Methodological Issues in Clinical Trials of Antidepressant Medications: Perspectives from Psychotherapy Outcome Research

Brandon A. Gaudiano\textsuperscript{a}  James D. Herbert\textsuperscript{b}

\textsuperscript{a}Department of Psychiatry and Human Behavior, Brown University School of Medicine and Butler Hospital, Providence, R.I., and \textsuperscript{b}Department of Psychology, Drexel University, Philadelphia, Pa., USA

\textbf{Abstract}

Despite their widespread use, the specific efficacy of antidepressant medications has been a source of debate in recent years. Examination of the literature reveals that a significant proportion of the benefit produced in antidepressant trials is duplicated in pill placebo conditions. Furthermore, early trials utilizing active placebos, or medications that mimic the common side effects of antidepressants, showed even smaller differences as compared with active medications. We examine issues surrounding the use of placebo control conditions in antidepressant trials, including the pros and cons of active placebos. We conclude that similar challenges are faced by psychotherapy outcome researchers who have focused more on the separation of specific from nonspecific treatment factors and on the effects of researcher allegiance and patient expectancy on outcome. Within this context, recommendations for improving future antidepressant research are discussed.

\textbf{Introduction}

Depression has been referred to as the ‘common cold’ of mental health problems, based on its high prevalence rates and heterogeneous clinical features. Kessler et al. [1] recently reported that lifetime and 12-month prevalence rates of major depressive disorders are estimated to be 16 and 6%, respectively, with 72% of the lifetime cases also meeting criteria for other psychiatric diagnoses. The newer antidepressant medications, called selective serotonin reuptake inhibitors (SSRIs), are promoted as having improved side effect profiles as compared with older medications, although this issue is very much a matter of debate [2]. The popularity of these medications has contributed to the widespread use of pharmacotherapy in the treatment of depression, making SSRIs the most commonly prescribed class of psychotropics [3]. Over the years, however, critics have suggested that the specific benefit of antidepressants above and beyond placebo effects is relatively small or even nonexistent when examined under rigorously controlled conditions. This debate has even raged in the popular media recently [4]. Therefore, this paper will examine the evidence for the specific benefits of antidepressants as compared with both inert and active placebos (i.e., medications that mimic common side effects of antidepressants) and will make recommendations to improve future studies by paying particular attention to perspectives from psychotherapy outcome research.
Placebo Response in Antidepressant Trials

The inclusion of a pill placebo condition in trials investigating the efficacy of new drugs has been standard practice for over 50 years [5]. The epistemological aim of the typical clinical trial is to provide controlled conditions under which specific treatment effects can be separated. Without adequate comparison conditions, it is impossible to differentiate any specific effects of a drug from ‘nonspecific’ factors, such as chance variation, regression to the mean, healthcare provider attention, treatment credibility and rationale, persuasion, expectancy effects, allegiance effects, effort justification, spontaneous remission, demand characteristics, and so on [6, 7]. Placebo controls may be particularly important when investigating the benefits of pharmacotherapy for psychiatric problems (e.g., mood and anxiety disorders) which by their very nature pose difficulties in diagnosis and assessment relative to medical conditions with objective, pathognomonic biological markers.

Several meta-analyses have called into question the magnitude of benefits derived from antidepressant treatment beyond placebo effects. For example, Greenberg et al. [8] found only modest effect size differences between active medications and placebos (d = 0.19–0.25) in trials comparing a new antidepressant, a standard antidepressant, and a placebo. Furthermore, effect sizes based on clinician ratings showed more improvement as compared with the gains found in patient reports which in contrast were not significantly different from placebo in the older established antidepressants [see 9 for differing conclusions].

In a more recent meta-analysis published in 1998, Kirsch and Sapirstein [10] compared the mean effect size changes in symptoms of depression across 19 double-blind antidepressant efficacy trials. The results demonstrated that placebos reproduced approximately 75% of the improvement found in active drugs. Furthermore, the authors assert that the explanation for the remaining 25% of improvement in the antidepressant condition may be attributable to an enhanced placebo response due to increased side effects experienced by patients taking the active drug or to other unidentified nonspecific factors.

The meta-analysis performed by Kirsch and Sapirstein [10] has been criticized extensively, most notably by Klein [11, 12] in a series of exchanges with Kirsch [13, 14]. Klein criticizes the study on several fronts, most notably arguing that the meta-analysis included a small, unrepresentative sample of antidepressant trials; that the use of completer-only analyses disadvantaged the drug group due to differential dropout rates; that even if small differences were found, they were still clinically significant, especially when examining the responder status; that averaging sensitive and nonsensitive measures obscured true differences, and that the studies that were included were methodologically flawed. However, Kirsch responded that other meta-analyses including different samples of studies reached similar conclusions; that other meta-analyses using intention-to-treat data found similar results; that clinician-administered and other simple categorical measures are prone to bias and that between-group differences are smaller when self-report measures are examined; that Klein argues for the inclusion of measures that support his position and for the exclusion of those that do not, and that Klein does not criticize trials showing the superiority of antidepressants over placebos, but only those that show no differences.

Recently, Kirsch et al. [15] replicated and extended the results of the meta-analysis performed by Kirsch and Sapirstein [10] using US Food and Drug Administration data. The main advantage of using the Food and Drug Administration database is that it reduces the substantial problem of publication bias in conventional meta-analyses that rely only on published reports [i.e., the so-called ‘file drawer problem’; 16]. Kirsch et al. [15] found only an 18% difference between drug and placebo, representing an average 2-point difference on the Hamilton Rating Scale for Depression (HAMD), a semistructured clinical interview most commonly used to assess the treatment outcome.

Do the findings by Kirsch et al. [15] suggest that the glass is half empty or half full (actually 82 vs. 18% in this case)? Thase [17] concluded that even though nonspecific factors account for most of the variability in antidepressant trials, these meta-analyses still show a reliable difference between drugs and placebos, and even a small difference is clinically significant from a public health perspective. Furthermore, recent evidence suggests that venlafaxine, which is a serotonin-norepinephrine reuptake inhibitor, may be more efficacious than traditional SSRI's [18], suggesting that outcomes may vary between different antidepressants/classes.

A recent large controlled trial provided an example of the difficulty in demonstrating the efficacy of antidepressants over pill placebos. The Hypericum Depression Trial Study Group (HDTSG) [19] conducted a double-blind, randomized trial comparing St. John’s wort (Hypericum perforatum), sertraline, or inert pill placebo in the treatment of 340 outpatients with major depression. Sertraline and St. John’s wort were not significantly different from
placebo in changes on the HAMD by 8 weeks, nor did the two active conditions differ from placebo in rates of full responders. However, sertraline was significantly better than placebo on the Clinical Global Impressions (CGI) improvement scale, an interviewer-rated measure, at the end of treatment. Adverse side effect profiles for St. John’s wort and sertraline differed from placebo, raising the possibility that rater bias contributed to the differences on interviewer ratings.

The HDTSG [19] trial holds important implications for pharmacotherapy research in depression. The study emphasizes the importance of including both active and inactive comparison treatments when testing antidepressants. The authors point out that if a placebo condition had not been included, it could have been concluded that St. John’s wort was as effective as standard antidepressant treatment. In other words, a trial including only two active comparison treatments that fails to find group differences could indicate that (1) both treatments were effective or that (2) neither treatment was effective, leaving much ambiguity in the interpretation of results. The findings of the HDTSG study highlight the fact that designs including only active comparison conditions address the relative but not necessarily the absolute efficacy of the treatments. The study also provides strong support for the use of a multimodal assessment strategy in psychiatric outcome studies. Pharmacotherapy outcome studies tend to rely heavily on interviewer rating measures. The CGI is comprised of a single item that may be more prone to rater bias than the more extensive ratings derived from the HAMD or the other self-report measures of depression used in the study. Finally, the HDTSG study raises the possibility that rater bias will continue to be a problem even in methodologically stringent randomized controlled trials because of the side effects experienced in active medication versus inert pill placebo conditions.

Are Active Placebos the Answer?

In a recent meta-analysis showing an increasing placebo response over the past 20 years in antidepressant trials, Walsh et al. [20] concluded that the use of a pill placebo arm in trials of investigational drugs should be continued. However, some have questioned the adequacy of inert pill placebo conditions in clinical trials. Much of the controversy stems from the possibility that patients and researchers, even in the context of a double-blind trial, may inadvertently become ‘unblinded’ due to medication side effects, such as anticholinergic symptoms (e.g., dry mouth, drowsiness, decreased sweating, blurred vision, cardiac irregularities, nausea) [21]. In other words, unblinding represents the unintentional disclosure of information to the previously naïve assessor regarding which condition the participant was assigned to, thereby potentially biasing the ratings. This also applies to the participants themselves whose expectancies may change based on knowledge of their treatment condition.

The Problems with Unblinding Effects

Several studies have suggested problems with unblinding in drug trials, although they often have produced more questions than answers. In a study of patients maintained on neuroleptics, Double [22] found that although patients’ guesses were no better than chance, raters were better than chance at detecting which patients were on active medication versus placebo. Bystritsky and Waikar [23] examined placebo-controlled trials for anxiety and depression and found that the patients generally were able to identify their study condition. White et al. [24] found similar results in their study, as an independent rater was able to guess accurately the treatment condition of patients with major depression receiving either an inert placebo or a tricyclic antidepressant (TCA). Recently, Piasecki et al. [25] assessed blind integrity in a double-blind trial comparing inert placebo to paroxetine. Reported side effects were significantly higher in the drug as compared with the placebo condition, and clinicians correctly guessed participants’ conditions in 12 out of 13 cases after treatment.

Although the inadvertent unblinding of raters or patients due to medication side effects or other factors may result in a bias in favor of the drug group in antidepressant trials, other explanations also are plausible. For example, Sharpe et al. [26] showed that unblinding often is confounded with treatment response. In other words, it is possible that participants figure out that they are in the active drug condition, because they are seeing improvements from taking the medication, in contrast to those who are taking the pill placebo. However, others have found that side effect profiles, but not treatment outcomes, were associated with unblinding, making this issue open to continued debate [27].

The Use of Active Placebo Conditions

Due to concerns about unblinding, some have suggested that so-called ‘active’ placebos, or drugs that mimic the common side effects of the active medication without providing the pharmacological agent theorized to be responsible for clinical improvement, should be included in
clinical trials [10, 21]. Providing a comparison condition, in which telltale medication side effects are kept constant between groups, could help to decrease this potential confound.

In an early review, Thomson [28] examined placebo-controlled TCA studies and found that fewer studies showed a significant difference between active placebo and TCA than between inert placebo and TCA. The author concluded that either atropine (the active placebo commonly used in these studies) has antidepressant qualities or that side effects amplify placebo responding.

More recently, meta-analyses have been conducted comparing inert versus active placebos. Moncrieff et al. [29], in their meta-analysis of nine clinical trials, found that all except one study showed a small or nonsignificant difference between antidepressants and active placebo. Moncrieff et al. [30] also conducted a similar meta-analysis for the Cochrane Review (i.e., an independent scholarly group that sponsors evidence-based reviews of treatments). When an outlying and questionable study was omitted from analyses, the effect size of antidepressants over active placebo was 0.17. The confidence interval included 0, indicating that the result was not statistically significant. Quitkin [31] agreed that the excluded study was an outlier. These results suggest that unblinding and expectancy effects may contribute to the differences typically found between antidepressants and inert placebos. However, few trials using active placebos exist for comparison. Furthermore, the ones conducted possess methodological limitations. At the present time, these results remain speculative but suggestive.

In an effort to explain these null results, it has been suggested that the active placebo commonly used, atropine, may itself have antidepressant effects [32, 33]. However, such post hoc explanations of null findings have questionable scientific merit. If an antidepressant fails to outperform a drug not considered to be an antidepressant, one cannot simply declare that the new drug possesses specific antidepressant qualities. This circular reasoning renders tests of antidepressants unfalsifiable by defining away the concept of placebo, when results are unfavorable to the active medication under study. For example, if an inert placebo condition had not been included in the St. John’s wort study [19], the authors may have reached the erroneous conclusion that the supplement was an effective treatment in the study, because it was not different than the antidepressant. Neither drug was more effective than placebo in this trial. Perhaps atropine does indeed have antidepressant effects. However, evaluation of this hypothesis will require more than post hoc maneuvers, in which a placebo condition is redefined as an active treatment, whenever an established treatment fails to outperform it.

Additional attempts to explain away null results also deserve discussion. For example, some argue that failed trials of established drugs are best explained by problems with ‘assay sensitivity’ (e.g., problems with sample selection, assessment, adherence) in a given study [34]. However, Otto and Nierenberg [35] asserted that requiring a new trial to replicate the results of a previous one in order to be considered valid constitutes a fundamental ‘derailment’ of the scientific method. Such assay sensitivity arguments are dangerous, because they assume that a trial should obtain certain preordained results before it even is conducted.

Other scientifically stronger arguments have been presented, contesting the need for the inclusion of active placebo conditions in antidepressant trials. Quitkin et al. [9] and Quitkin [31] argue that the reviews by Thomson [28] and Moncrieff et al. [29] are flawed and that their conclusions are contradicted by the data. Thomson [28] reported that antidepressants were shown to be superior in 59% of the trials using inert placebos versus only 14% of those using active placebos. However, Quitkin et al. [9] calculated the percentage of responders from these studies. They reported that the response rate to active placebo was about 30% which is comparable to the response consistently demonstrated in the literature using inert placebos. Furthermore, Quitkin et al. [9] argue that the studies using active placebos possessed serious methodological weaknesses that preclude definitive conclusions, including inadequate sample sizes, medication dosing, treatment duration, and diagnostic specificity.

How can two reviews of the same studies come to such completely different conclusions? Some of the confusion may be understood when examining the methodology used to examine the literature. Thomson [28] and Quitkin et al. [9] used different empirical approaches as compared with Moncrieff et al. [29, 30]. For example, Thomson [28] only examined whether or not the active placebo condition was significantly different from the active drug condition in each study. Quitkin et al. [9] examined a different categorical variable – responder status. It is well known that categorization procedures provide clearer differentiation between groups than examination of continuous variables [36]. Interestingly, Tedlow et al. [37] found that the relationship between baseline severity and outcome varied as a function of the type of measurement used (i.e., percent change vs. categorical response rate). However, meta-analysis also has its inherent flaws as a
Trials

Methodological Issues in Antidepressant

ing active placebos in antidepressant trials is a purely

spread use constitute an important public health issue.

efficacy of antidepressants which because of their wide-

sary precaution, at least in some trials to fully examine the

sus-benefit context. Active placebos might well be a neces-

ethical dilemmas may best be examined within a cost-ver-

tive placebos would require more stringent safeguards

methodologically appealing, studies designed to use ac-

sirable side effects. Therefore, although conceptually and

drugs mimic common side effects, they not only provide

also have been criticized on ethical grounds. Because the

SSRIs relative to placebos [40]. However, active placebos

opposite trend – higher rates of suicidality observed with

pressant trials [39], and recent data actually suggest the

does not appear to lead to a higher suicide risk in antide-

pressants reported more side effects than those on the active placebo which could have resulted in the unblind-

of raters. Therefore, it also appears likely that any

methodological flaws could have produced biases against

the active placebo condition. Most importantly, Mon-

crief et al. [30] found that the study quality was inversely correlated with effect size (r = –0.78, with one outlying

study excluded). In other words, studies with higher meth-

odological rigor showed smaller differences between active

placebos and antidepressants. This is consistent with the

findings of the meta-analysis performed by Greenberg et al. [8], examining studies using inert placebos.

Furthermore, no compelling evidence exists that pill

placebos are associated with any identifiable risk of harm
to participants. For example, the use of inert placebos
does not appear to lead to a higher suicide risk in antide-

ressant trials [39], and recent data actually suggest the

opposite trend – higher rates of suicidality observed with

SSRIs relative to placebos [40]. However, active placebos

also have been criticized on ethical grounds. Because the

drugs mimic common side effects, they not only provide

no intentional therapeutic benefit, but also produce unde-

sirable side effects. Therefore, although conceptually and

methodologically appealing, studies designed to use ac-

active placebos would require more stringent safeguards

and procedures for protecting participants. These types of

ethical dilemmas may best be examined within a cost-ver-
sus-benefit context. Active placebos might well be a neces-

sary precaution, at least in some trials to fully examine the

efficacy of antidepressants which because of their wide-

spread use constitute an important public health issue.

Finally, perhaps the biggest problem with incorporat-

ing active placebos in antidepressant trials is a purely

practical one. The active placebos used in previous re-

search were mainly in trials examining TCAs. Drugs that

mimic the problems associated with other popular classes

of medication, such as SSRIs, need further development.

Other possibilities for active placebos for SSRIs are pe-

ripherally acting anticholinergic and antihistamine medi-
cations that would produce side effects without the possi-

bility of clinical improvement [33]. Some have suggested

that active placebos are not needed, as other psychotropic

drugs (e.g., neuroleptics, barbiturates, and benzodiazep-

ines) have been compared with antidepressants for de-

pression. Results have been fairly mixed, although some

studies using neuroleptics or benzodiazepines have shown

either equivalency or superiority to antidepressants [36,

41]. These investigations assured that patients would

experience side effects. However, drugs such as neurolep-
tics and benzodiazepines already have demonstrated psy-

choactive properties with established efficacy for treating

other conditions, making them methodologically undesir-

able for use as active 'placebos'.

Improving Antidepressant Trials

Although others [42–44] have made recommendations

for improving antidepressant trials recently, the following

suggestions focus specifically on how better to separate

specific from nonspecific treatment effects and to reduce

allegiance and expectancy effects. Separating the nonspe-
cific from the specific active ingredients of effective psy-

chiatric treatments traditionally has been the domain of

psychotherapy outcome research. Psychotherapy studies

also traditionally have had to contend with strong alle-
giance effects (i.e., researchers’ biases affecting the results

from clinical trials) [45] and patient expectancies skewing

results. Therefore, researchers who are involved in antide-

pressant medication trials may benefit from examining

this literature on empirically supported psychosocial

treatments [see 46 for a recent discussion in psycho-

therapy]. Within this context, the recommendations

shown in table 1 were developed.

Controlling for Nonspecific Factors

Little attention is given in psychopharmacology trials

as to how expectancy influences the outcome. Further-

more, unblinding may be confounded with treatment

effect in studies showing drug superiority to inert place-

bos. Keeping raters blind to the study design and hypothe-
ses offers an important degree of protection against such

expectancy effects. Another option would be to conduct

studies that manipulate patient/rater expectancy as an
Follow guidelines in the CONSORT statement [70] when designing and reporting trials. Provide full disclosure of financial or other competing interests in treatments under investigation. Conduct multisite trials to reduce allegiance biases. If possible, ask patients and raters to guess treatment conditions, ask the reasons for their guesses, and obtain percentage confidence in guesses (at multiple time points). Administer ‘reaction to treatment’ questionnaires to assess expectancy effects (at multiple time points).

Measurement issues:
- Assess treatment outcome in a multi-modal fashion and examine convergence of measures.
- Rate degree of blindness achieved in the study on standardized scales.
- Ask patients and raters to guess treatment conditions, ask the reasons for their guesses, and obtain percentage confidence in guesses (at multiple time points).
- Administer ‘reaction to treatment’ questionnaires to assess expectancy effects (at multiple time points).

Statistical issues:
- Analyze differences between placebo responders and nonresponders based on side effect profiles.
- Contrast early fleeting, early maintained, and late-onset improvement patterns.
- Examine the disparity between patient and clinician ratings to identify potential confounds.
- Contrast results from completer-only and intention-to-treat analyses.
- Examine the clinical significance of results based on the methods of Jacobson and Truax [65].
- Contrast continuous and categorical measures of improvement.

Table 1. Potential strategies for separating specific from nonspecific effects in antidepressant trials

<table>
<thead>
<tr>
<th>Design issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Include active placebo arms in methodologically stringent trials.</td>
</tr>
</tbody>
</table>

| Conduct multisite trials to reduce allegiance biases. | Keep raters blind to study design and hypotheses when possible. | Provide full disclosure of financial or other competing interests in treatments under investigation. | Follow guidelines in the CONSORT statement [70] when designing and reporting trials. |

| Measurement issues | |
|-------------------|
| Assess treatment outcome in a multi-modal fashion and examine convergence of measures. |
| Rate degree of blindness achieved in the study on standardized scales. |
| Ask patients and raters to guess treatment conditions, ask the reasons for their guesses, and obtain percentage confidence in guesses (at multiple time points). |
| Administer ‘reaction to treatment’ questionnaires to assess expectancy effects (at multiple time points). |

| Statistical issues | |
|--------------------|
| Analyze differences between placebo responders and nonresponders based on side effect profiles. |
| Contrast early fleeting, early maintained, and late-onset improvement patterns. |
| Examine the disparity between patient and clinician ratings to identify potential confounds. |
| Contrast results from completer-only and intention-to-treat analyses. |
| Examine the clinical significance of results based on the methods of Jacobson and Truax [65]. |
| Contrast continuous and categorical measures of improvement. |

Furthermore, Lohr et al. [6] propose that additional treatment arms should be included within studies, because comparisons of conditions between studies are frequently unreliable. Along this vein, Kirsch and Sapirstein [10] argue for the inclusion of the following conditions in antidepressant trials: active placebos, inert Placebos, active medication, and wait list controls for natural history. However, before active placebos can be incorporated into

Table 1. Potential strategies for separating specific from nonspecific effects in antidepressant trials

<table>
<thead>
<tr>
<th>Design issues</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Include active placebo arms in methodologically stringent trials.</td>
<td>Conduct dismantling studies based on underlying biological theories.</td>
</tr>
<tr>
<td>Manipulate patient/rater expectancy as an independent variable.</td>
<td>Increase the number of study arms within studies in large trials.</td>
</tr>
<tr>
<td>Include wait list control groups when possible.</td>
<td>Explore alternate experimental designs (e.g., ‘sequential parallel-comparison design’) [43].</td>
</tr>
</tbody>
</table>

| Conduct multisite trials to reduce allegiance biases. | Keep raters blind to study design and hypotheses. | Provide full disclosure of financial or other competing interests in treatments under investigation. | Follow guidelines in the CONSORT statement [70] when designing and reporting trials. |

<table>
<thead>
<tr>
<th>Measurement issues</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess treatment outcome in a multi-modal fashion and examine convergence of measures.</td>
<td>Rate degree of blindness achieved in the study on standardized scales.</td>
</tr>
<tr>
<td>Ask patients and raters to guess treatment conditions, ask the reasons for their guesses, and obtain percentage confidence in guesses (at multiple time points).</td>
<td></td>
</tr>
<tr>
<td>Administer ‘reaction to treatment’ questionnaires to assess expectancy effects (at multiple time points).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statistical issues</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyze differences between placebo responders and nonresponders based on side effect profiles.</td>
<td>Contrast early fleeting, early maintained, and late-onset improvement patterns.</td>
</tr>
<tr>
<td>Examine the disparity between patient and clinician ratings to identify potential confounds.</td>
<td>Contrast results from completer-only and intention-to-treat analyses.</td>
</tr>
<tr>
<td>Examine the clinical significance of results based on the methods of Jacobson and Truax [65].</td>
<td>Contrast continuous and categorical measures of improvement.</td>
</tr>
</tbody>
</table>

independent variable. Interestingly, Benedetti et al. [47] manipulated patients’ knowledge of whether or not they were receiving treatment and found that hidden administration was less effective than open administration of psychopharmacological agents. Another approach would be to conduct a 2 (drug vs. placebo) by 2 (believe they are receiving drug vs. believe they are not receiving drug) factorial design that manipulates participant expectation [10]. In this design, which has been used in the study of alcohol intoxication, participants (1) are told they will receive the drug and do receive the drug; (2) are told they will not receive the drug but do receive the drug; (3) are told they will receive the drug but do not receive the drug; and (4) are told they will not receive the drug and do not receive the drug. Such a design is experimentally elegant, but may be difficult to implement in clinical trials due to ethical concerns.

An alternative to the above design that would be less ethically problematic would involve the use of active placebos. Active placebos could help control for expectancy by keeping side effects constant between groups. The analysis of appropriate comparison conditions in behavior therapy by Lohr et al. [6] may be a useful model here. These authors assert that the use of simple comparison conditions in psychosocial treatment research, such as wait list controls, is necessary but not sufficient to control for the strong influencing effects of nonspecific and common treatment factors. They recommend the inclusion of more stringent comparison conditions that can separate the incidental and characteristic elements of an investigational treatment. Furthermore, they assert that this type of investigation should be guided by an examination of the underlying theory of psychopathology on which the treatment is based.
modern antidepressant trials, work will need to be done to find appropriate drugs for this use, especially in trials with SSRIs.

Measuring Bias Systematically and Statistically

All studies are imperfect, and no design, either ideally or practically, can reduce all sources of bias and error. Conflict of interest is a pervasive problem in psychopharmacology [52]. For example, Kjærgard and Als-Nielsen [53] found that clinical trials favored the investigational treatment, if the researchers declared financial competing interests. The inclusion of active placebos or other experimental controls may help to reduce unblinding and expectancy effects, but other steps also may be necessary to reduce potential confounds. Specifically, making better attempts to measure and analyze bias is essential to interpreting results accurately and assuring generalizability. Common biasing effects include those of unblinding, allegiance, and expectancy.

Kirsch and Lynn [54] outlined the potential role of expectancy effects in psychotherapy outcome. To date, too few psychopharmacology studies have systematically examined and reported on these factors. However, more researchers are beginning to address these concerns in the literature. For example, ‘reaction to treatment’ questionnaires can be incorporated into antidepressant trials. These measures are increasingly being used in psychotherapy research to assess patients’ expectancies about treatment and the believability of the treatment rationale [55]. Treatment credibility questionnaires are given typically early on in treatment, making them unlikely to be confounded with treatment effect.

Asking raters and patients to identify who is in which group, or which group will likely show greater improvement, can provide simple yet indispensable information when interpreting results [56]. Furthermore, asking participants how they came to their conclusions could prove useful. For example, do they believe they are in the medication group because of side effects experienced or observed improvement? Blindness assessments taken at multiple points that indicate percentage of confidence may provide added protection [25]. To aid in measurement, Even et al. [57] devised the blindness assessment and protection checklist, a seven-item checklist for evaluating the blindness protection of antidepressant trials. Analyzing the relationship between these variables and treatment outcome can help investigators examine the effectiveness of the controls used in the study.

Newer statistical techniques also may prove useful. Petkova et al. [58] developed a method to quantify rater bias in antidepressant trials by contrasting patient and clinician ratings. Katz and Deveaug-Geiss [59] recommended that the outcomes of subgroups of participants in the placebo condition be compared based on their side effect profiles. Ross et al. [60] suggested a two-step data analysis process that does not assume that placebo responders are a subset of medication responders. They developed a model to assess early fleeting, early maintained, and late-onset clinical improvement and suggested that this method can differentiate drug from placebo responding. However, because it is based on categorical analyses, it should be supplemented with information from continuous measures to ensure convergence of evidence. In addition, Stassen et al. [61] have adapted survival analysis techniques to investigate onset of improvement in antidepressant trials. They found that more participants dropped out due to lack of improvement (in contrast to side effects, etc.) in the placebo as compared with the antidepressant condition. Surprisingly, the time course of improvement for responders was identical regardless of treatment condition.

We recommend that researchers conduct and report both completers only and intention-to-treat (i.e., including all those who were assigned to a condition) analyses. High or differential dropout rates between groups may produce unrealistically positive results of overall benefits or may artificially inflate the superiority of one condition over another [see 62 for an example in psychotherapy research]. Kirsch et al. [15] found that the placebo response in completer-only analyses was significantly greater than that obtained in intention-to-treat analyses. Others have found the opposite relationship [36].

Finally, we suggest that antidepressant trials make better attempts to assess treatment outcomes in a multimodal fashion (e.g., self-report, clinician ratings, collateral information, behavioral ratings, and physiological indices) to examine convergence of data, as is fundamental to modern psychotherapy trials [63]. To date, multimodal approaches to assessment have most successfully been used in the study of anxiety disorders [64], and more thought needs to be given to the use of this strategy in studying depression. As discussed previously, outcome trials, especially those investigating pharmacological agents, tend to rely too heavily on simple interviewer ratings of outcome that can be biased, such as with the CGI. More valid and reliable improvement criteria, such as methods based on the work by Jacobson and Truax [65] related to ‘clinical significance’, deserve increased attention in pharmacological trials as well. Other commonly used instruments such as the HAMD include symptom
items that relate to changes in other nondepressive disorders or medical conditions that may skew results [36]. Some suggest that Bech’s six-item subscale of the HAMD may be a more sensitive in determining changes in core depressive symptoms [66].

Conclusions

It is important to note that the controversy over the specific efficacy of treatments for depression is not confined to pharmacotherapy. The ‘mechanisms of action’ debate has raged in the psychosocial intervention literature over some of the most common and successful interventions. Over a decade and a half after the publication of the seminal book by Beck et al. [67] on the use of cognitive therapy for depression, Jacobson et al. [68] conducted a dismantling study that implicated behavioral activation, not cognitive techniques, as the active ingredient in the treatment. Modern psychotherapy research is based largely on the designs and theories initially developed for pharmacological trials. Perhaps it is time for researchers of pharmacological treatments to pay attention to the refinements in methodology that psychotherapy researchers have made to help disentangle specific from nonspecific treatment effects [see 69 for a comprehensive review]. Only future research using improved methodology will allow us to piece together the puzzle of the optimal treatment of depression.

Acknowledgments

We would like to thank David Antonuccio, PhD, for his helpful feedback on an earlier draft of the manuscript. This paper was supported in part by Grant No. R01 MH052232 from the National Institute of Mental Health (NIMH), Bethesda, Md., USA.

References


6 Loth JM, DeMaio C, McGlynn FD: Specific and nonspecific treatment factors in the experimen


18 Smith D, Dempster C, Glanville J, Freemantle N, Anderson I: Efficacy and tolerability of ven


20 Walsh BT, Seidman SN, Sysko R, Gould M: Placebo response in studies of major depres

21 Greenberg RP, Fisher S: Examining antidepressant effectiveness: Findings, ambiguities, and some vexing puzzles; in Fisher S (ed): The Limits of Biological Treatment for Psychologi

