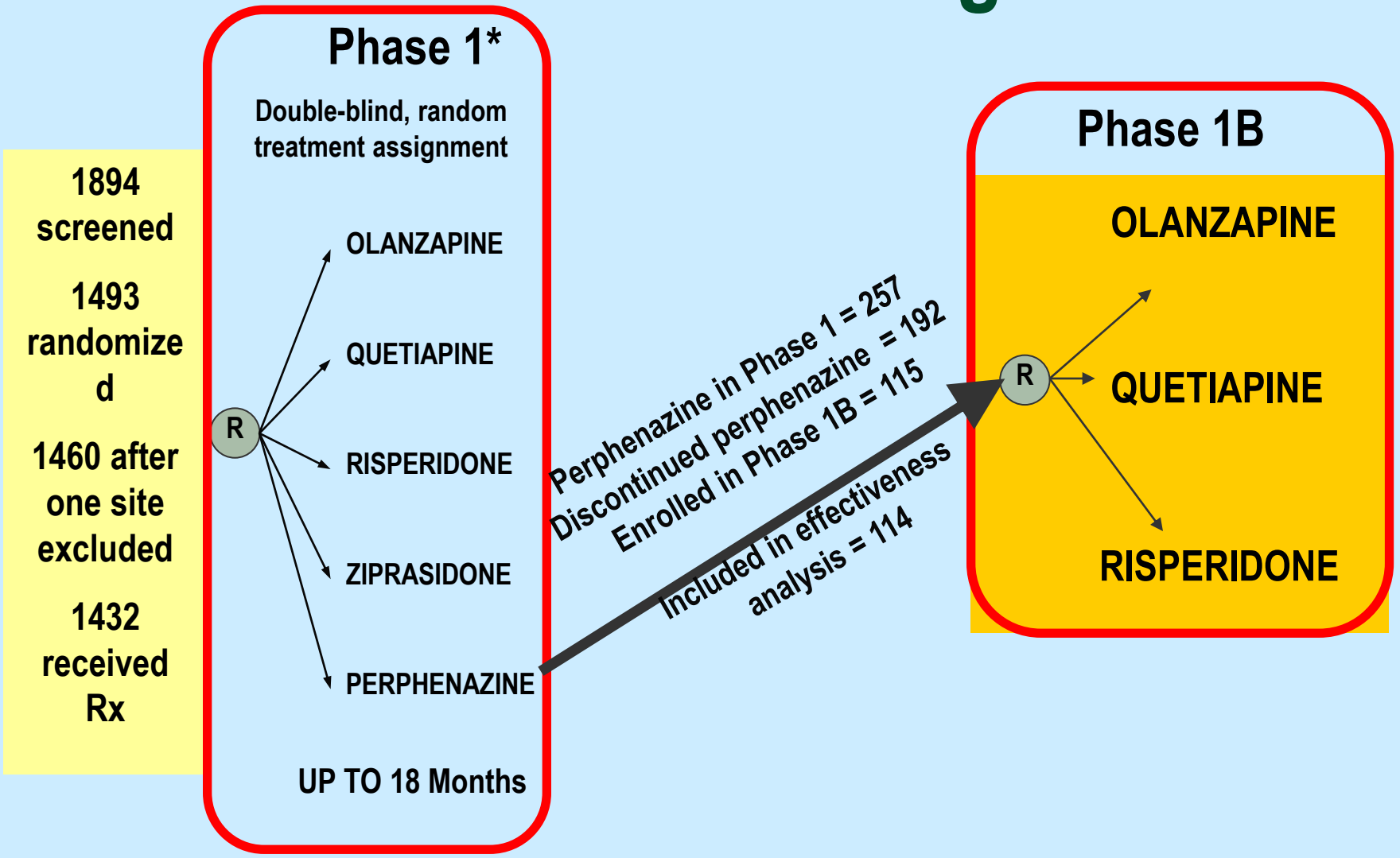
Phase 3

Participants who discontinue Phase 2 choose one of the following open-label treatments

- ARIPIPRAZOLE
- CLOZAPINE
- FLUPHENAZINE DECANOATE
- OLANZAPINE
- PERPHENAZINE
- QUETIAPINE
- RISPERIDONE
- ZIPRASIDONE
- 2 of the antipsychotics above

McEvoy JP et al. American Journal of Psychiatry 2006;163:600-610; Stroup TS et al. American Journal of Psychiatry 2006;163:611-622.

CATIE Trial Design



*Phase 1A: participants with TD (N=231) do not get randomized to perphenazine; phase 1B: participants who fail perphenazine will be randomized to an atypical (olanzapine, quetiapine, or risperidone) before eligibility for phase 2.

Stroup TS et al. American Journal of Psychiatry 2007;164:415-427.

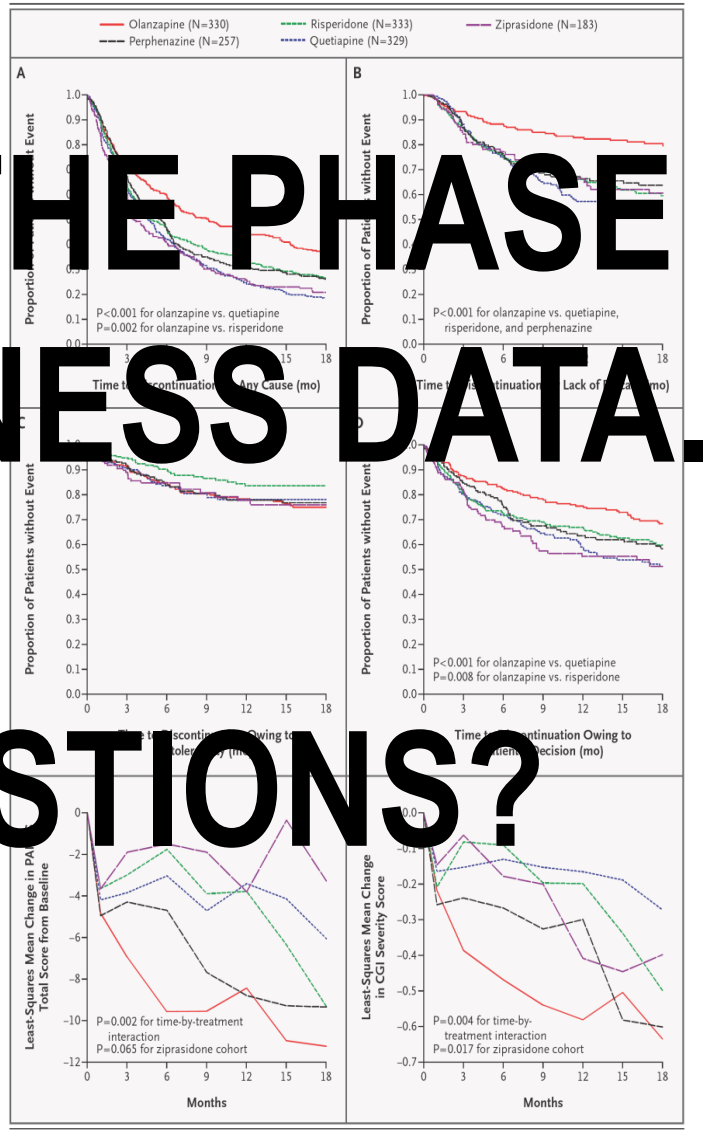
3) Appraise the Evidence

- **Methods**
  - **Concealed randomization? Yes**
  - **Double blind? Yes, except for clozapine pathway in Phase 2**
  - **Were groups comparable? Yes, except for the perphenazine cohort for whom TD was an exclusion criterion**
    - **Aside from experimental treatment, treated equally? Yes**

Table 2. Outcome Measures of Effectiveness in the Intention-to-Treat Population.*

Outcome	Olanzapine (N=330)	Quetiapine (N=329)	Risperidone (N=333)	Perphenazine (N=257)†	P Value‡	Ziprasidone (N=183)§
Dose¶						
Mean modal dose — mg per day/total no. of patients	20.1/312	543.4/309	3.9/305	20.8/245		112.8/165
Maximal dose received — no. of patients (%)	124/312 (40)	137/309 (44)	122/305 (40)	98/245 (40)	<0.001	80/165 (48)
Discontinuation of treatment for any cause						
Discontinuation — no. of patients (%)	210 (64)	269 (82)	245 (74)	192 (75)		145 (79)
Kaplan–Meier time to discontinuation — mo						
Median (95% CI)	9.2 (6.9–12.1)	4.6 (3.9–5.5)	4.8 (4.0–6.1)	5.6 (4.5–6.3)		3.5 (3.1–5.4)
Cox-model treatment comparisons‖						
Olanzapine						
Hazard ratio (95% CI)		0.63 (0.52–0.76)	0.75 (0.62–0.90)	0.78 (0.63–0.96)	0.004**	0.76 (0.60–0.97)
P value		<0.001**	0.002**	0.021		0.028
Quetiapine						
Hazard ratio (95% CI)			1.19 (0.99–1.42)	1.14 (0.93–1.39)		1.01 (0.81–1.27)
P value			0.06	0.21		0.94
Risperidone						
[illegible]				[illegible]		[illegible]
Perphenazine						
[illegible]						
Discontinuation of treatment for lack of efficacy						
Discontinuation — no. of patients (%)	48 (15)	[illegible]	91 (27)	[illegible]		[illegible] (24)
Kaplan–Meier time to discontinuation —						
25th percentile (95%		6.[illegible]	[illegible] (4.4–9.0)	6.1 (4.5–9.[illegible])		6.[illegible]
Cox-model treatment comparisons‖						
Olanzapine						
Hazard ratio (95% CI)		0.41 (0.29–0.57)	0.45 (0.32–0.64)	0.47 (0.31–0.70)	<0.001**	0.59 (0.37–0.93)
P value		<0.001**	<0.001**	<0.001**		0.026
Quetiapine						
P value			0.49	0.47		0.69
Risperidone						
P value						0.93
Perphenazine						
P value						0.4
Discontinuation of treatment owing to intolerance†††						
Discontinuation — no.			(10)	40 (16)		28
Cox-model treatment comparisons‖						
Risperidone						
Hazard ratio (95% CI)		0.62 (0.41–0.95)	0.65 (0.42–1.00)	0.60 (0.36–[illegible])	0.05[illegible]	0.79 (0.[illegible])
P value		0.027		0.043		0.[illegible]
Olanzapine						
P value			0.84	0.49		0.28
Quetiapine						
P value				0.97		0.87
Perphenazine						
P value						0.19
Patient's decision to discontinue treatment§§						
Discontinuation — no. (%)	78 (24)	109 (33)	101 (30)	77 (30)		63 (34)
Kaplan–Meier time to discontinuation — mo						
25th percentile (95% CI)	12.3 (8.0–17.8)	4.9 (3.1–7.0)	4.5 (3.1–8.8)	6.2 (4.7–8.1)		3.4 (3.0–6.1)
Cox-model treatment comparisons‖						
Olanzapine						
Hazard ratio (95% CI)		0.56 (0.42–0.75)	0.67 (0.50–0.90)	0.70 (0.50–0.98)	0.034**	0.63 (0.43–0.93)
P value		<0.001**	0.008**	0.036		0.018
Quetiapine						
P value			0.21	0.46		0.63
Risperidone						
P value				[illegible]		[illegible]
Perphenazine						
P value						
Duration of successful treatment¶¶						
Kaplan–Meier time to discontinuation — mo						
Median (95% CI)	[illegible]	1 [illegible]	(0–1)	1 (1–2)		[illegible]
Cox-model treatment comparisons‖						
Olanzapine						
Hazard ratio (95% CI)		0.53 (0.43–0.67)	0.69 (0.55–0.87)	0.73 (0.57–0.93)	<0.001**	0.75 (0.58–0.94)
P value		<0.001**	0.002**	0.013**		0.017
Quetiapine						
Hazard ratio (95% CI)			1.30 (1.04–4.63)	1.28 (1.00–1.64)		1.06 (0.85–1.33)
P value			0.02**	0.05		0.61
Risperidone						
P value				0.72		0.74
Perphenazine						
P value						0.25

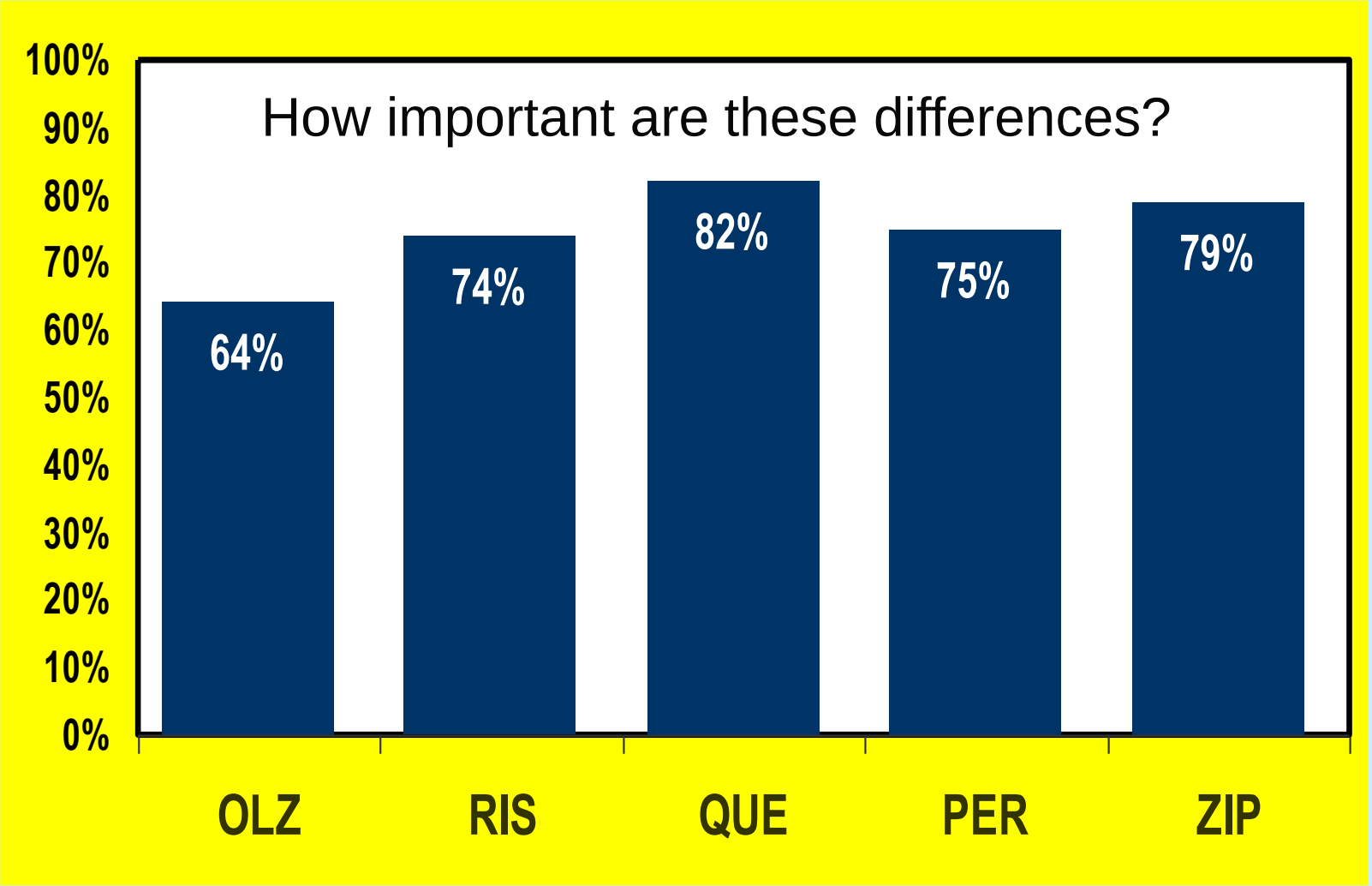
* CI denotes confidence interval.
† Patients with tardive dyskinesia were excluded from the perphenazine group.
‡ The overall P value is for the comparison of olanzapine, quetiapine, risperidone, and perphenazine with the use of a 3 df test from a Cox model for survival outcomes, excluding patients with tardive dyskinesia. If the difference among the groups was significant at a P value of less than 0.05, the three atypical agents were compared with each other by means of step-down or closed testing to identify significant differences (P<0.05) between groups. Each atypical agent was then compared with perphenazine by means of a Hochberg adjustment. The smallest P value for the perphenazine group was compared with a value of 0.017 (0.05÷3).
§ Statistical analyses involving the ziprasidone group were confined to the cohort of patients who underwent randomization after ziprasidone was added to the study, with the use of a Hochberg adjustment for four pairwise comparisons. The smallest P value was compared with a value of 0.013 (0.05÷4).
¶ The modal dose and percentages of patients taking the maximal dose are based on the number of patients with data on the dose. Information on dose was not available for some patients who dropped out early. The P values for the percentage of patients reaching the maximal dose were calculated with the use of a 4 df test comparing all treatment groups from a Poisson regression accounting for differential exposure times, and adjusting for whether the patient had had an exacerbation in the preceding three months.
‖ For pairwise comparisons of treatment groups, Cox-model hazard ratios of less than 1 indicate a greater time to the discontinuation of the first treatment listed.
** P value is statistically significant.
†† The Kaplan–Meier 25th percentile for discontinuation owing to lack of efficacy could not be estimated for olanzapine because of the low event rates.
‡‡ The Kaplan–Meier 25th percentile for discontinuation owing to intolerability could not be estimated because of the low event rates.
§§ This category includes decisions made by both patients and their advocates.
¶¶ Successful treatment was defined by a CGI severity score of at least 3 (mildly ill) or by a score of 4 (moderately ill) with an improvement of at least two points from baseline.



THESE ARE THE PHASE 1 EFFECTIVENESS DATA.

ANY QUESTIONS?

Phase I: All-Cause Discontinuation



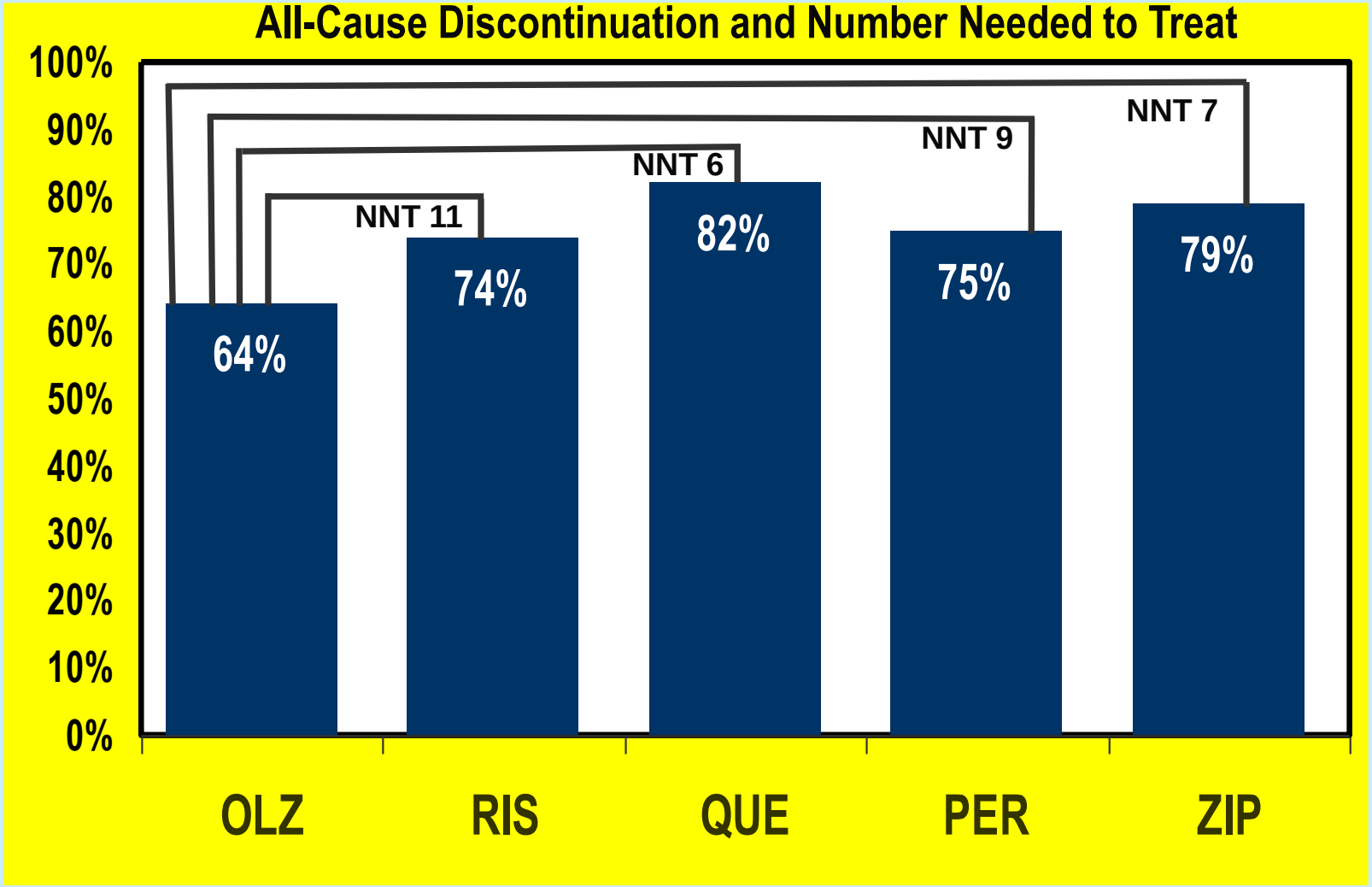
Lieberman JA et al. New England Journal of Medicine 2005;353:1209-1223.

Methods: NNT in CATIE

- Data was extracted from the principal results of CATIE Phases 1 and 2
- Attributable risk was calculated by subtracting the rate (frequency) of an event seen with Drug A from the rate observed with Drug B
    - For example all cause discontinuation on olanzapine in Phase 1 was observed at a rate of 210/330 (0.636) (number of patients on olanzapine discontinuing early divided by the number of randomized patients receiving olanzapine), and that for perphenazine was 192/257 (0.747); attributable risk in this case was 0.111
- The number of people that the intervention has to be given in order to avoid the outcome (NNT) is calculated by taking the reciprocal of the attributable risk, in this case dividing 1 by 0.111, resulting in a NNT of 9.0
- Confidence intervals were calculated for each NNT

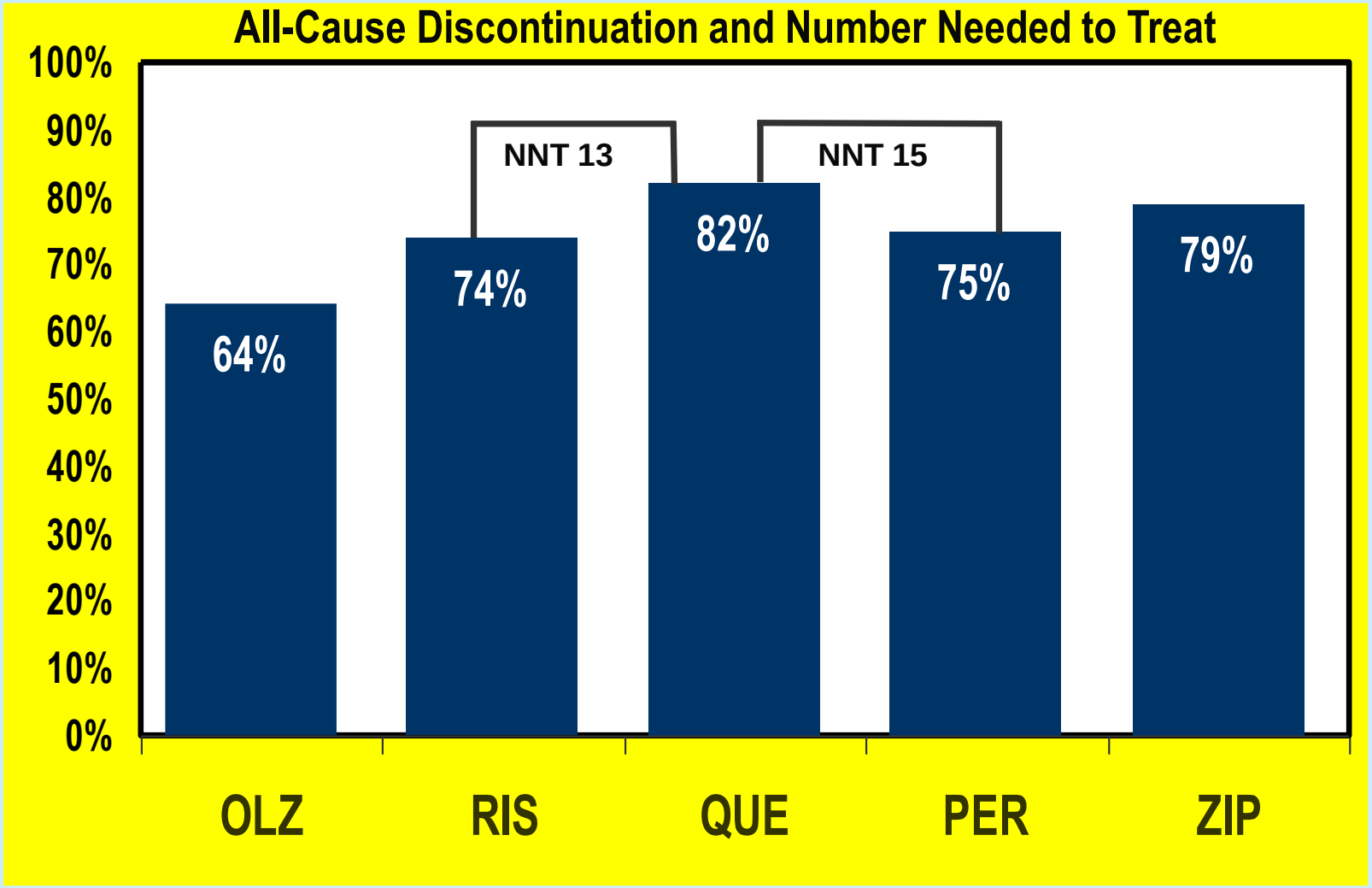
Citrome L, Stroup TS. International Journal of Clinical Practice 2006;60:933-940.

Switching to Olanzapine Has Advantages



Lieberman JA et al. New England Journal of Medicine 2005;353:1209-1223; Karagianis J et al. Current Medical Research and Opinion 2007;23:2551-2557; Citrome L, Stroup TS. International Journal of Clinical Practice 2006;60:933-940.

Switching to Risperidone or Perphenazine Has Advantages Too



Lieberman JA et al. New England Journal of Medicine 2005;353:1209-1223; Karagianis J et al. Current Medical Research and Opinion 2007;23:2551-2557; Citrome L, Stroup TS. International Journal of Clinical Practice 2006;60:933-940.

Table 1 Phase 1 effectiveness outcomes – number needed to treat (NNT) and confidence intervals (CI) for discontinuation on randomised medication*

Outcome	*NNT*	*95% CI*	*98.33% or 98.75% CI†*
OLZ ($n = 330$) vs. PER ($n = 257$)			
All-cause	9.0	5.4 to 27.4	5.0 to 50.0
Lack of efficacy	9.3	5.8 to 23.8	5.3 to 36.2
Intolerability	−31.0	−10.7 to ∞ to 34.6	−9.4 to ∞ to 23.6
Patient decision	15.8	−109.6 to ∞ to 7.4	−39.8 to ∞ to 6.6
Other reasons	−36.0	−15.7 to ∞ to 124.0	−14.0 to ∞ to 62.6
OLZ vs. QUE ($n = 329$)			
All-cause	5.5	4.0 to 8.7	3.8 to 10.0
Lack of efficacy	7.4	5.1 to 13.8	4.8 to 17.0
Intolerability	−25.7	−10.4 to ∞ to 55.2	−9.2 to ∞ to 32.5
Patient decision	10.5	6.1 to 37.8	5.6 to 88.2
Other reasons	−112.2	−21.8 to ∞ to 35.8	−18.5 to ∞ to 27.7
OLZ vs. RIS ($n = 333$)			
All-cause	10.1	5.9 to 34.4	5.4 to 73.6
Lack of efficacy	7.8	5.3 to 15.0	4.9 to 18.8
Intolerability	−11.7	−7.2 to −30.7	−6.6 to −48.1
Patient decision	14.9	−2314.9 to ∞ to 7.4	−65.3 to ∞ to 6.7
Other reasons	−104.1	−21.6 to ∞ to 37.0	−18.4 to ∞ to 28.4
OLZ vs. ZIP ($n = 183$)			
All-cause	6.4	4.3 to 12.9	3.9 to 17.8
Lack of efficacy	10.5	6.0 to 44.8	5.3 to 420.5
Intolerability	−28.7	−9.8 to ∞ to 31.1	−8.3 to ∞ to 19.8
Patient decision	9.3	5.2 to 39.7	4.7 to 399.3
Other reasons	−83.2	−18.3 to ∞ to 32.8	−15.1 to ∞ to 23.7

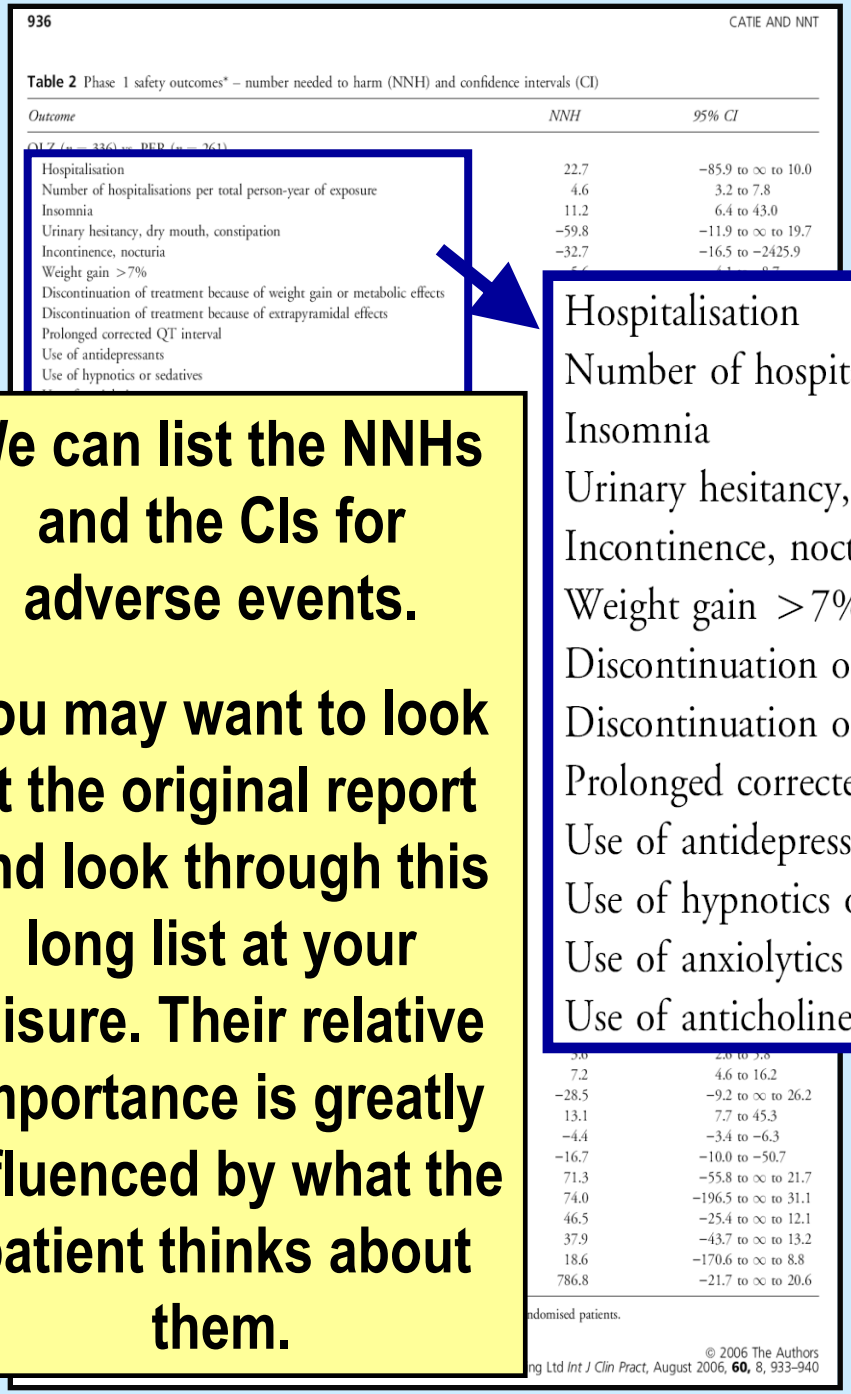
OLZ, olanzapine; PER, perphenazine; QUE, quetiapine; RIS, risperidone; ZIP, ziprasidone. *Intention-to-treat population. †98.33% CI listed for comparisons with PER, QUE and RIS; 98.75% CI listed for comparisons with ZIP.

We can list the NNTs and the CIs for all-cause discontinuation and for discontinuation for a specific reason.

When the CI includes "infinity" the NNT is not statistically significant.

 Int J Clin Pract, August 2006, **60,** 8, 933–940

Citrome L, Stroup TS. International Journal of Clinical Practice 2006;60:933-940.



936 CATIE AND NNT

Table 2 Phase 1 safety outcomes* – number needed to harm (NNH) and confidence intervals (CI)

Outcome	*NNH*	*95% CI*
Hospitalisation	22.7	−85.9 to ∞ to 10.0
Number of hospitalisations per total person-year of exposure	4.6	3.2 to 7.8
Insomnia	11.2	6.4 to 43.0
Urinary hesitancy, dry mouth, constipation	−59.8	−11.9 to ∞ to 19.7
Incontinence, nocturia	−32.7	−16.5 to −2425.9
Weight gain >7%		
Discontinuation of treatment because of weight gain or metabolic effects		
Discontinuation of treatment because of extrapyramidal effects		
Prolonged corrected QT interval		
Use of antidepressants		
Use of hypnotics or sedatives		
	7.2	4.6 to 16.2
	−28.5	−9.2 to ∞ to 26.2
	13.1	7.7 to 45.3
	−4.4	−3.4 to −6.3
	−16.7	−10.0 to −50.7
	71.3	−55.8 to ∞ to 21.7
	74.0	−196.5 to ∞ to 31.1
	46.5	−25.4 to ∞ to 12.1
	37.9	−43.7 to ∞ to 13.2
	18.6	−170.6 to ∞ to 8.8
	786.8	−21.7 to ∞ to 20.6

ndomised patients.

ng Ltd *Int J Clin Pract*, August 2006, **60**, 8, 933–940

Hospitalisation
Number of hospitalisations per total person-year of exposure
Insomnia
Urinary hesitancy, dry mouth, constipation
Incontinence, nocturia
Weight gain >7%
Discontinuation of treatment because of weight gain or metabolic effects
Discontinuation of treatment because of extrapyramidal effects
Prolonged corrected QT interval
Use of antidepressants
Use of hypnotics or sedatives
Use of anxiolytics
Use of anticholinergics

We can list the NNHs and the CIs for adverse events.

You may want to look at the original report and look through this long list at your leisure. Their relative importance is greatly influenced by what the patient thinks about them.

Citrome L, Stroup TS. International Journal of Clinical Practice 2006;60:933-940.

NNT in CATIE

The smaller the NNT, the larger the differences between the two drugs
The larger the NNH, the smaller the differences between the two drugs

COMPARISON (Phase 1)	OLZ vs RIS	OLZ vs QUE	OLZ vs ZIP	OLZ vs PER
D/C All Cause	11*	6*	7*	9*
D/C Efficacy loss	8*	8*	11*	10*
D/C In				31
D/C Pa				16
Hospitalization	26	12	16	23
D/C Weight or Metabolic	-14*	-18*	-17*	-13*
Rx Antidiabetic	-82	-67	-71	-61
Rx Statin	-81	-323	-30*	-57

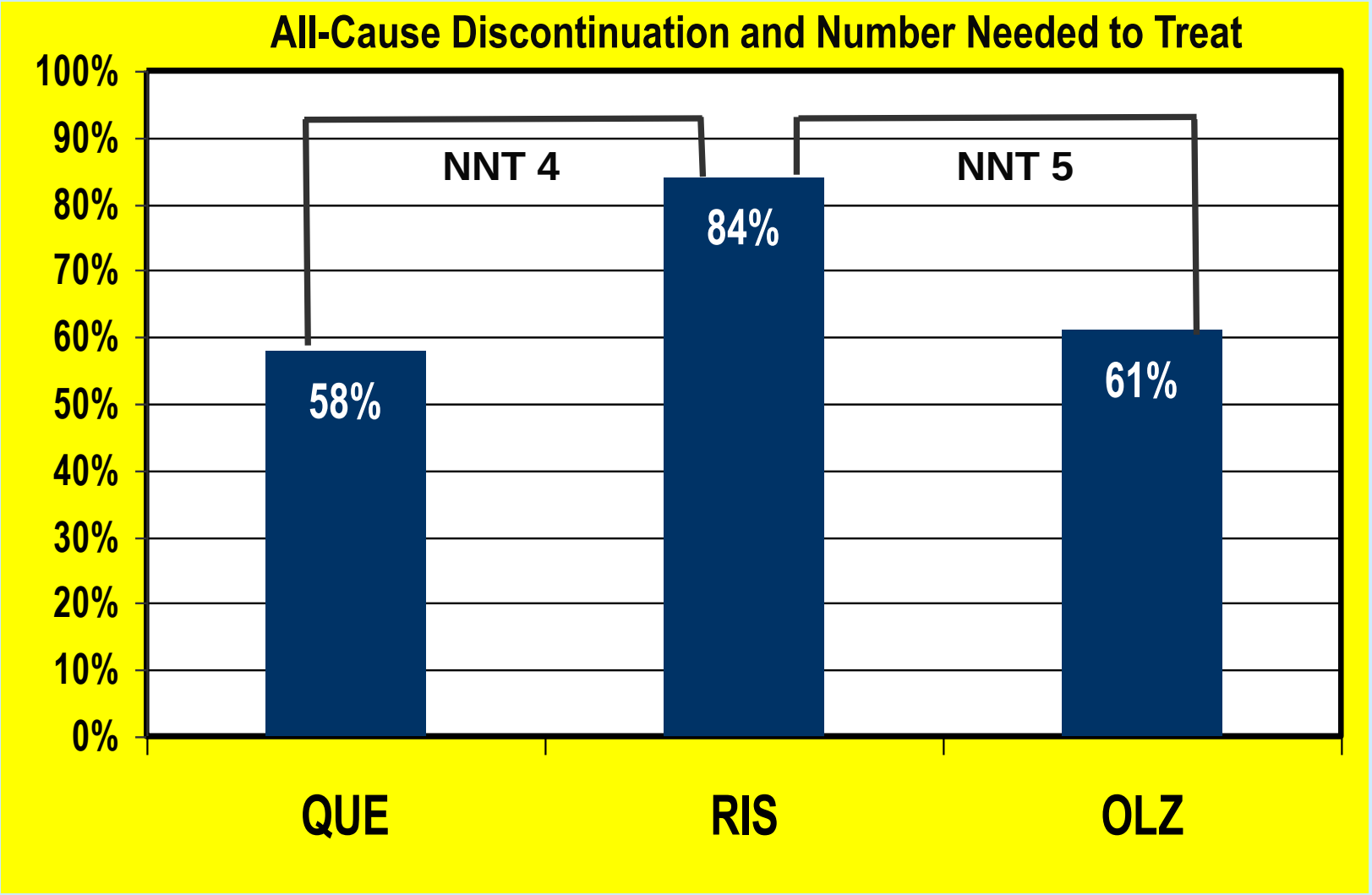
Olanzapine performed well in Phase 1 overall because the signal for efficacy had a larger effect size than the signal for discontinuation due to weight gain or metabolic effects.

*Statistically significant (95% CI did not cross from + to -)

Negative numbers indicate advantage for the non-olanzapine comparator

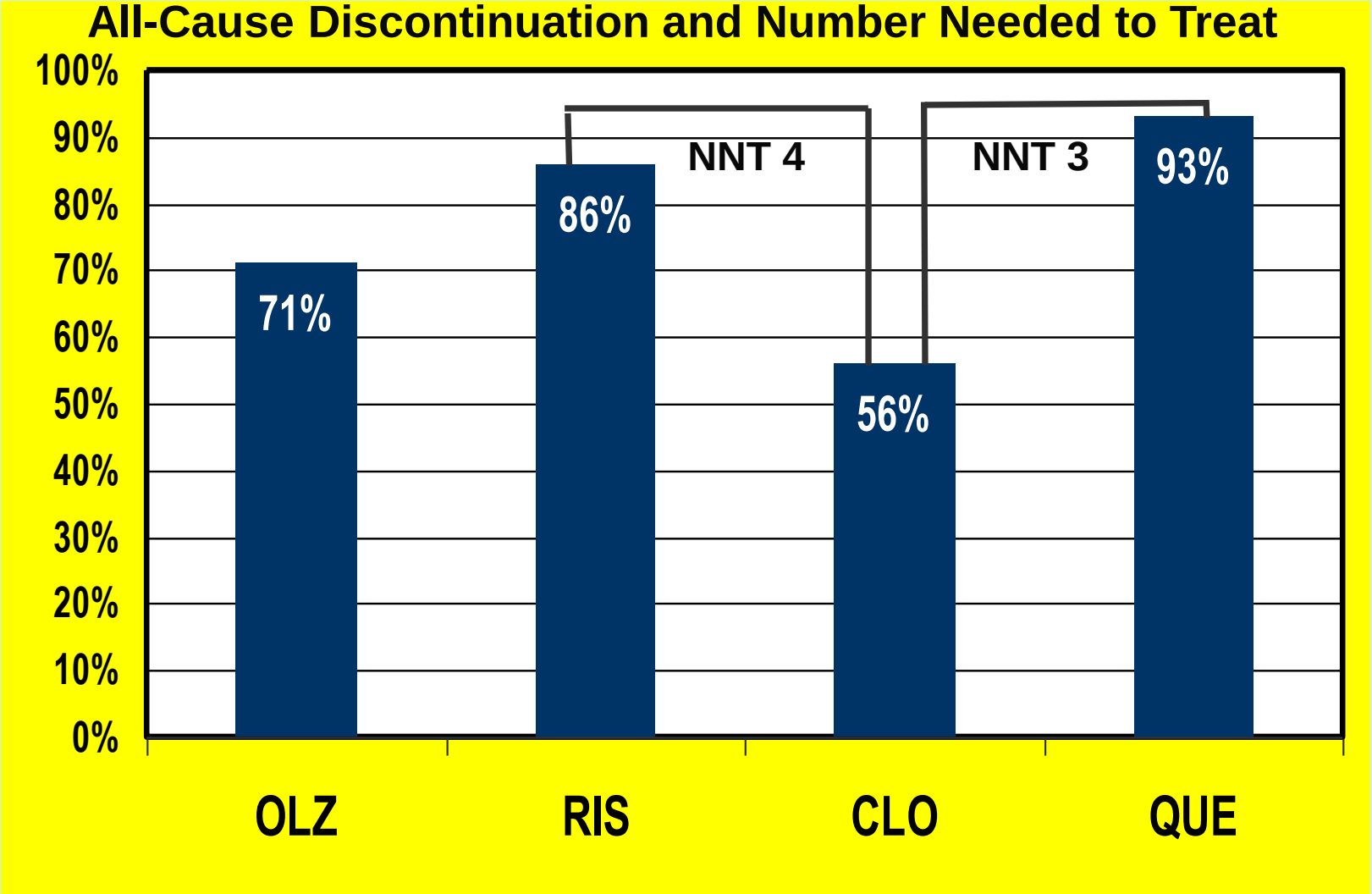
Citrome L, Stroup TS. International Journal of Clinical Practice 2006;60:933-940

Quetiapine Looks (A Lot) Better in Phase 1B



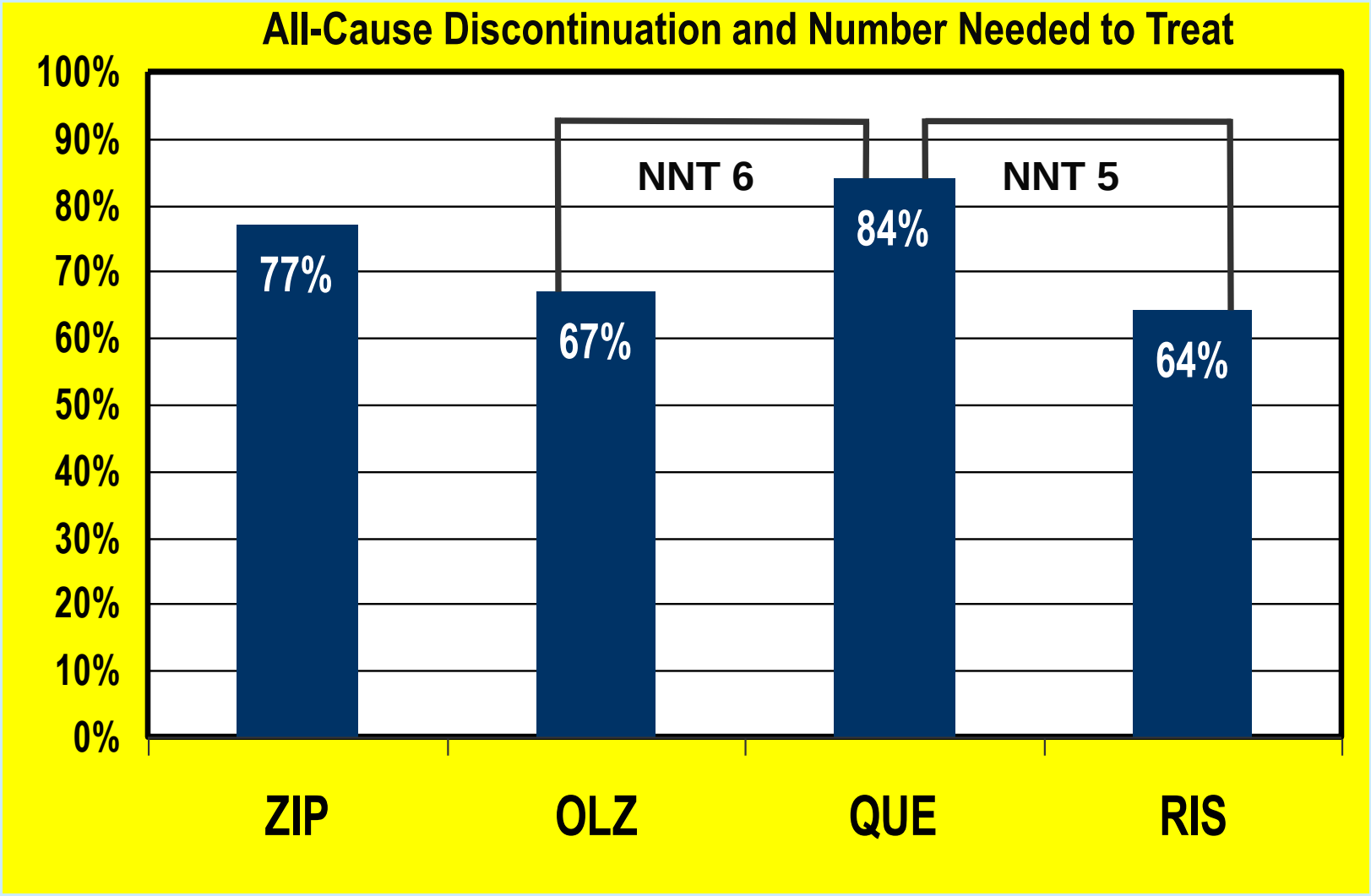
Stroup TS et al. American Journal of Psychitry 2007;164:415-427; Citrome L. Psychiatry MMC 2007;4(10):23-29;
Citrome L and Stroup TS. International Journal of Clinical Practice 2006;60:933-940.

Clozapine Pathway Results



McEvoy JP et al. American Journal of Psychiatry 2006;163:600-610; Citrome L. Psychiatry MMC 2007;4(10):23-29;
Citrome L and Stroup TS. International Journal of Clinical Practice 2006;60:933-940.

Ziprasidone Pathway Results



Stroup TS et al. American Journal of Psychiatry 2006;163:611-622; Citrome L. Psychiatry MMC 2007;4(10):23-29;
Citrome L and Stroup TS. International Journal of Clinical Practice 2006;60:933-940.

Table 3 Phase 2 effectiveness outcomes – number needed to treat (NNT) and confidence intervals (CI) for discontinuation on randomised medication*

Outcome	*NNT*	*95% CI*	*98.33% CI*
Clozapine pathway			
CLO ($n = 45$) vs. OLZ ($n = 17$)			
All-cause	6.6	−9.1 to ∞ to 2.4	−6.0 to ∞ to 2.1
Lack of efficacy	4.1	−312.7 to ∞ to 2.0	−17.4 to ∞ to 1.8
Intolerability	−19.1	−5.1 to ∞ to 10.8	−4.4 to ∞ to 8.0
Patient decision	10.6	−6.6 to ∞ to 2.9	−4.8 to ∞ to 2.5
Other reasons	−7.5	−4.3 to −29.4	−3.9 to −82.9
CLO vs. RIS ($n = 14$)			
All-cause	3.3	1.9 to 14.8	1.7 to 62.2
Patient decision	−15.6	−5.3 to ∞ to 16.9	−4.7 to ∞ to 11.6
Other reasons	47.8	−23.4 to ∞ to 11.8	−17.6 to ∞ to 10.1
ZIP vs. QUE ($n = 63$)			
All-cause	14.1	−22.8 to ∞ to 5.4	−14.4 to ∞ to 4.7
Lack of efficacy	26.2	−9.7 to ∞ to 5.6	−7.4 to ∞ to 4.8
Intolerability	29.5	−13.0 to ∞ to 6.9	−9.9 to ∞ to 5.9
Patient decision	−16.9	−5.4 to ∞ to 14.6	−4.6 to ∞ to 10.4
Other reasons	17.2	−47.7 to ∞ to 7.3	−26.0 to ∞ to 6.5

CLO, clozapine; OLZ, olanzapine; QUE, quetiapine; RIS, risperidone; ZIP, ziprasidone. *Intention-to-treat population.

Table 4 Phase 2 safety outcomes* – number needed to harm (NNH) and confidence intervals (CI)

Outcome	*NNH*	*95% CI*
Clozapine pathway		
CLO ($n = 49$) vs. OLZ ($n = 19$)		
Insomnia	8.5	−17.9 to ∞ to 3.4
Urinary hesitancy, dry mouth, constipation	−4.9	−3.2 to −11.0
Sialorrhoea	−4.5	−2.4 to −32.5
CLO vs. RIS ($n = 16$)		
Insomnia	3.7	2.0 to 26.4
Urinary hesitancy, dry mouth, constipation	−7.1	−3.3 to ∞ to 45.2
Sialorrhoea	−5.0	−2.4 to ∞ to 142.0
CLO vs. QUE ($n = 15$)		
ZIP vs. QUE ($n = 95$)		
Hospitalisation	25.4	−16.2 to ∞ to 7.1
Insomnia	−6.4	−3.8 to −20.4
Sex drive, sexual arousal, sexual orgasm	−20.8	−7.4 to ∞ to 26.1
Orthostatic faintness	11.1	6.1 to 62.5
Skin rash	24.7	−39.8 to ∞ to 9.4
Discontinuation of treatment because of weight gain or metabolic effects	10.6	6.5 to 27.9
Weight gain >7%	13.3	−923.4 to ∞ to 6.6

CLO, clozapine; OLZ, olanzapine; QUE, quetiapine; RIS, risperidone. *All randomised patients.

Similar to what we did for Phase 1, we can list the NNTs and NNHs, with their respective CIs for the two pathways tested in Phase 2.

When the CI includes "infinity" the NNT or NNH is not statistically significant. Many are not statistically significant. These are more difficult to interpret.

Citrome L, Stroup TS. International Journal of Clinical Practice 2006;60:933-940.

NNT in CATIE

The smaller the NNT, the larger the differences between the two drugs
The larger the NNH, the smaller the differences between the two drugs

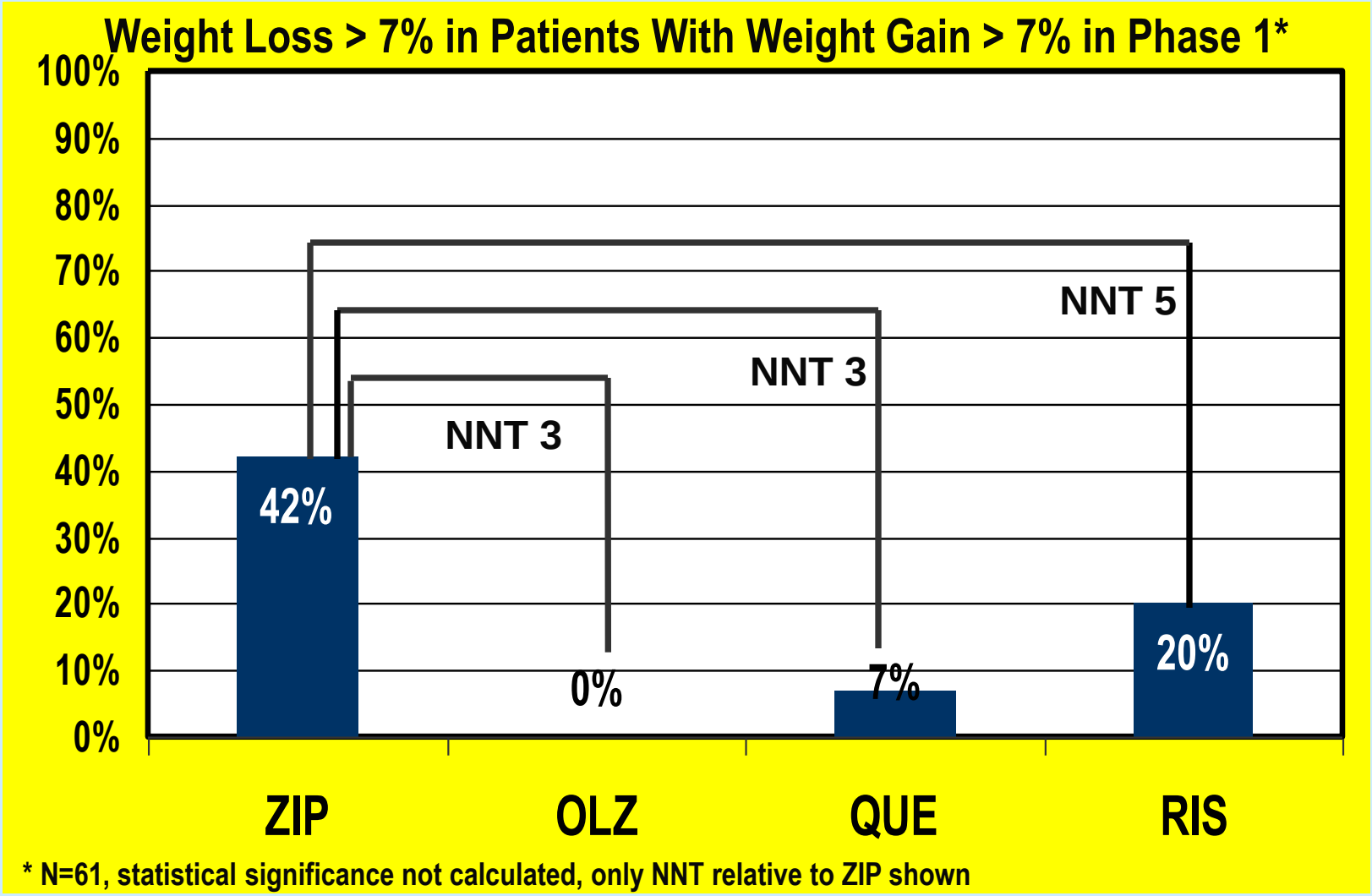
COMPARISON (Phase 2T)	ZIP vs OLZ	ZIP vs RIS	ZIP vs QUE
D/C All cause	-10	-8	15
D/C Efficacy loss	-12	-20	27
D/C Intolerability	18	-26	30
D/C Weight or metabolic	12*	21*	11*
Weight gain > 7%	6*	16	14
Sex drive, sexual arousal, sexual orgasm	75	8*	-21
Orthostatic faintness	27	48	12*
Insomnia	-6*	-12	-7*

*Statistically significant (95% CI did not cross from + to -)

Citrome L, Stroup TS. International Journal of Clinical Practice 2006;60:933-940.

Negative numbers indicate advantage for the non-ziprasidone comparator

What Was Ziprasidone's Principal Advantage?



* N=61, statistical significance not calculated, only NNT relative to ZIP shown

Stroup TS et al. American Journal of Psychiatry 2006;163:611-622; Citrome L. Journal of Clinical Psychiatry 2007;68(Suppl 12):12-17;
Citrome L and Stroup TS. International Journal of Clinical Practice 2006;60:933-940.

What Was Olanzapine's Most Impressive Advantage?

Table 4. *Prevention of hospitalization events for exacerbation of schizophrenia based on 1-year risk ratios (hospitalizations per total person year of exposure)*

Drug comparison	AR	NNT (95% CI)	NNT rounded up	AR × 100
Olanzapine vs. quetiapine	0.37	2.7 (2.2–3.5)	3	37
Olanzapine vs. risperidone	0.16	6.2 (4.1–13.0)	7	16
Olanzapine vs. ziprasidone	0.28	3.6 (2.6–5.8)	4	28
Olanzapine vs. perphenazine	0.22	4.6 (3.2–7.8)	5	22

AR = attributable risk; NNT = number needed to treat, extracted from Citrome and Stroup[7].
AR = $f_a - f_b$, where f_a = olanzapine rate and f_b = comparator rate. NNT = 1/AR

Karagianis J et al. Current Medical Research and Opinion 2007;23:2551-2557; Citrome L, Stroup TS. International Journal of Clinical Practice 2006;60:933-940.

4) Apply the Results

- Is my patient like those studied?
  - Ambulatory patient, non-treatment refractory?
  - Not schizoaffective
  - Not first-episode
- Is treatment consistent with my patient's values and preferences?
- Is treatment feasible in my practice setting?
  - Formulary?
  - Cost?

How Does This Apply to My Patient?

- Switches offer both opportunity and risk
- Where you end depends on where you start
  - Did the patient fail a “tight” D2 binding agent?
  - Did the patient fail because of efficacy or tolerability?
  - Is weight gain greater than 7% the predominant concern?
  - Is risk for hospitalization the predominant concern?

Citrome L: Interpreting and applying the CATIE results – With CATIE, context is key, when sorting out Phases 1, 1A,1B, 2E, and 2T. Psychiatry MMC 2007;4(10):23-29.

Interpreting Clinical Trials

- What is the problem?
- What is EBM?
- More about benefit, risk, and how NNT can help us understand this
- Applying EBM and NNT
- **Summary**

Evidence Based Medicine Summary

- EBM goes beyond anecdotal evidence, and allows the integration of clinical research into clinical practice
- The tools of EBM include the calculation of effect size such as NNT—this tells us the clinical significance of a statistically significant result
- EBM requires us to use clinical judgment in order to weigh benefits and risk for the individual patient

*

NNT Summary

- The concept of NNT allows the clinician to estimate a medication's potential relevant effect

- Examining the magnitudes of NNT (and NNH), the clinician can start to make risk-benefit decisions tailored to the individual patient's needs or preferences

Citrome L, Stroup TS. International Journal of Clinical Practice 2006;60:933-940.

*

Bottom Line

- 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

Post-Test 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

Post-Test 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

Post-Test 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

Post-Test 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

Post-Test 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

Answers to Pre & Post Questions

1. C
2. B
3. D
4. B
5. E