Evaluating the Research Literature

By

Eric D Peselow M.D
NYU School of Medicine

Lecture Statement

The accompanying slides are to given to present a lecture for psychiatric residents in how to critique the research literature

There are slides discussing types of studies with their advantages and disadvantages along with the opportunity to critique hypothetical and published studies to assess their conclusions

There are also comparisons between published studies and real world clinical practice

The lecture is a template. Although it can be given in its entirety, the hope is for the teacher at the facility to use some of the work presented here with his own material to enhance the learning experience

Outline (Objectives) of Talk

To assess how to critique the research literature.

To understand the types of studies in the literature (open, double-blind) and assess the advantages and disadvantages of study types

To understand the differences between findings in published studies and what happens in real world clinical practice

To learn how evaluate studies in the literature and see if they compare with real world clinical practice

To understand how to assess efficacy in clinical studies

Major teaching points

Though the double-blind placebo controlled study is the gold standard in establishing efficacy other types of published studies may be informative

Published studies are clearly different from real world clinical practice

Response to treatment usually means a reduction of symptoms which may still leave significant psychopathology.

Only about 30% of patients treated achieve remission (no symptoms)

Pre-lecture Questions

1) The type of study that must be done for a new drug to be approved by the FDA is

a) an open evaluation
b) a crossover study
c) a test of the new drug to see how it compares with historical controls
d) a double-blind placebo control parallel design study
e) a case series

Pre-lecture Questions

2) In critiquing the literature the features of a good study are

a) Prospective random assignment of treatment
b) No concomitant active medications
c) Double blind placebo control
d) Adequate sample
e) All of the above

Pre-lecture Questions

3) Features of a discontinuation design study include

a) an initial double-blind placebo control phase
b) an initial single blind phase followed by giving all responders continued drug or placebo in double blind fashion and assess relapse in drug group
c) giving individuals drug or placebo first and then stopping the treatment and switching to the other choice
d) an initial single blind phase followed by giving all responders continued drug or placebo in double blind fashion and continued response
e) stopping a standard drug and then giving the new drug

Pre-lecture Questions

4) In discussing the issue of research studies vs. real world clinical practice

a) What is shown in clinical studies mirrors real world practice
b) Most patients in clinical studies are representative of what is seen in clinical practice
c) In a clinical trial often the sickest patients are excluded
d) A clinical trial is more concerned with functional outcomes as opposed to symptoms
e) In a clinical trial the patients are often on multiple treatments

Pre-lecture Questions

5) Response to treatment in a double-blind placebo controlled clinical trial clinical trial means

a) complete alleviation of psychopathology
b) a 50% reduction in symptoms from baseline in depressed patient
c) no placebo response
d) a statistically significant difference between drug and placebo
e) both b and d

Pre-lecture Questions

6) Assuming drug a placebo/difference in clinical studies problems that exist in interpreting studies

a) are the results clinically significant
b) are there quality of life improvements in addition to symptom reduction
c) placebo is clearly inferior to any treatment making conclusions invalid
d) both a and b
e) all of the above

Evidenced Based Medicine

- **Evidenced base means a randomized double blind controlled trial (usually involving placebo). This is the basis for "efficacy" of various treatments.**

- **Randomization is extremely important to avoid bias in giving one group a specific treatment**

- **One needs to be aware of the evidence to justify your treatment-- the FDA considers the double-blind trial as proof of efficacy and allows the marketing of drugs for these indications as it avoids bias**

Non-Evidence Based Medicine

Though other evidence can be used one must make sure that the type of treatment one is giving has some basis in fact

One should in the patient's record document the reason and utility of non-FDA approved treatment.

Though a physician can use a drug once it is approved for anything, one must make sure there is some evidence that it works for the disorder you use it for.

There is greater scrutiny in using drugs for non-approved indication and the FDA has come down hard on drug companies for this (one cannot endorse Gabapentin for anxiety as formal FDA testing has not been done)

The 5 Step Evidence Based Medicine Process

Step 1 **Formulate the question**

Step 2 **Search for answers**

Step 3 **Appraise the evidence**

Step 4 **Apply the results**

Step 5 **Assess the outcome**

Types of Studies Used to Address Treatment Effectiveness

Uncontrolled Studies

- **Single case reports**
- **Case series**
- **All or none case series**
- **Uncontrolled clinical trials**

Controlled Studies

- **Cases with historical controls**
- **Studies with concurrent non-randomized controls**
  - **Patients of other physicians or clinical sites**
  - **Patients or physicians choice of treatment**
  - **Systematic allocation**

Randomized Control Trials

- **With blinding (strongest clinical design)**
- **Without blinding**

Cohort Study

FDA Approval Process for New Drugs

- **Before a drug can be approved for sale to the public there is a set of clinical tests that must be performed.**

- **There is the Pre-Clinical Research Stage.**

- **Here the drug is synthesized and purified.**

- **Animal tests are performed, and institutional review boards assess the studies and make recommendations on how to proceed.**

- **If the recommendations are positive, then an application to the FDA occurs and clinical tests begin.**

FDA Approval Process for New Drugs

Phase 1: clinical studies

•In this phase represent the first time that an IND is tested on humans either healthy volunteers or sometimes patients.

•The purpose of these studies is study in a clinical setting the metabolism, structure-reactivity relationships, mechanism of action, and side effects of the drug in humans.

•If possible, phase 1 studies are used to determine how effective the drug is. Phase 1 studies are usually conducted on 20 to 80 subjects.

Phase 2 clinical trials

•Their purpose is to determine the efficacy of a drug to treat patients with a specific disease or condition, as well as learn about common short-term side effects or risks.

•These studies are conducted on a larger scale than phase 1 studies and typically involve several hundred patients.

Phase 3 clinical trials

•They provide more information about the effects and safety of the drug and they allow scientists to extrapolate the results of clinical studies to the general population.

•Phase 3 studies generally involve several hundred to several thousand people

FDA Approval Process for New Drugs

•There are several checks and balances in the process of clinical trials; among them is the use of institutional review boards (IRBs) and advisory committees.

•IRBs are designed to protect the rights and welfare of people participating in clinical trials both before and during the trials.

•IRB's are made up of a group of at least five experts and lay people with diverse backgrounds to provide a complete review of clinical proceedings.

•The CDER uses advisory committees of various experts in order to obtain outside opinions and advice about a new drug.

•It also provides new information for a previously approved drug, as well as labeling information about a drug, guidelines for developing particular kinds of drugs, or data showing the adequate safety and effects of the drug.

Hierarchy For Evidence of Studies of Effectiveness or Side Effects

1a Standardized review of Randomized Clinical Trials (the best)
1b Individual Randomized Clinical Trial with a narrow confidence interval
1c All or none case series-if everyone died as a result of a disease and a new drug improves survival this is evidence of efficacy

2a Systematic review of cohort studies-A cohort is followed over time and the number of disease developed or other outcome measure is assessed. Typically a cohort is divided into those who are exposed to a potential risk factor and those who are not
2b An individual cohort study
2b Randomized clinical trial with less than 80% followup
2c Outcomes research

3a Systematic review of case studies
3b Individual case controlled study

4 A case series

5 Expert opinion--**It doesn't matter what the expert thinks--The worst evidence**

WHAT MAKES A GOOD STUDY

From a methodological point of view

1) Random assignment (prospective)
2) No concomitant active medications
3) Parallel (or appropriate crossover) design
4) Double blind placebo control
5) Adequate sample
6) Appropriate population
7) Standardized assessments
8) Either clear presentation of the data or appropriate statistics
9) Adequate dose of treatment
10) Active controls

Class 1- First nine criteria met
Class 2- 6 of 10 criteria met
Class 3- 5 of 10 criteria met

The above "what makes a good study" is from a design point of view. The issue of how it meets clinical reality is another story)

TYPES OF STUDIES IN THE LITERATURE

1) OPEN EVALUATION

2) CROSSOVER STUDIES

3) RANDOMIZED CLINICAL STUDIES

4) DISCONTINUATION DESIGN

5) COHORT STUDY

CLINICAL TRIAL DESIGNS FOR TREATMENT EVALUATION

1) OPEN EVALUATION

THE PURPOSE OF OPEN TRIALS (WITHOUT RANDOMIZATION) OR BLINDING IS TO FORMULATE HYPOTHESES FOR LATER TESTING AS TO THE METHOD AND ROLE OF NEW AGENTS IN TREATMENT.

CLINICAL TRIAL DESIGNS FOR TREATMENT EVALUATION

1) OPEN EVALUATION.

OPEN TRIALS YIELD USEFUL PRELIMINARY KNOWLEDGE REGARDING TARGET POPULATIONS AND THE FOLLOWING ASPECTS AND USES OF THE DRUG

1) THERAPEUTIC DOSE RANGE (MINIMUM BELOW WHICH DOSE IS INEFFECTIVE TO MAXIMUM ABOVE WHICH THERE IS NO FURTHER BENEFIT)

2) MAXIMUM TOLERABLE DOSE

3) NECESSARY FREQUENCY OF DAILY DOSAGE

4) SPEED OF DOSAGE INCREMENT

5) THE VARIETY AND DEGREE OF COMMON SIDE EFFECTS

CLINICAL TRIAL DESIGNS FOR TREATMENT EVALUATION

1) OPEN EVALUATION

THE MAIN DISADVANTAGE OF AN OPEN TRIAL IS BIAS-

- **The investigator or drug company wants the treatment to work**
- **Indeed it has been shown when a drug company sponsors a trial of its drug vs. a competitor the vast majority of the time the companies' agent has some advantage**

CLINICAL TRIAL DESIGNS FOR TREATMENT EVALUATION

2) CROSSOVER STUDIES

The main focus of a crossover study is to examine 2 treatments for alternating consecutive periods of time

- **The positive aspect of a crossover study is that the patient acts as his own control**

- **The patient is unique as opposed to randomizing 100 patients in 2 groups with the same condition**

- **100 people who meet criteria for depression still gives you 100 different people**

CLINICAL TRIAL DESIGNS FOR TREATMENT EVALUATION

2) CROSSOVER STUDIES

THE DISADVANTAGE OF A CROSSOVER TRIAL IS THAT THERE IS A CARROVER EFFECT

A) There are effects of previous treatment-whether pharmacological or psychosocial

B) Does the changing status of the underlying clinical condition over time (characteristic of most psychiatric disorders) affect the subsequent course and response to treatment

C) Crossover studies may be most useful in chronic stable conditions where within subject variation is less than between subject variation and where patients return to baseline after the first condition.

D) It may be particularly useful to crossover if patients do not respond to the first condition

CLINICAL TRIAL DESIGNS FOR TREATMENT EVALUATION

3) RANDOMIZED CLINICAL STUDIES

A) THE MAINSTAY OF TRIALS THAT ALLOWS US TO DETERMINE A DRUG'S SAFETY AND EFFICACY. USUALLY DONE WITH PLACEBO CONTROL.

B) PLACEBO CONTROLS ARE NEEDED BECAUSE IF ONE SIMPLY TESTS A NEW DRUG VS A STANDARD DRUG, THE FINDINGS MAY BE DIFFICULT TO INTERPRET (IF NO DIFFERENCE IS FOUND) DUE TO:

A) INSENSITIVE OUTCOME MEASURES

B) INVESTIGATOR OR PATIENT BIAS OR EXPECTATIONS

C) STRONG THERAPEUTIC BENEFITS OF THE TREATMENT SETTING OR SUPPORT SYSTEMS

D) MAY NOT HAVE LARGE ENOUGH SAMPLE TO YIELD STATISTICALLY SIGNIFICANT DIFFERENCES

E) MAY BE WORKING ON A REFRACTORY POPULATION

CLINICAL TRIAL DESIGNS FOR TREATMENT EVALUATION

4) DISCONTINUATION DESIGN

IT HAS BEEN SUGGESTED THAT PHASE 2 STUDY TREATMENTS (EITHER OPEN OR DOUBLE-BLIND) BE AMPLIFIED BY A DOUBLE-BLIND PLACEBO SUBSTITUTION DESIGN IN TREATMENT RESPONDERS

PATIENTS WHO HAVE IMPROVED ON UNCONTROLLED TRIALS AND ARE THUS PUTATIVE RESPONDERS TO AN INVESTIGATIONAL TREATMENT ARE RANDOMLY ASSIGNED TO BE MAINTAINED ON THAT DRUG OR BE WITHDRAWN ONTO PLACEBO WITH A DOUBLE-BLIND EVALUATION

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CLINICAL TRIAL DESIGNS FOR TREATMENT EVALUATION

4) DISCONTINUATION DESIGN

THE DOUBLE-BLIND DISCONTINUATION DESIGN FOCUSES DISTINCTLY ON THOSE PATIENTS WHO HAVE SHOWN DIRECT BENEFIT FROM THE DRUG.

THE DOUBLE-BLIND DISCONTINUATION DESIGN MAY BE USEFUL IN THAT IT MAY BE AN ALTERNATIVE TO THE PARALLEL DESIGN STUDY. THIS WOULD BE APPROPRIATE IF A LARGE # OF INAPPROPRIATE PATIENTS ARE TREATED WITHIN A PARALLEL DESIGN.

IN THIS CASE, THE MAGNITUDE OF THE DRUG EFFECT WILL BECOME DILUTED (IE RESPONDERS TO DRUG TREATMENT MIGHT HAVE RESPONDED ANYWAY)

THE DOUBLE-BLIND DISCONTINUATION DESIGN ALLOWS FOR THE SYSTEMATIC BLIND-ASSESSMENT OF WITHDRAWAL EFFECTS, RELAPSE AND DRUG BENEFIT

CLINICAL TRIAL DESIGNS FOR TREATMENT EVALUATION
COHORT STUDY

- **This is an observational study in which a defined group of people (the cohort) is followed over time. The outcomes of people in subsets of this cohort are compared, to examine people who were exposed or not exposed (or exposed at different levels) to a particular intervention or other factor of interest ...**

- **It involves identification of two groups (cohorts) of patients, one which did receive the exposure of interest, and one which did not, and following these cohorts forward for the outcome of interest.**

- **Thus we are dealing with an observational study in which outcomes in a group of patients that received an intervention are compared with outcomes in a similar group ie, the cohort, either contemporary or historical, of patients that did not receive the intervention.**

DESIGN FEATURES OF A CLINICAL STUDY

IN ASSESSING CLINICAL STUDIES AND REVIEWING THE LITERATURE ONE SHOULD:

A) IS THE OBJECTIVE OF THE STUDY CLEAR AND SUFFICIENTLY DESCRIBED

B) ARE CLEAR DIAGNOSTIC CRITERIA USED

C) IS A CLEAR STATEMENT GIVEN ABOUT THE SOURCE OF SUBJECTS

D) ARE THERE CONTROLS-CONCURRENT CONTROLS, MIRROR IMAGE CONTROLS OR HISTORICAL CONTROLS

E) ARE THE TREATMENTS WELL DEFINED

DESIGN FEATURES OF A CLINICAL STUDY (continued)

IN ASSESSING CLINICAL STUDIES AND REVIEWING THE LITERATURE ONE SHOULD:

F) ARE YOU USING RANDOM ALLOCATION

G) WILL THE TRIAL BE BLIND AND HOW DO YOU ENSURE THIS

H) DO YOU HAVE APPROPRIATE OUTCOME MEASURES

I) USING THESE MEASURES DO YOU HAVE DEFINED CRITERIA FOR OUTCOME

J) HAVE YOU CARRIED OUT A POWER CALCULATION TO HELP DETERMINE THE MOST APPROPRIATE SAMPLE SIZE.

K) IS THE STUDY CLINICALLY APPLICABLE (TO A GENERAL PSYCHIATRIC POPULATION)

PROBLEMS CONCERNING CORRELATIONS BETWEEN RESEARCH AND CLINICAL PRACTICE

A) POOR OR BIASED SELECTION OF TARGETED POPULATION BY INEXPERIENCED OR BIASED (CONFLICT OF INTEREST) CLINICIANS

B) INCORRECT PROJECTION OF DOSE LEVEL OF DRUG

C) INCORRECT LENGTH OF STUDY PERIOD-SHOULD BE AT LEAST 6 WEEKS FOR ACUTE TREATMENT OF MOST DRUGS

D) INAPPROPRIATE RATING MEASURES-ONE MUST ATTEMPT TO DOCUMENT NEW SCALES AND USE OLD ONES APPROPRIATELY TO CATEGORIZE A WIDE RANGE OF BEHAVIOR

PROBLEMS CONCERNING CORRELATIONS BETWEEN RESEARCH AND CLINICAL PRACTICE (CONTINUED)

E) UNREPRESENTATIVE SAMPLES

1) RESEARCH SUBJECTS ARE SELF-SELECTED. THIS SKEWS THE SAMPLE TO PATIENTS WHO ARE REFRACTORY TO PREVIOUS TREATMENTS WHICH MAKE DETECTION OF DRUG DIFFERENCES DIFFICULT

2) MANY PATIENTS MAY BE FRIGHTENED BY RESEARCH

F) HIGH ATTRITION RATES-FROM BOTH PLACEBO AND TREATMENT GROUPS MAY INVALIDATE THE STUDY AND INDEED MAY LEAD TO POOR CONCLUSION BASED ON THE STATISTICAL ANALYSIS OF THE LAST OBSERVATION BEING CARRIED FORWARD

G) IGNORING THE EFFECTS OF PSYCHOTHERAPY OR OTHER SUBTLE TREATMENT MODES DURING A CLINICAL TRIAL

H) IGNORING WITHDRAWAL PROBLEMS-FOR PATIENTS ENTERING A CLINICAL TRIAL WHO ARE ALREADY ON PSYCHOTROPICS. WITHDRAWAL SYNDROME MAY EMERGE OR CLINICAL STATUS MAY WORSEN

PROBLEMS CONCERNING CORRELATIONS BETWEEN RESEARCH AND CLINICAL PRACTICE (CONTINUED)

G) IGNORING THE EFFECTS OF PSYCHOTHERAPY OR OTHER SUBTLE TREATMENT MODES DURING A CLINICAL TRIAL

H) IGNORING WITHDRAWAL PROBLEMS-FOR PATIENTS ENTERING A CLINICAL TRIAL WHO ARE ALREADY ON PSYCHOTROPICS. WITHDRAWAL SYNDROME MAY EMERGE OR CLINICAL STATUS MAY WORSEN

I) IGNORING ISSUES AT INDUCTION OF TREATMENT

A) PATIENTS WHO COME TO TREATMENT MAY BE SLIGHTLY IMPROVED AND MAY BE IMPROVING FROM THEIR LOW POINT. THEY MAY NATURALLY IMPROVE AND THUS DROPOUT OF RX

B) OTHER PATIENTS ARE VERY ANXIOUS ABOUT STARTING PILLS

C) THIS ISSUE IS USUALLY HANDLED BY A SINGLE-BLIND PLACEBO PHASE WHICH DIMINISHES UNNECESSARY DRUG EXPOSURE AND ALLOWS FOR INDIVIDUALS TO GET USED TO TAKING DRUGS

PROBLEMS CONCERNING CORRELATIONS BETWEEN RESEARCH AND CLINICAL PRACTICE (CONTINUED)

J) NEGLECTING THE ISSUE OF LONG-TERM MAINTENANCE-THE VAST MAJORITY OF TREATMENT STUDIES LAST 6 WEEKS OR LESS. ISSUES REGARDING SUSTAINED RESPONSE OF DRUG OR PLACEBO ARE UNKNOWN

K) STATISTICAL ANALYSIS- THIS FOCUSES ON RATING SCALE SCORES (IE HAMILTON, BPRS) TO DETECT DRUG-PLACEBO DIFFERENCES.

L) ONE WOULD TRULY LIKE TO KNOW GLOBALLY WHAT PERCENTAGE OF PATIENTS SHOWED MARKED REMISSION, WHO SHOWED MARKED IMPROVEMENT, WHO SHOWED MINIMAL IMPROVEMENT AND WHO WAS UNCHANGED OR WORSE

PROBLEMS CONCERNING CORRELATIONS BETWEEN RESEARCH AND CLINICAL PRACTICE (CONTINUED)

M) WITH REGARD TO THE STATISTICAL ANALYSIS, THERE IS OFTEN A FAILURE TO APPRECIATE THAT MANY OF THE RATING SCALES USED MAY BE COMPOSED OF THE ITEMS THAT ARE NOT NECESSARILY PART OF THE SYNDROME BEING TREATED

1) BPRS- ONLY 4 OF THE 18 ITEMS (HALLUCINATIONS, PARANOIA, UNUSUAL THOUGHT CONTENT, & CONCEPTUAL DISORGANIZATION OF THOUGHT) ARE CLEARLY RELATED TO THE POSITIVE SYMPTOMS OF SCHIZOPHRENIA

2) THE HAMILTON DEPRESSION SCALE CONTAINS ITEMS FOR ANXIETY, SOMATIC DISTURBANCE, DEPERSONALIZATION, PARANOIA & OBSESSIONS AND COMPULSIONS WHICH ARE NOT ALWAYS RELATED TO DEPRESSION. ONE CAN OBTAIN A HAMILTON SCORE OF 20 (16-18 IS THOUGHT TO BE A MINIMUM CRITERIA FOR STUDIES) WITHOUT BEING DEPRESSED

Differences Between Randomized Clinical Trials (RCT) and Routine Clinical Practice

Is the randomized clinical trial in any way similar to routine clinical practice

The answer NO

There is a need for pragmatic trials in psychiatry since many feel we can't generalize the randomized clinical trial with routine clinical practice

- **Wenzer et al 1997 (British Journal of Psychiatry) noted that only 17% of manic patients admitted to one psychiatric service made it to a proposed clinical trial. Those in the trial had less severe illness and less psychosis**

- **Studies of patients who entered into depression trials-Zimmerman et al 2002 (Journal of Clinical Psychopharmacology) and schizophrenia trials-Woods et al 2000 (Psychiatric Services) had similar findings**

- **Patients excluded from trial are those thought to be more ill-i.e those at higher risk for suicide or homicide exactly the patients who one needs help with**

Differences Between Randomized Clinical Trials (RCT) and Routine Clinical Practice

What happens in a randomized clinical trial	What happens in the real world
Patients recruited from specialized centers or from advertising	Patients are mainly treated in primary care
Patients with comorbid medical and psychiatric disorders are excluded	Patients are likely treated whatever the comorbid disorders are
Patients are carefully selected to generate homogenous diagnostic groups according to DSM criteria	Patients with heterogenous diagnosis according to DSM criteria are lumped together
Patients are allocated the treatment at random	Treatment is allocated via a complex process of negotiation and interpretation
Patients are provided detailed information (which may be overinclusive) for informed consent	Patients are provided brief information (which may be underinclusive) for informed consent

Differences Between Randomized Clinical Trials (RCT) and Routine Clinical Practice

What happens in a randomized clinical trial	What happens in the real world
Patients are given a 1 week "placebo run in period" to exclude placebo responders	All patients are given active treatment from the start
Placebo is used to compare active treatment	No placebo is used; choice is between active treatment and no treatment
Patients are followed at frequent intervals and given detailed evaluation of clinical symptoms and detailed check lists of side effects	Patients are followed at very varying lengths according to haphazard practice
Assessment endpoint is typically 4-6 weeks after treatment has begun	Patient is continued on treatment for at least 6 months and clinician is interested in much longer endpoints

Differences Between Randomized Clinical Trials (RCT) and Routine Clinical Practice

What happens in a randomized clinical trial	What happens in the real world
Assessment of outcome is based on change in clinical symptoms (manic, psychotic, depressive, anxious) symptoms and side effects	To the patient and the MD, functional outcomes (return to work) may be more important
Patient and clinician are “blind” to the treatment group	Both (usually) are aware of the drug the patient is given (along with the fact that he is receiving active drug treatment)

Differences Between Randomized Clinical Trials (RCT) and Routine Clinical Practice

Conclusions

- **A randomized clinical trial has patients:**
  - **Who are less ill (not suicidal, homicidal, or too psychotic to sign informed consent)**
  - **Who are not comorbid for other psychiatric disorders**
  - **Who have minimal medical problems**
  - **Who only are on monotherapy**
  - **Has anyone ever treated such a patient? Not common**

How to Critically Appraise Guidelines and Studies Involving Treatment

Is the guideline (treatment) valid

- **Did the developers carry out a systematic review of the literature**
- **Were all relevant treatment options and outcomes considered**
- **Did the developers specify and make explicit the values associated with various outcomes**
- **Did the developers indicate the level of evidence and sources upon which each recommendation is based**

How to Critically Appraise Systemic Reviews of the Literature

- **Did the review address a clearly defined issue**
  - **Are the question clearly identified or the topic too broad or narrow**

- **Did the authors select the right types of studies**
  - **Are the inclusion criteria specified**
  - **Do the authors specify the appropriate type of studyto answer the question**

- **Were all the relevant studies included**
  - **How comprehensive was the search and were electronic databases used**

- **Was the quality of the study addressed**
  - **Were explicit criteria used**
  - **Were 2 raters used with a procedure for evaluating differences**

How to Critically Appraise Systemic Reviews of the Literature (continued)

- **Are the results similar from study to study--If not was heterogeneity addressed**
  - **Are the results clearly displayed**
  - **Is there evidence for heterogeneity- are the difference in results clearly displayed**
  - **What is the number needed to treat for my patient to give a valid result**
  - **What are the results of the study and are there differences between the 2 groups**

- **Can I apply the results to my patients**
  - **Is my patient too different from those in the study**
  - **Is the treatment feasible in my setting**

What Does Response to Treatment Really Mean

- **In medicine, if one has a streptococcal infection, one expects that medication will eliminate all the organisms and you are "cured"**

- **In psychiatry you are better but still ill**

RESPONSE TO TREATMENT IN PSYCHIATRY

For instance in depression studies that evaluate efficacy

- **Criteria for entry into the study usually requires a minimum score on the scale used for that disorder**
  - **Hamilton Depression score (score of 18 or greater)**
  - **Young-Mania Rating Scale (score of 20 or greater)**

- **For mania and depression response to treatment implies a 50% reduction in symptoms based on the scale used and a final CGI rating of much or very much improved**

- **Thus a starting score of 26 on the Hamilton Depression Scale which improves to 13 at endpoint may be considered response to treatment but still leaves one with mild-moderate psychopathology**

- **Remission in depression implies final Hamilton Depression score of 7 or less**

EXAMPLES OF OUTCOME STUDIES--COMPILATION OF 9 ANTIDEPRESSANT VS PLACEBO STUDIES-HYPOTHETICAL RESULTS

Improvement From Depression-What Really Happened

	Drug (N=239)	Placebo (N=146)	Probability
*Responder/ Non-Responder	136/103 (57%)	67/79 (43%)	p=.03

HOWEVER TRUE REMISSION

Final Hamilton Score

7 or less	76/163 (32%)	31/115 (21%)	p=.025

*Denotes 50% improvement in Hamilton score from baseline and CGI improvement score of 1 or 2 (very much or much improved)

EXAMPLES OF OUTCOME STUDIES

Improvement From Depression-What Really Happened-Hypothetical scores

	Drug (N=239)	Placebo (N=146)	Probability
Hamilton start	24.53	24.57	
Ham end	13.83	16.88	p=.004
Ham change	10.70	7.70	
Average Improvement	43.2%	32.9%	

EXAMPLES OF OUTCOME STUDIES

Improvement on Specific Item

	Drug (N=239)	Placebo (N=146)	Probability
Item 1 Final Score--Core Depressed mood			
0	**62 (25.9%)**	**23 (13.7%)**	
1	**79 (33.1%)**	**45 (30.8%)**	
2	**74 (31.0%)**	**33 (22.6%)**	
3	**21 (8.8%)**	**33 (22.6%)**	
4	**3 (1.3%)**	**12 (8.2%)**	
Score 0 or 1*	**141/239 (59.0%)**	**68/146 (44.5%)**	**Chi square (X^2=5.90 1 df p<.01)**

0 or 1 at endpoint implies no or minimal depression

Conclusions From The Hypothetical Compilation of Studies

- **When examining the issue of responder/non-responder the drug is statistically significantly better vs. placebo but there is a high placebo response and the gap is narrow**

- **When looking at true remission (Hamilton 7 or less) again the drug is statistically significantly better vs. placebo but the overall remission rate (implying complete alleviation of symptoms) is low**

- **The rating scale (the Hamilton depression scale) shows a minimal endpoint difference between drug and placebo though the difference is statistically significant**

- **When measuring the core Hamilton item (depressed mood) the more people on drug vs. placebo had a score of 0 (no depression) or 1 (minimal depression) after treatment 41% on drug had a final score of 2 or more or moderate depression or worse**

EXAMPLES OF SCIZOPHRENIA RESEARCH (Hypothetical Example)

In evaluating the course of 291 schizophrenic patients in 1 of 9 antipsychotic trials following characterizes their response to treatment

ENTRY CRITERIA INTO AFOREMENTIONED STUDIES

- **Following a 3 day-1 week placebo washout period the patient had to have:**
  - **A total BPRS score of 36 or higher (1-7 BPRS scale-18 total items range is 18-126)**
  - **A score of 4 or greater on 2 of the 4 core BPRS items (auditory hallucinations, paranoid ideation, unusual thought content, conceptual disorganization of thought-(range is 4-28)**
  - **A CGI severity score of 4 or greater—moderately ill or worse**

BRIEF PSYCHIATRIC RATING SCALE (BPRS)

Please enter the score for the term which best describes the patient's condition.

0 = not assessed, **1** = not present, **2** = very mild, **3** = mild, **4** = moderate, **5** = moderately severe, **6** = severe, **7** = extremely severe

1. SOMATIC CONCERN
Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not.
SCORE

2. ANXIETY
Worry, fear, or over-concern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defense mechanisms.
SCORE

3. EMOTIONAL WITHDRAWAL
Deficiency in relating to the interviewer and to the interviewer situation. Rate only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation.
SCORE

4. CONCEPTUAL DISORGANIZATION
Degree to which the thought processes are confused, disconnected, or disorganized. Rate on the basis of integration of the verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning.
SCORE

5. GUILT FEELINGS
Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defenses.
SCORE

6. TENSION
Physical and motor manifestations of tension "nervousness", and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient.
SCORE

7. MANNERISMS AND POSTURING
Unusual and unnatural motor behavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here.
SCORE

8. GRANDIOSITY
Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation-to-others, not on the basis of his demeanor in the interview situation.
SCORE

9. DEPRESSIVE MOOD
Despondency in mood, sadness. Rate only degree of despondency; do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints.
SCORE

10. HOSTILITY
Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defenses, anxiety, nor somatic complaints. *(Rate attitude toward interviewer under "uncooperativeness").*
SCORE

11. SUSPICIOUSNESS
Belief *(delusional or otherwise)* that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances.
SCORE

12. HALLUCINATORY BEHAVIOR
Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people.
SCORE

13. MOTOR RETARDATION
Reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient only; do not rate on the basis of patient's subjective impression of own energy level.
SCORE

14. UNCOOPERATIVENESS
Evidence of resistance, unfriendliness, resentment and lack of readiness to cooperate with the interviewer. Rate only on the basis of the patient's attitude and responses to the interviewer and the interview situation; do not rate on basis of reported resentment or uncooperativeness outside the interview situation.
SCORE

15. UNUSUAL THOUGHT CONTENT
Unusual, odd, strange or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganization of thought processes.
SCORE

16. BLUNTED AFFECT
Reduced emotional tone, apparent lack of normal feeling or involvement.
SCORE

17. EXCITEMENT
Heightened emotional tone, agitation, increased reactivity.
SCORE

18. DISORIENTATION
Confusion or lack of proper association for person, place or time.
SCORE

WHAT IS RESPONSE TO TREATMENT

For the purposes of this evaluation response to treatment was defined as a

- **30% reduction in BPRS**
- **30% reduction in core BPRS items (auditory hallucinations, paranoid ideation, unusual thought content, conceptual disorganization of thought)**
- **Final CGI improvement score of 2 or 1 (2=much improved, 1=very much improved)**

HYPOTHETICAL RESULTS

Total patients----------291

Initial BPRS average----------58.97±13.1
Final BPRS average----------44.85 ±12.8

Initial core 4 items----------18.03 ±5.0
Final core 4 items---------- 12.89 ±4.2

Initial CGI----------5.05 ±0.4
Final CGI----------4.34 ± 0.5

RESULTS

Total patients----------291

Responded to treatment with all 3 criteria----------144

Responder BPRS score below 36----------67

BPRS score 31-35----------42

BPRS score 26-30----------22

BPRS score 21-25----------3

Responder BPRS score above 36----------77

BPRS score 36-40---------- 44

BPRS score 41-45----------25

BPRS score 46-50----------8

RESULTS

Overall 55/291 patients (19%) were felt to be well enough to be discharged and independently function in the community-these patients were felt to have been rated a CGI of 3 or less

Overall 77 of the 144 patients who were classified as treatment responders had a BPRS score of 36 or greater implying they had enough psychopathology that they could have re-qualified for the study the study after “responding to treatment

Critique of Drug studies in the literature

What do some of the classical drug studies showing efficacy of the psychotropic drugs really show

OUTCOME STUDIES IN SCHIZOPHRENIA
Pivotal Risperidone study that led to FDA approval

	Placebo (n=64)	Risperidone 2m (n=63)	Risperidone 6mg (n=63)	Risperidone 10m (n=63)	Risperidone 16mg (n=61)	Haldol 20mg (n=64)
Total PANSS						
Baseline	**92.2**	**87.4**	**93.8**	**92.5**	**93.8**	**92.9**
Endpoint	**95.5**	**85.6**	**77.7**	**83.6**	**79.3**	**88.8**
Positive PANSS						
Baseline	**23.3**	**22.5**	**23.5**	**24.0**	**23.3**	**23.9**
Endpoint	**24.2**	**22.1**	**18.8**	**20.4**	**19.1**	**21.5**
Negative PANSS						
Baseline	**23.8**	**23.1**	**25.2**	**24.3**	**24.8**	**24.6**
Endpoint	**24.2**	**22.3**	**21.9**	**22.8**	**21.4**	**24.3**

OUTCOME STUDIES IN SCHIZOPHRENIA

- **For the PANSS**
  - **A score of 70-75 generally makes you eligible for studies**
  - **A score of 40 or less indicates minimal pathology**

- **The average patient who was treated with Risperidone had a final score of 78.**

- **The above indicates significant pathology with “efficacious drugs”.**

- **At the generally considered best dose of risperidone-6mg the average endpoint PANSS was 77.7 in this example**

OUTCOME STUDIES IN MANIA-PIVOTAL OLANZAPINE STUDY THAT LED TO FDA APPROVAL

Young Mania Rating Scale (minimum entry score was 20)

	Olanzapine Group (N=70)	Placebo Group (N=69)	Probability
Young Mania Score			
Baseline	**28.66**	**27.65**	
Young Mania Score			
Endpoint	**18.40**	**22.77**	
Change	**10.26**	**4.88**	**p=.02**

Response from treatment is defined as a 50% reduction in Young mania rating score. 48.6 % of the Olanzapine patients responded vs 24.2% of the placebo patients

Of the 11 items on the Young on only 2 were there statistically greater improvement on Olanzapine vs placebo (Sleep and irritability)

YOUNG MANIA RATING SCALE (YMRS)

GUIDE FOR SCORING ITEMS

The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating.

The keys provided are guides. One can ignore the keys if that is necessary to indicate severity, although this should be the exception rather than the rule.

Scoring between the points given (whole or half points) is possible and encouraged after experience with the scale is acquired. This is particularly useful when severity of a particular item in a patient does not follow the progression indicated by the keys.

Specify **one** of the reasons listed below by putting the appropriate number in adjacent box.

1. ELEVATED MOOD

☐

0 - Absent
1 - Mildly or possibly increased on questioning
2 - Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
3 - Elevated, inappropriate to content; humorous
4 - Euphoric; inappropriate laughter; singing

2. INCREASED MOTOR ACTIVITY ENERGY

☐

0 - Absent
1 - Subjectively increased
2 - Animated; gestures increased
3 - Excessive energy; hyperactive at times; restless (can be calmed)
4 - Motor excitement; continuous hyperactivity (cannot be calmed)

3. SEXUAL INTEREST

☐

0 - Normal; not increased
1 - Mildly or possibly increased
2 - Definite subjective increase on questioning
3 - Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
4 - Overt sexual acts (toward patients, staff, or interviewer)

4. SLEEP

☐

0 - Reports no decrease in sleep
1 - Sleeping less than normal amount by up to one hour
2 - Sleeping less than normal by more than one hour
3 - Reports decreased need for sleep
4 - Denies need for sleep

5. IRRITABILITY

☐

0 - Absent
2 - Subjectively increased
4 - Irritable at times during interview; recent episodes of anger or annoyance on ward
6 - Frequently irritable during interview; short, curt throughout
8 - Hostile, uncooperative; interview impossible

6. SPEECH (Rate and Amount)

☐

0 - No increase
2 - Feels talkative
4 - Increased rate or amount at times, verbose at times
6 - Push; consistently increased rate and amount; difficult to interrupt
8 - Pressured; uninterruptible, continuous speech

7. LANGUAGE - THOUGHT DISORDER

☐

0 - Absent
1 - Circumstantial; mild distractibility; quick thoughts
2 - Distractible; loses goal of thought; change topics frequently; racing thoughts
3 - Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
4 - Incoherent; communication impossible

8. CONTENT

☐

0 – Normal
2 - Questionable plans, new interests
4 - Special project(s); hyperreligious
6 - Grandiose or paranoid ideas; ideas of reference
8 - Delusions; hallucinations

9. DISRUPTIVE - AGGRESSIVE BEHAVIOR

☐

0 - Absent, cooperative
2 - Sarcastic; loud at times, guarded
4 - Demanding; threats on ward
6 - Threatens interviewer; shouting; interview difficult
8 - Assaultive; destructive; interview impossible

10. APPEARANCE

☐

0 - Appropriate dress and grooming
1 - Minimally unkempt
2 - Poorly groomed; moderately dishevelled; overdressed
3 - Dishevelled; partly clothed; garish make-up
4 - Completely unkempt; decorated; bizarre garb

11. INSIGHT

☐

0 - Present; admits illness; agrees with need for treatment
1 - Possibly ill
2 - Admits behavior change, but denies illness
3 - Admits possible change in behavior, but denies illness
4 - Denies any behavior change

Anxiety Studies

The outcome measure for anxiety studies is the Hamilton Anxiety Scale

This is a 14 item scale rated 0-4 (total 0-56) with 7 items of psychic anxiety and 7 items of somatic anxiety

The usual criteria for entry into a study is 18-20.

Response to treatment is defined as a 50% reduction in Hamilton score and a CGI improvement score of 1 or 2 (very much or much improved)

Remission is a Hamilton score of 7 or less

Hamilton Anxiety Scale

INSTRUCTIONS: *Code 01 under Sheet Number.*
Be sure to record your answers in the appropriate spaces (positions 0 through 4), Columns 1 – 5, on the left half of the General Scoring Sheet.

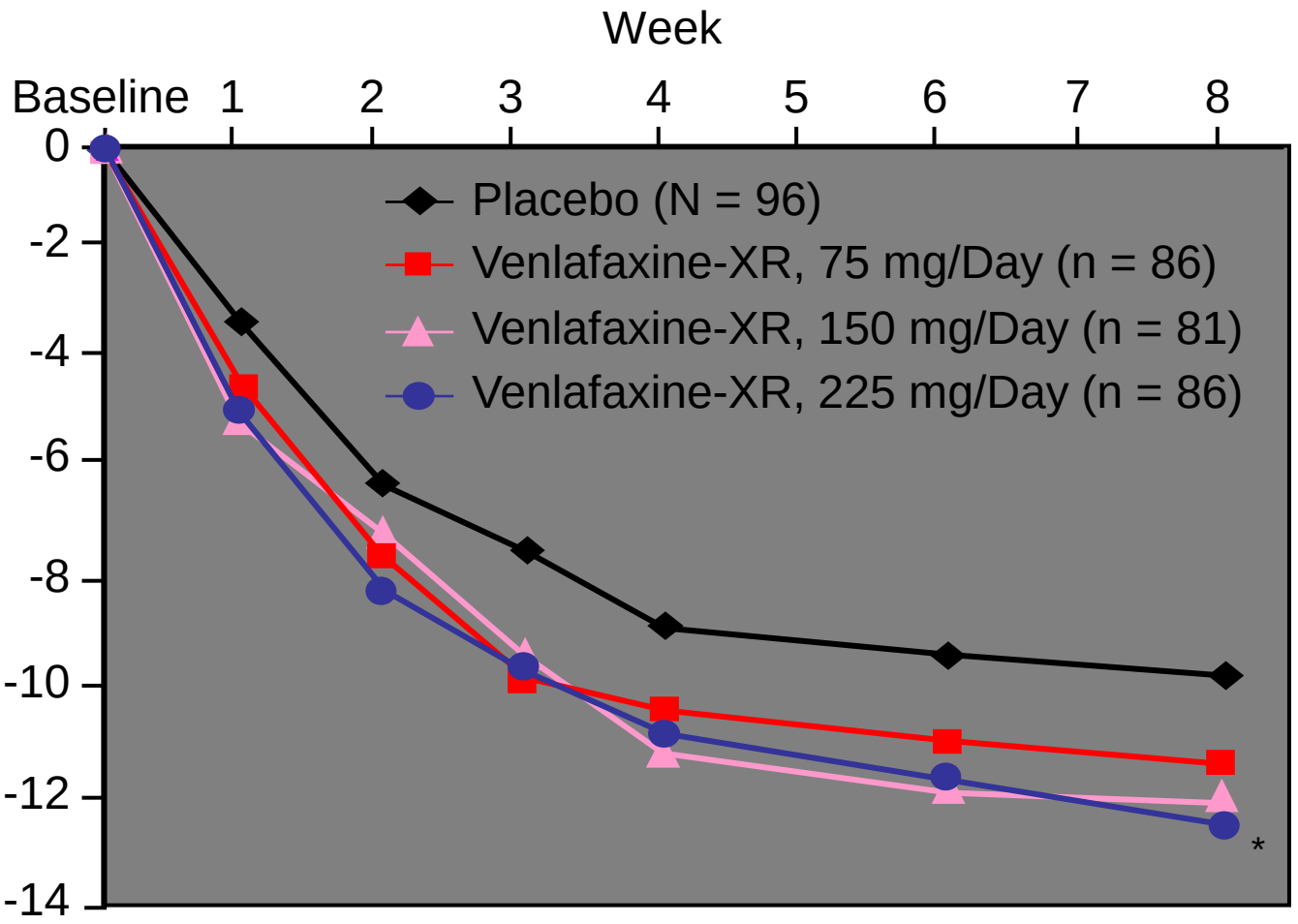
NO. 2 LEAD PENCIL. BE SURE TO MAKE MARKS HEAVY AND DARK. ERASE COMPLETELY ANY MARKS YOU WISH TO CHANGE.

0 NOT PRESENT	1 MILD	2 MODERATE	3 SEVERE	4 VERY SEVERE
24 ::0::	::1::	::2::	::3::	::4::
25 ::0::	::1::	::2::	::3::	::4::
26 ::0::	::1::	::2::	::3::	::4::
27 ::0::	::1::	::2::	::3::	::4::
28 ::0::	::1::	::2::	::3::	::4::
29 ::0::	::1::	::2::	::3::	::4::
30 ::0::	::1::	::2::	::3::	::4::
31 ::0::	::1::	::2::	::3::	::4::
32 ::0::	::1::	::2::	::3::	::4::
33 ::0::	::1::	::2::	::3::	::4::
34 ::0::	::1::	::2::	::3::	::4::
35 ::0::	::1::	::2::	::3::	::4::
36 ::0::	::1::	::2::	::3::	::4::
37 ::0::	::1::	::2::	::3::	::4::
	1	2	3	4	5

ROW NO.	Mark on left half of scoring sheet on row specified. Mark in response positions 0 – 4, columns 1 – 5. Follow rating scale on header template.
	0 = Not Present 1 = Mild 2 = Moderate 3 = Severe 4 = Very Severe
24	**ANXIOUS MOOD** Worries, anticipation of the worst, fearful anticipation, irritability
25	**TENSION** Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax
26	**FEARS** Of dark, of strangers, of being left alone, of animals, of traffic, of crowds
27	**INSOMNIA** Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors
28	**INTELLECTUAL** Difficulty in concentration, poor memory
29	**DEPRESSED MOOD** Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing
30	**SOMATIC (Muscular)** Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone
31	**SOMATIC (Sensory)** Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation
32	**CARDIOVASCULAR SYMPTOMS** Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, sighing, dyspnea
33	**RESPIRATORY SYMPTOMS** Pressure or constriction in chest, choking feelings, sighing, dyspnea
34	**GASTROINTESTINAL SYMPTOMS** Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation
35	**GENITOURINARY SYMPTOMS** Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence
36	**AUTONOMIC SYMPTOMS** Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair
37	**BEHAVIOR AT INTERVIEW** Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.

Venlafaxine Treatment of GAD

HAM-A Total Score



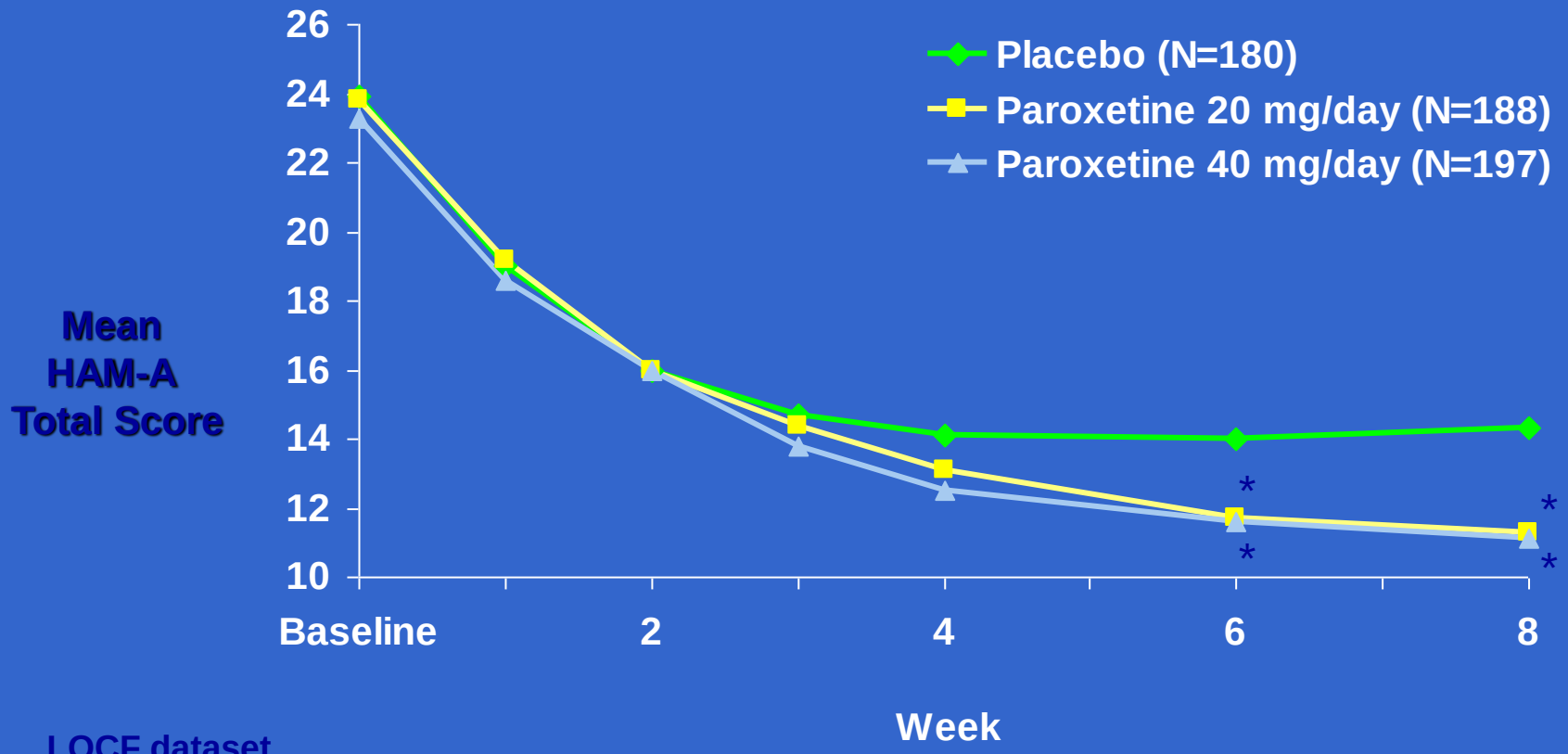
HAM-A Total Score (Mean Change from Baseline)

*P = .03.

Rickels K et al. *Am J Psychiatry.* 2000;157:968-974.

Paroxetine Fixed-Dose GAD Study

HAM-A Total Score



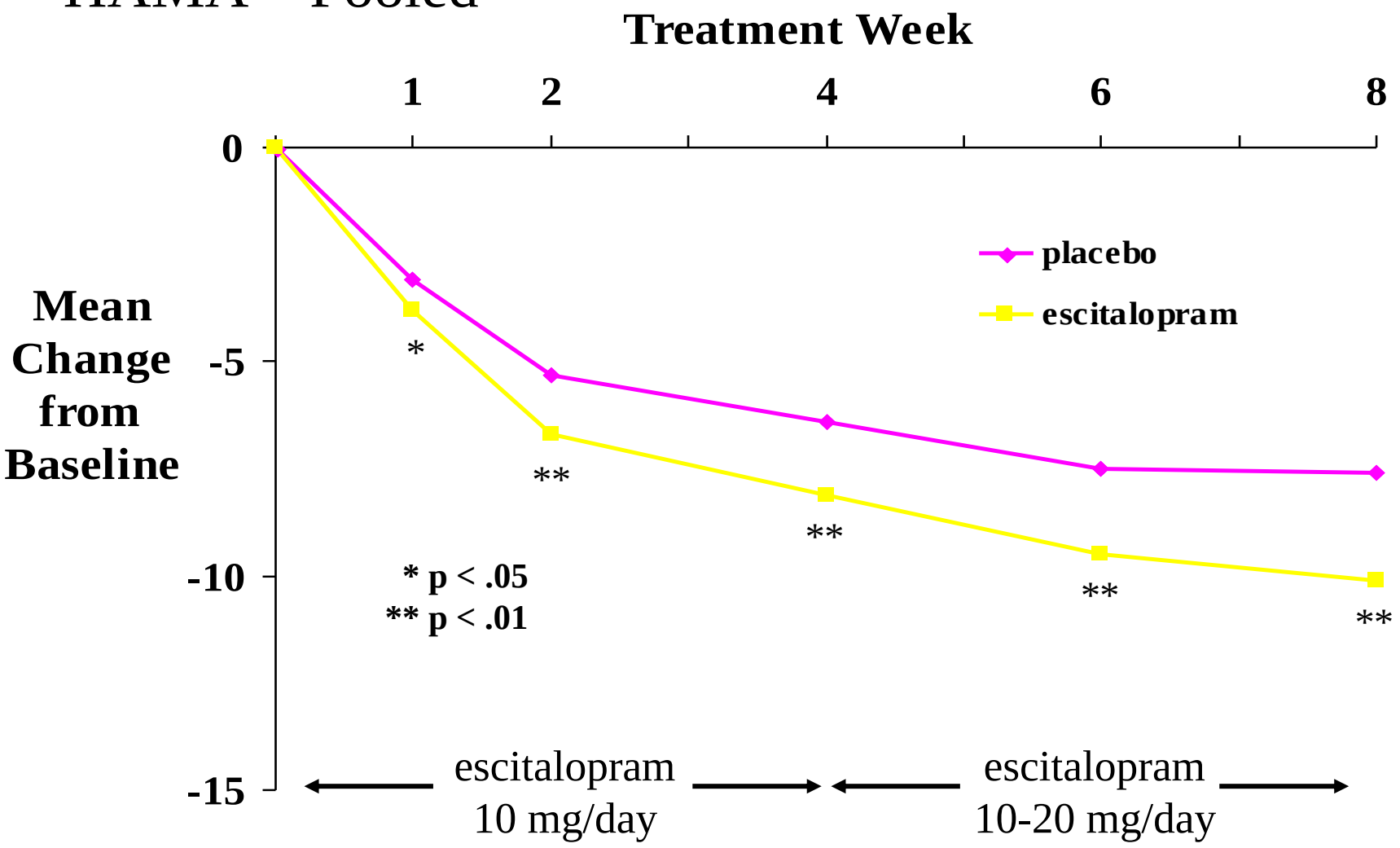
LOCF dataset

***p < .027 vs placebo**

Data on File. GlaxoSmithKline. Study 641

Escitalopram Flexible-Dose GAD Studies

HAMA – Pooled

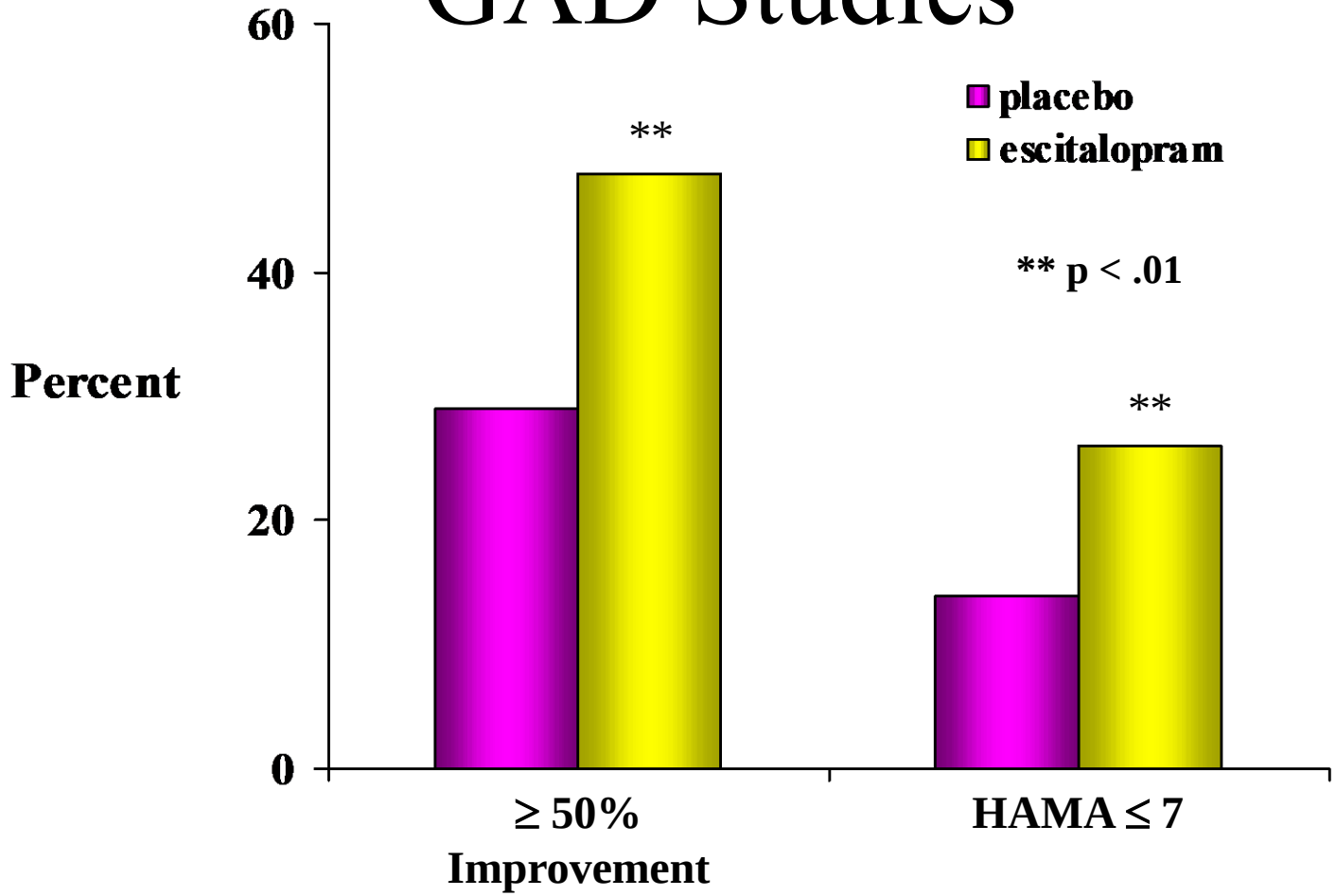


Goodman et al., 2003.

Escitalopram Flexible-Dose

HAMA Response and Remission Rates - Pooled (LOCF)

GAD Studies



Goodman et al., 2003.

Meaning of the Anxiety Studies

The 3 prior studies of venlafaxine, paroxetine and escitalopram were studies presented to the FDA for approval of these drugs for generalized anxiety disorder

In all 3 of the studies Venlafaxine, paroxetine and escitalopram based on improvement in Hamiton anxiety score the drugs were 2-4 points better than placebo

The average endpoint Hamilton score for drug treatment was 12. Remission of anxiety is defined as 7

In looking at the escitalopram data remission for the drug group was 25% vs 15% for the placebo group

The findings are statistically significant but are they really clinically significant

YALE-BROWN OBSESSIVE-COMPULSIVE SCALE

1. TIME OCCUPIED BY OBSESSIVE THOUGHTS How much of your time is occupied by obsessive thoughts? How frequently do they occur? [Be sure to exclude ruminations and preoccupations which, unlike obsessions, are ego-syntonic and rational (but exaggerated).]	0 = None. 1 = Mild, occasional intrusion (less than 1 hr/day). 2 = Moderate, frequent intrusion (1 to 3 hrs/day). 3 = Severe, very frequent intrusion (greater than 3 to 8 hrs/day). 4 = Extreme, near constant intrusion (greater than 8 hrs/day).
2. INTERFERENCE DUE TO OBSESSIVE THOUGHTS How much do your obsessive thoughts interfere with your social or work (or role) functioning? Is there anything that you don't do because of them? [If currently not working determine how much performance would be affected if patient were employed.]	0 = None. 1 = Mild, slight interference with social or occupational activities, but overall performance not impaired. 2 = Moderate, definite interference with social or occupational performance, but still manageable. 3 = Severe, causes substantial impairment in social or occupational performance. 4 = Extreme, incapacitating.
3. DISTRESS ASSOCIATED WITH OBSESSIVE THOUGHTS How much distress do your obsessive thoughts cause you? [In most, but not all cases, distress is equated with anxiety; e.g., patients may report that their obsessions are "disturbing" but deny "anxiety". Only rate anxiety that seems triggered by obsessions, not generalized anxiety or anxiety associated with other symptoms.]	0 = None. 1 = Mild, infrequent, and not too disturbing. 2 = Moderate, frequent, and disturbing, but still manageable. 3 = Severe, very frequent, and very disturbing. 4 = Extreme, near constant, and disabling distress.
4. RESISTANCE How much of an effort do you make to resist the obsessive thoughts? How often do you try to disregard or turn your attention away from these thoughts as they enter your mind? [Only rate effort made to resist, not success or failure in actually controlling the obsessions.]	0 = Makes an effort to always resist, or symptoms so minimal doesn't need to actively resist. 1 = Tries to resist most of the time. 2 = Makes some effort to resist. 3 = Yields to all obsessions without attempting to control them, but does so with some reluctance. 4 = Completely and willingly yields to all obsessions.
5. DEGREE OF CONTROL OVER OBSESSIVE THOUGHTS How much control do you have over your obsessive thoughts? How successful are you in stopping or diverting your obsessive thinking?	0 = Complete control. 1 = Much control, usually able to stop or divert obsessions with some effort and concentration. 2 = Moderate control, sometimes able to stop or divert obsessions. 3 = Little control, rarely successful in stopping obsessions, can only divert attention with difficulty. 4 = No control, experienced as completely involuntary, rarely able to even momentarily divert thinking.
	OBSESSION SUBTOTAL (Add items 1-5) _____

YALE-BROWN OBSESSIVE-COMPULSIVE SCALE

6. TIME SPENT PERFORMING COMPULSIVE BEHAVIORS How much time do you spend performing compulsive behaviors? How frequently are they performed? [When rituals involving activities of daily living are chiefly present, ask:] How much longer than most people does it take to complete routine activities because of your rituals? [In most cases compulsions are observable behaviors (e.g. hand washing), but there are instances in which compulsions are not observable (e.g., silent checking).]	0 = None. 1 = Mild, spends less than 1 hr/day performing compulsions, or occasional performance of compulsive behaviors. 2 = Moderate, spends from 1 to 3 hrs/day performing compulsions, or frequent performance of compulsive behaviors. 3 = Severe, spends more than 3 and up to 8 hrs/day performing compulsions, or very frequent performance of compulsive behaviors. 4 = Extreme, spends more than 8 hrs/day performing compulsions, or near constant performance of compulsive behaviors.
7. INTERFERENCE DUE TO COMPULSIVE BEHAVIORS How much do your compulsive behaviors interfere with your social or work (or role) functioning? Is there anything that you don't do because of the compulsions? [If currently not working determine how much performance would be affected if patient were employed.]	0 = None. 1 = Mild, slight interference with social or occupational activities, but overall performance not impaired. 2 = Moderate, definite interference with social or occupational performance, but still manageable. 3 = Severe, causes substantial impairment in social or occupational performance. 4 = Extreme, incapacitating.
8. DISTRESS ASSOCIATED WITH COMPULSIVE BEHAVIOR How would you feel if prevented from performing your compulsion(s)? [Pause.]. How anxious would you become? [Rate degree of distress patient would experience if performance of the compulsion were suddenly interrupted without reassurance offered. In most, but not all cases, performing compulsions reduces anxiety. If, in the judgement of the interviewer, anxiety is actually reduced by preventing compulsions in the manner described above, then ask:] How anxious do you get while performing compulsions until you are satisfied they are completed?	0 = None. 1 = Mild, only slightly anxious if compulsions prevented, or only slight anxiety during performance of compulsions. 2 = Moderate, reports that anxiety would mount but remain manageable if compulsions prevented, or that anxiety increases to manageable levels during performance of compulsions. 3 = Severe, prominent and very disturbing increase in anxiety if compulsion interrupted, or prominent and very disturbing increase in anxiety during performance of compulsions. 4 = Extreme, incapacitating anxiety from any intervention aimed at modifying activity, or incapacitating anxiety develops during performance of compulsions.
9. RESISTANCE How much of an effort do you make to resist the compulsions? [Only rate effort made to resist, not success or failure in actually controlling compulsions.]	0 = Makes an effort to always resist, or symptoms so minimal doesn't need to actively resist. 1 = Tries to resist most of the time. 2 = Makes some effort to resist. 3 = Yields to almost all compulsions without attempting to control them, but does so with some reluctance. 4 = Completely and willingly yields to all compulsions.
10. DEGREE OF CONTROL OVER COMPULSIVE BEHAVIOR How strong is the drive to perform the compulsive behavior? [Pause.]. How much control do you have over the compulsions?	0 = Complete control. 1 = Much control, experiences pressure to perform the behavior, but usually able to exercise voluntary control over it. 2 = Moderate control, strong pressure to perform behavior, can control it only with difficulty. 3 = Little control, very strong drive to perform behavior. Must be carried to completion, can only delay with difficulty. 4 = No control, drive to perform behavior experienced as completely involuntary and overpowering, rarely able to even momentarily delay activity.
	COMPULSION SUBTOTAL (Add items 6-10) _____ **TOTAL SCORE:** _____

OCD STUDIES

•SERTRALINE VS PLACEBO

SERTRALINE		PLACEBO	
BASELINE YBOCS	ENDPT YBOCS	BASELINE YBOCS	ENDPT YBOCS
23.30	18.20	23.43	22.20

ANAFRANIL		PLACEBO	
BASELINE YBOCS	ENDPT YBOCS	BASELINE YBOCS	ENDPT YBOCS
24.42	15.06	23.91	22.02

Note the Y-BOCS is a 10 item scale rated 0-4 (total score is 0-40). There are 5 items rating obsessions and 5 rating compulsions.

Response is generally defined as a Y-BOCS decrease of 35% and a Y-BOCS score of 15 or less. A score of 7 or less indicates remission of symptoms (12-15 is moderate OCD, 8-11 is mild OCD)

CONCLUSIONS OF OCD STUDIES

The Y-BOCS score is rated from 0-44

Often a score of 20 is serious psychopathology

Both Anafranil and Sertraline are approved by the FDA based on the aforementioned studies

However the improvement based on Y-BOCS score vs placebo is small and there is still significant psychopathology (>18 after treatment with sertraline)

Journal Club-Critical Review Form
Adapted E. Brooke Lerner 1999-version 1.1

Name: _____

Journal Club Date:_____ 1st Author, Title, Pub Date_____

Introduction

Hypothesis:_____

Are objectives clearly stated? ☐No ☐Yes

Methods

Study Design: ☐Correlational ☐Case Report ☐Case Series ☐Cross-Section
☐Cohort ☐Case control ☐Experimental ☐Meta-Analysis
☐RCT ☐Review – if yes-Where selection criteria specified? Yes/No ☐Other_____

Time Frame: ☐Prospective ☐Retrospective ☐Not Applicable

Randomized: ☐Random ☐Nonrandom ☐Not Applicable

Blinded: ☐Unblinded ☐Single Blinded ☐Double Blinded ☐Not Applicable

Enrollment: ☐Convenience ☐Consecutive ☐Other_____

Subject Source (population)_____

Inclusion Criteria:_____

Exclusion Criteria:_____

How are controls different from cases?_____ ☐Not applicable

Journal Club-Critical Review Form
Adapted E. Brooke Lerner 1999-version 1.1 (cont.)

Descriptive Variables: _____

_____

Outcome Variables: _____

_____

Main Dependent Variable:_____ ☐Parametric ☐Non-Parametric

Main Independent Variable:_____ ☐Parametric ☐Non-Parametric

Statistical Test (check all that apply): ☐T-test ☐Anova ☐Kruskal-Wallis ☐Mann Whitney ☐Chi2 ☐Fishers Exact ☐Logistic Reg. ☐Linear Reg. ☐Survial Analysis ☐Other_____ ☐Not applicable ☐Correlations

Is there a Power Calculation? ☐No ☐Yes Alpha:_____ Beta:_____

Smallest Detectable Difference_____

Results

Is there a difference between Groups: ☐No ☐Yes ☐Not applicable

Magnitude of the difference between groups?_____ 95%CI_____ P Value_____

List any other relevant findings?_____

_____

Percent of subjects lost to follow-up or non-response_____%

Are participants different from non-participants? ☐No ☐Yes

If they are different: How are they different?_____

Journal Club-Critical Review Form
Adapted E. Brooke Lerner 1999-version 1.1 (cont.)

Discussion

Was there bias in the study? ☐No ☐Yes Where:_____

Who can the results be generalized to?_____

Conclusion

Did the results support the hypothesis? ☐No ☐Yes

Will you change your practice from this study? ☐No ☐Yes How:_____

SHORTCOMING OF STUDIES

- **Response to treatment is defined as a reduction in symptoms.**

- **The response says nothing about quality of life measures such as**

  - **Ability to manage and care for the patient's basic needs**

  - **Ability to work**

  - **Ability to relate to others**

CONCLUSIONS

- **Though medications (and treatments) clearly help (beat placebo), the degree of improvement remains questionable**

- **When you have given patients 6 weeks of antipsychotic medication and they have "improved", you haven't finished the treatment, you are just starting as you are interested in longer term outcomes**

- **Future studies (CATIE or STAR-D) need to be carried out to assess how these treatments work in a pragmatic real world setting**

Post-lecture Questions

1) The type of study that must be done for a new drug to be approved by the FDA is

a) an open evaluation
b) a crossover study
c) a test of the new drug to see how it compares with historical controls
d) a double-blind placebo control parallel design study
e) a case series

Post-lecture Questions

2) In critiquing the literature the features of a good study are

a) Prospective random assignment of treatment
b) No concomitant active medications
c) Double blind placebo control
d) Adequate sample
e) All of the above

Post-lecture Questions

3) Features of a discontinuation design study include

a) an initial double-blind placebo control phase
b) an initial single blind phase followed by giving all responders continued drug or placebo in double blind fashion and assess relapse in drug group
c) giving individuals drug or placebo first and then stopping the treatment and switching to the other choice
d) an initial single blind phase followed by giving all responders continued drug or placebo in double blind fashion and continued response
e) stopping a standard drug and then giving the new drug

Post-lecture Questions

4) In discussing the issue of research studies vs. real world clinical practice

a) What is shown in clinical studies mirrors real world practice
b) Most patients in clinical studies are representative of what is seen in clinical practice
c) In a clinical trial often the sickest patients are excluded
d) A clinical trial is more concerned with functional outcomes as opposed to symptoms
e) In a clinical trial the patients are often on multiple treatments

Post-lecture Questions

5) Response to treatment in a double-blind placebo controlled clinical trial clinical trial means

a) complete alleviation of psychopathology
b) a 50% reduction in symptoms from baseline in depressed patient
c) no placebo response
d) a statistically significant difference between drug and placebo
e) both b and d

Post-lecture Questions

6) Assuming drug a placebo/difference in clinical studies problems that exist in interpreting studies

a) are the results clinically significant
b) are there quality of life improvements in addition to symptom reduction
c) placebo is clearly inferior to any treatment making conclusions invalid
d) both a and b
e) all of the above

Answers to Pre and Post Test Questions

1) D

2) E

3) B

4) C

5) E

6) D