

## Methodological Issues in Clinical Trials of Drug and Behavior Therapies

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**Trials that compare drug and behavior therapies or evaluate combination therapy raise special methodological issues. This article reviews these methodological issues and, where possible, offers guidelines for addressing them. Sources of bias in the selection and recruitment of participants and in the measurement of treatment outcomes are discussed. In addition, methodological problems presented by the differing structures of behavior and drug therapy, by confounding variables, such as allegiance effects, differential expectations and preferences for drug or behavior therapy, and differential adherence with drug or behavior therapy also are reviewed. Issues in the selection of appropriate control groups are also discussed.**

**Key words:** clinical trial, methodology, behavior therapy, drug therapy, headache

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Trials that compare the efficacy or effectiveness of drug and behavior therapy, or combine these two therapy modalities present special methodological problems as well as unique scientific opportunities.<sup>1-3</sup> Neither the methodology used to evaluate drug therapies nor the methodology used to evaluate behavioral therapies can be transferred wholesale to such trials. Thus, this article addresses methodological issues that are specific to the design of studies that evaluate the separate and combined effects of drug and behavior therapy.

Methodological issues in drug-behavioral trials differ for pragmatic (effectiveness) and explanatory (efficacy) trials. Thus, these two types of trials will be distinguished here. Pragmatic trials seek to determine the utility or cost effectiveness of a treatment, while explanatory trials seek to establish the mechanism(s)

whereby a treatment produces improvement.<sup>4,5</sup> The difference of primary interest here is that explanatory trials attempt to control for the role of nonspecific treatment elements, such as number of treatment sessions, therapy contact time and, demand characteristics across treatments; so differences in treatment outcome can be attributed to the putative “active” elements of each treatment. Thus, behavioral and drug treatments as they are practiced clinically may be altered so that treatments are matched on nonspecific treatment elements; pill placebo and behavioral “placebo” (eg, pseudotherapy) control groups also may be used to assess the role of nonspecific elements of drug or behavioral treatment in observed treatment outcomes. Conversely, pragmatic trials emphasize the clinical relevance of treatments: nonspecific treatment elements are considered part of treatment packages being compared and may be allowed to vary dramatically across treatments. Typically, a treatment as clinically practiced is compared to a clinically relevant alternative, such as no treatment, treatment as usual, or an alternate treatment as clinically practiced. Pill placebo, if used at all, serves as a pragmatic benchmark to assure that behavioral and drug treatment effects are not trivial<sup>5</sup>; behavioral “placebo” control groups are not needed.

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## RECRUITMENT AND SELECTION

It is important that recruitment and selection procedures yield an unbiased sample that is appropriate for either treatment modality.<sup>2</sup> For example, excluding previous nonresponders to one treatment modality will introduce bias. More generally, prognostic variables typically are unknown, and may differ for drug and behavioral treatment; randomization is thus relied upon to equate unknown prognostic variables across participants receiving different treatments. This argues for the recruitment of a wide range of participants from multiple sources to maximize the variability in prognostic variables relevant to drug and to behavior therapy in trial participants. Recruitment procedures also need to be clearly specified.

Participants often have a preference for drug or behavioral therapy and this preference may undermine adherence, influence dropout rate, and even affect treatment response.<sup>1,6</sup> Recruitment strategies that primarily yield participants with one therapy preference (eg, recruitment only from a clinic known primarily for either drug or behavior therapy) thus may introduce bias. Potential trial participants who do not want drug therapy (and may be particularly appropriate and motivated for behavior therapy) appear to be more likely to refuse randomization than participants who do not want behavior therapy, or are not willing to put forth the effort required in behavior therapy. The latter, may agree to randomization, but not attend treatment sessions or engage in behavior therapy.\* This creates a differential sieve that yields a sample more cooperative with and motivated for drug therapy than behavior therapy. No solution to this methodological problem is available at this time. Assessing and reporting reasons for refusal of randomization and participants' treatment preferences can help identify these possible confounds even if they cannot be controlled.

\*For example, in a current trial (K.A.H.), 13 potential participants indicated they preferred behavior therapy and, thus, would not consent to possible randomization to drug therapy; in contrast, no one refused randomization to behavior therapy. However, following randomization, 12 participants refused behavior therapy at the first treatment session, while no participant refused drug therapy at this time.

Additional information is needed about the influence of participant expectations and preferences on treatment adherence, attrition, and treatment outcome. This could be investigated in a design with two levels of randomization. First, trial participants are randomized to two conditions; one where they subsequently are randomized to drug and behavior therapy, as in the typical randomized trial; and one where they receive their preferred treatment. If participants are more adherent and show better outcomes when they can choose the treatment they prefer, results will be better in the latter condition than in the former condition. It is possible that behavior therapy, which demands greater time and effort than drug therapy, is particularly sensitive to patient preferences.

## TREATMENT

**Structure of Therapies.**—As practiced clinically, the number, frequency, and length of treatment and follow-up sessions differ for drug and behavior therapy. Separately, drug therapy and behavior therapy also may differ from the combined treatment in the number or length of treatment sessions. Because clinical relevance is the primary consideration in pragmatic trials, differences in treatment structure may be ignored if they reflect clinical practice. In explanatory trials, where such differences in structure of therapies may confound inferences about the active ingredients of therapy, the structure of therapies needs to be equated to the degree possible.

Typically, behavior therapy has terminated but drug therapy has continued when treatment outcome is assessed. However, important information about long-term outcomes can only be obtained if treatment effects also are assessed following drug withdrawal.<sup>7</sup> For example, the question “Does combining behavior therapy with drug therapy enhance the maintenance of treatment effects following drug withdrawal?” can only be addressed following drug withdrawal.<sup>3</sup>

Behavior therapy may include periodic booster or relapse prevention sessions following the primary treatment period.<sup>8</sup> Particularly in explanatory trials, this also can be a means of equating treatment structures (eg, number of treatment visits, contact time, etc.) in drug and behavioral treatment during longer-term evaluation periods.

**Control Groups.**—Assay sensitivity<sup>†</sup> is not established for treatments for headache.<sup>9</sup> Thus, if drug and behavior therapy produce similar outcomes it remains unclear if both treatments were effective, ineffective, or even harmful in the absence of a control or reference group. In some pragmatic trials this ambiguity may be tolerated, because the trial has no practical implication unless the treatments differ in effectiveness.<sup>4</sup> However, pill placebo provides a useful common reference for both drug and behavior therapy eliminating this ambiguity.<sup>5</sup> While pill placebo does not control for all “nonspecific” elements of behavioral treatment, this is not of primary concern in a pragmatic trial: a treatment that does not “beat” pill placebo is unlikely to be of practical interest.

Explanatory trials focus on elucidating the mechanisms whereby treatments produce improvement. For behavioral treatments there are no agreed upon control groups that include all elements of therapy except the “active” ingredients<sup>10-15</sup>; so the pros and cons of different control groups need to be weighed. Examples of possible control groups include biofeedback training procedures that alter the direction<sup>16,17</sup> or nature<sup>16</sup> of the physiological response that is being trained in “true” biofeedback training and equally credible psychological procedures, such as “pseudomeditation,”<sup>18</sup> that appear to have no significant therapeutic benefit for headaches. Issues in the selection of control groups for trials involving behavior therapy are discussed in more detail in a companion article in this series and will not be further addressed here.

**Confounds.**—*Allegiance Effects and Therapy Fidelity.*—Allegiance effects, or the tendency of investigators and trial sites to obtain better results with the therapy modality they have primary allegiance to, than with other therapies, are an important methodological confound, in drug-behavioral treatment

comparisons.<sup>19,20</sup> The effective implementation of drug or behavior therapy also can be compromised if investigators have greater training, experience, or familiarity with one therapy modality than the other modality.<sup>1,19</sup> These methodological confounds can be minimized when drug and behavioral therapy are each administered by health care professionals who have a primary allegiance to the type of therapy they are administering and expertise in its administration.

Health care professionals administering either drug or behavior therapy also may inadvertently fail to adhere or “drift” from treatment protocol. In some pragmatic trials where the goal is to duplicate clinical practice, including practitioners’ clinical judgments in tailoring treatments to patients, considerable leeway may be allowed in implementing treatment. However, therapy protocols need to be clearly specified and fidelity to treatment protocols maintained if a clearly defined therapy is to be evaluated, and the therapy is to be duplicated by others. Explicit treatment manuals, ongoing supervision of treatment providers, examination of medical files, and independent ratings of audio or video recording of treatment sessions, are all methods of encouraging and monitoring treatment fidelity.

*Adherence and Attrition.*—Differential adherence with drug and behavior therapy limits inferences about the relative effectiveness of these therapies. Adherence data provide useful information about treatment acceptability in pragmatic trials. However, high adherence with both drug and behavior therapy is necessary if differences in treatment outcomes are to be attributed to differences in the effectiveness of treatments, rather than to differences in adherence. Adherence is important with placebo as well as with active treatment, because adherence is associated with more positive outcomes than nonadherence, even in placebo treatment.<sup>21,22</sup> Adherence appears to be more easily assessed with drug therapy, where various technologies such as electronic pill bottles, analysis of drug blood levels, absorption distribution, and metabolism are available. However, these apparently “objective” biological measures lack reliability, and thus rarely are used in drug trials of preventive medication for headaches. Measures of adherence with behavior therapy are often limited to self-report, though completion

<sup>†</sup>Assay sensitivity refers to whether the active comparison treatment has an effect ( $M$ ) of the size that is expected in the trial that was carried out. The effect of available active comparisons treatments for headache may vary across samples. In a particular trial sample it is thus possible that the effect of the active comparison treatment will be less than expected ( $<M$ ), for example, no greater than pill placebo. In the absence of assay sensitivity, even when the treatment of interest and the active comparison treatment have equivalent outcomes, it cannot be concluded that the treatment of interest is effective ( $\geq M$ ).

of in-therapy tasks and/or homework assignments and tape recorders capable of electronic monitoring use of relaxation tapes have been used as “objective” measures of adherence.

A number of methods have been used to maximize adherence with therapy. Written materials that provide clear information about the drug and the drug regimen, phone calls to identify and correct adherence problems, and flexible dose adjustment schedules that minimize side effects, have all been used to improve adherence with drug therapy.<sup>23</sup> Procedures that have been used to improve adherence with behavior therapies include written guidelines for homework assignments, phone calls to identify and correct adherence problems, problem solving with participants to identify and plan ways of managing barriers to adherence, and limiting the time demands made by homework assignments.

Attrition, like adherence, may reflect treatment acceptability and thus be one indicator of treatment outcome in pragmatic trials. However, differential (nonrandom) attrition from drug and behavior therapy complicates the analysis and interpretation of treatment outcome. Documenting the reasons for early termination can facilitate the interpretation of findings when there is differential attrition. Comparison of the demographic and clinical characteristics of dropouts from each treatment condition also can be helpful as different types of participants may drop out of drug and behavior therapy.

*Participant Expectations.*—Potential trial participants typically rate combined drug and behavior therapy as more likely to be effective and as more credible than its component therapies, probably because a common assumption is that different therapy modalities are likely to have additive effects. Equating perceptions of credibility and expectations of improvement across treatment conditions is thus likely to prove difficult in trials examining the separate and combined effects of drug and behavior therapy. This is not a concern in pragmatic trials. In explanatory trials, credibility differences may occasionally confound the interpretation of observed outcome differences between combination therapy and drug or behavior therapy alone. A 2 (drug vs placebo) × 2 (behavior therapy vs pseudotherapy) factorial design attempts to equate contact time, attention, and demand characteristics

across all four treatment conditions, and thus may also equate treatment credibility across all four conditions.

## TREATMENT EFFECTS

**Outcome and Process Measures.**—Even if drug therapy and behavior therapy have a similar impact on the primary outcome variable (typically headache frequency or headache days), the impact of these two treatment modalities may differ on other measures of functioning (eg, psychological symptoms, quality of life, efforts to manage headaches).<sup>24-26</sup> and even other aspects of headache.<sup>27</sup> (See also the companion article in this issue on outcome measures.) If the primary outcome for drug and behavior therapy are hypothesized to differ, a primary endpoint for each hypothesized outcome might be included and the trial powered for both outcomes. In general, capturing possible differences in the impact of the two therapy modalities requires the inclusion of outcome measures that encompass the full range of outcomes likely to be impacted by either therapy modality.<sup>2,3</sup>

The time course of change also may differ with behavioral and drug therapies. For example, drug therapies may work rapidly or behavior therapy may have a delayed onset of effect.<sup>23,24</sup> The valid comparison of behavioral and drug therapies requires that the evaluation period be of sufficient length to capture the likely impact of each treatment modality.

Measurement strategies differ in pragmatic and explanatory trials. The latter, but not necessarily the former trials, requires the inclusion of measures of therapeutic mechanisms. However, even pragmatic trials may provide useful information about the active ingredients of behavioral treatments. For example, it can reasonably be assumed drug and behavioral therapies work via different therapeutic mechanisms. Thus, trials of drug and behavior therapy can tell us if changes in indices of putative therapeutic mechanisms occur uniquely with behavioral treatment, or also with drug therapy. In the latter case, indices of “therapeutic mechanisms” may actually change as a consequence, rather than as a cause of improvement. Information obtained from drug-behavior therapy trials might thus be maximized if measures of the putative therapeutic mechanisms of behavioral treatment (eg, self-efficacy, headache-related coping) are obtained even in pragmatic trials.

## BEHAVIOR THERAPY AND ACUTE DRUG THERAPY

The above methodological considerations refer primarily to trials of preventive drug therapy and behavior therapy. The effect of behavior therapy on acute therapy of individual headache episodes has yet to be evaluated. Concurrent behavior therapy might render migraines more responsive to acute therapy; use of cognitive and behavioral pain management skills during headaches treated with acute therapy might enhance the effectiveness of acute therapy, or behavioral adherence interventions might improve adherence and thus the effectiveness of acute therapy.<sup>28</sup> Trials evaluating these hypotheses would be guided by the methodological recommendations for trials of acute drug therapy<sup>29</sup> and, where applicable, the methodological considerations addressed above.

## CONCLUSION

This article reviewed methodological issues that are specific to the effective design of studies that evaluate the separate and combined effects of drug and behavior therapy. Sources of bias in the selection and recruitment of participants and in the measurement of treatment outcomes were discussed. In addition, methodological problems presented by the differing structures of behavior and drug therapy, by confounding variables, such as allegiance effects, differential expectations and preferences for drug or behavior therapy, and differential adherence with drug or behavior therapy also are discussed. Issues in the choice of control groups also were addressed. Where possible, solutions to the identified methodological problems were suggested. The methodological guidelines offered here are not considered immutable, but are expected to evolve as investigators creatively tackle design issues when conducting drug-behavioral trials.

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