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Unique Ethical Concerns in Clinical Trials Comparing Psychosocial and Psychopharmacological Interventions

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Abstract

In recent years, there has been a particular emphasis placed on conducting randomized controlled trials (RCTs) that compare the relative efficacy of psychosocial and pharmacological interventions. This article addresses relevant ethical considerations in the conduct of these treatment trials, with a focus on RCTs with children. Ethical concerns, including therapeutic misconception, treatment preference, therapeutic equipoise, structure of treatments, and balancing risks versus benefits, are introduced through a clinical scenario and discussed as they relate to psychotherapy versus medication RCTs. In each case, suggestions are made for researchers seeking to minimize the impact of these ethical concerns on research participants.

Keywords

clinical trials; ethical dilemmas; psychosocial interventions; psychopharmacological interventions

In the past several decades, numerous efficacious psychosocial and pharmacological treatment options have been identified for childhood psychological and behavioral disorders (for reviews, see Barrett & Ollendick, 2004; Lilienfeld, 2005). More recently, in part because of a shift in National Institute of Mental Health priorities toward treatment comparison and effectiveness research and the demands of managed care to identify superior and cost-effective treatment approaches, there has been a particular emphasis placed on conducting randomized clinical trials (RCTs) that compare these divergent interventions (Brown & Ievers, 1999; Norquist, Lebowitz, & Hyman, 1999). In this article, we focus specifically on the potential ethical concerns raised in clinical trials that compare psychotherapy to pharmacotherapy for child psychopathology, although the ethical issues we address certainly have relevance to other types of research designs. We use examples drawing from a range of childhood psychopathology, but the focus is on general ethical issues that may arise in trials regardless of the specific pathology being examined. This article is the first of which we are aware that specifically addresses the unique concerns that emerge in these types of comparative clinical trials.

In this review, we address the following ethical concerns: therapeutic misconception (failure to appreciate the differences between the receipt of treatment through an RCT and receiving treatment-as-usual), treatment preference (what influence might a preference for one treatment modality over another have on RCTs?), therapeutic equipoise (to what extent, and from whose perspective, must the existing data on treatment outcome be ambiguous or unknown to justify a clinical trial vs. direct treatment recommendations), structure and

burden of treatments (how do the expectations for each treatment under comparison in an RCT differ, how do the burdens of RCT participation differ from those during treatment as usual, and what impact do these differences have on enrollment and outcome?), and balancing risks versus benefits (how does a researcher deal with differing risks and potential benefits associated with very different treatment modalities and what are the ethical implications?). Because research with children is limited with regard to some of the ethical concerns under review in this article, we rely on the adult literature to inform discussion where relevant. Each subsection begins with a clinical scenario presented to illustrate the ethical concern and concludes with suggestions for researchers seeking to minimize the impact of these ethical concerns on research participants. We offer a set of research-related recommendations in conclusion.

THERAPEUTIC MISCONCEPTION

During the informed consent process, you have spent about 45 min describing a treatment study for posttraumatic stress disorder to Mr. Smith and his daughter, Jane. The purpose of the study is to compare a trauma-focused cognitive behavioral therapy (CBT) to a selective serotonin reuptake inhibitor (SSRI), and assignment to treatment is random. After discussing the study, Mr. Smith and Jane both say they have no questions, and sign the consent and assent forms. After signing, Mr. Smith says to you, “I know you will do what is best for my child, and as long as you’re making the treatment decisions, we’ll do whatever you say.”

The *term therapeutic misconception* was coined by Appelbaum, Roth, and Lidz (1982) to describe the confusion that often exists for participants in RCTs, who sometimes fail to perceive true differences between clinical care as usual and participation in treatment research. Participants may assume that researchers providing treatment as part of an RCT are acting in a manner analogous to a treatment provider in routine care: with the patient’s best interest in mind (Appelbaum, Lidz, & Grisso, 2004; Appelbaum et al., 1982; Dresser, 2002). In fact, the ultimate priority for researchers it is to oversee data collection that may provide generalizable knowledge regarding treatment efficacy or effectiveness, which differs from the priority of those providing primary clinical care (i.e., individual patient welfare). Participants are not always able to understand or articulate this difference, and Appelbaum (2002) proposed several factors that contribute to this therapeutic misconception, including incomplete discussions during informed consent of the differences between receiving clinical treatment as usual and participating in a clinical trial and, less frequently, deceit regarding such differences to increase rates of enrollment into RCTs.

This therapeutic misconception may be exaggerated in psychosocial versus pharmacological treatment trials among children. First, the experience of being evaluated for and providing assent to participate in a clinical trial is likely to mirror a child’s experience of receiving medical care as usual. RCTs conducted in medical settings provide contextual cues that may inadvertently blur the distinction between treatment and research (Dresser, 2002). Of importance, because trials comparing psychosocial and pharmacological interventions are often designed to evaluate treatments that have collective equipoise (i.e., each treatment has demonstrated efficacy, but relative efficacy is unknown), children and parents may incorrectly believe that this indicates that either treatment will be effective for that child on the individual level (Lidz, Appelbaum, Grisso, & Renaud, 2004). Finally, both children and parents are likely to have been socialized to respect the position of the physician or psychologist conducting the clinical trial and, based on previous experience, have an expectation that the researcher is functioning with the individual’s needs as top priority. Collectively, these factors may contribute to confusion regarding the therapeutic benefit of participation in a clinical trial to the individual child.

Clinical researchers can attempt to reduce this therapeutic misconception by ensuring their own clear understanding of the critical differences between treatment as usual and clinical research, including differential benefits and risks associated with each approach (Appelbaum, 2002). Researchers need to state frankly that participation in RCTs is not analogous to receiving treatment outside of the study and should consistently use language in accordance with this notion both with participants and with other professionals (e.g., “treatment study” rather than “treatment program”). Such a thorough understanding and specific language may positively influence the *dialogue* that takes place between the researcher, parents, and children during informed consent. A detailed discussion regarding treatment possibilities outside of the RCT may serve to help potential participants understand the distinction between usual clinical care and receiving treatment as part of an RCT, to limit therapeutic misconception. The burden is on the investigator to define explicitly their role as researcher rather than clinician to potential participants and to be clear regarding the limitations inherent in such a role. This may be particularly difficult for researchers whose functional role or professional identity is as a clinician, and it is related to the concept of therapeutic equipoise, which is discussed in greater detail next. A more radical solution to reduce this misconception may be to have an independent party, one who is not affiliated with the research protocol, obtain informed consent for participation, as has been suggested elsewhere (e.g., Dresser, 2002).

In the situation presented in the previous vignette, it would be appropriate to remind Mr. Smith and Jane that assignment to treatment is at random, meaning that the treatment Jane will receive is not chosen for her based on her individual symptoms or needs and is not chosen based on professional opinion, but rather is determined in a manner similar to “flipping a coin.” It would also be important to remind the family that the research is being conducted to determine the relative efficacy of the treatments, thus we do not know which treatment would be best for Jane. To reduce the possibility of any misconception, a quiz could be used following the review of information in informed consent with both the child and parent to assess their level of understanding of key variables such as randomization, the primary goals of RCTs, and differences between receipt of treatment through the RCT and treatment as usual.

TREATMENT PREFERENCE

Mr. and Mrs. Mendoza bring their 14-year-old son, Alex, in for an evaluation as part of a clinical trial comparing a behavioral intervention to a stimulant medication for the treatment of attention deficit/hyperactivity disorder, in which participants will be randomly allocated to treatment condition. The Mendozas provide written consent, and Alex provides assent to participate in this study. Subsequently, Alex is randomized to the behavioral intervention. Throughout the early phase of treatment, Alex struggles to comply with the demands of treatment, and during his fourth treatment session reports that he has a strong preference for medication.

Strong treatment preference may result in refusal to participate in clinical research or noncompliance with treatment protocols. Fear of eliciting treatment preference from potential study participants may actually result in researchers limiting the amount of information presented in the informed consent process. The problems associated with treatment preference are particularly salient for trials comparing psychotherapy to pharmacotherapy given that, with such substantial differences in the nature of the treatments, a preference for a psychotherapy or medication may exert a powerful impact on willingness to consider enrollment in a RCT, consent for randomization, rates of attrition, and treatment compliance (Elkin, Pilkonis, Docherty, & Sotsky, 1988). Parents who hold a strong preference for the treatment their child is assigned to in an RCT may prevent the child from participating despite the child’s desires. Alternatively, if a child or adolescent

holds a preference for treatment whereas the parent does not, the child may feel coerced into accepting the treatment to which he or she is randomly assigned.

The impact of individuals' treatment preferences has traditionally been controlled through the processes of randomization and blinding participants to their treatment condition (e.g., Kazdin, 1992). Blinding participants to their treatment is obviously a much easier process in medication trials than psychotherapy trials, but an even more complex, if not impossible, task in trials that compare psychotherapy to pharmacotherapy. Rather than conceptualizing treatment preference as a threat to internal validity to be controlled for within clinical trials, emerging research is beginning to examine patient preferences empirically across a range of treatment options for a variety of psychological disorders. In addition, a variety of hybrid randomized/nonrandomized treatment designs have been developed to allow researchers to examine the impact of preference on treatment outcome (e.g., Rucker, 1989). For example, participants in an RCT could be randomized first to a choice (i.e., nonrandomized) or no-choice (i.e., randomized) condition. Then, those in the nonchoice condition are randomized to treatment condition, whereas those in the choice condition are able to choose and receive their preferred treatment.

Across adult clinical samples, a growing number of studies suggest a general preference for psychotherapy over pharmacotherapy (e.g., Chilvers et al., 2001; Roy-Byrne, Berliner, Russo, Zatzick, & Pitman, 2003; Zoellner, Feeny, Cochran, & Pruitt, 2003). In contrast, there has been little research to date regarding children's preferences for treatment approaches for psychological disorders. In part, this may reflect the multifaceted issues surrounding children as a vulnerable population and the complexities associated with child assent in informed consent (see Miller, Drotar, & Kodish, 2004). Because children cannot consent to participate in research independently without parental permission, and because their decision-making capabilities may be underdeveloped, their choices and preferences for treatment may be viewed as secondary to their parents'. Nonetheless, inclusion of children in a thoughtful, comprehensive informed consent process is an important ethical principle, and children's preferences may influence their willingness to participate in RCTs and provide assent. Thus, future research should explore children's treatment preferences and their potential impact on treatment outcome. In the event that a child expresses a preference for a particular treatment whereas a parent is willing to provide permission for their child to participate in a RCT, researchers would be advised to offer further education regarding the treatments and alternatives, including the costs associated with receipt of no treatment, and ensure child assent before entering a child into the RCT.

It is notable that there is growing evidence within the adult depression literature that providing clinical trial participants with their preferred treatment may contribute to improved treatment outcome, compliance, and cost-effectiveness (Chilvers et al., 2001; Lin et al., 2005; Pyne et al., 2004). Therefore, it may be possible to influence treatment gains by matching participants with their desired treatment approach. In the case of psychosocial versus psychopharmacologic treatment trials, which are often designed to compare treatments that have established efficacy, what is a researcher to do if a participant expresses a clear preference for one treatment, particularly if there is reason to believe that treatment match may offer better therapeutic outcome? To what extent should researchers engaged in the informed consent process work to assess treatment preferences? Is there a threshold for "degree" of preference, such that someone with only a moderate preference but willingness to be randomized should be entered but another with a strong preference should be excluded? Participants may be willing to be randomized to treatment, only to drop out if they are not allocated to their preference, which is clearly problematic from a research design perspective but may also pose an ethical concern if time spent in the initial evaluation

and randomization process might have been avoided by an earlier assessment of treatment preference.

With regard to the situation described in the previous vignette, it would be important to remind Alex and his parents of the treatment options available to him outside of the study. Once in a treatment study, participants are not obligated to complete it and can withdraw their consent if they so chose. It is important that the researcher is willing to recognize and offer appropriate responses when strong treatment preferences emerge at any point in the research protocol. In our RCTs comparing psychotherapies and medication, we elicit treatment preferences at the initial phone screen level by explicitly asking whether a potential participant would be willing to consider either treatment modality and offering referrals to community-based agencies in cases where a strong preference for treatment is expressed and the potential participant is unwilling to consider the other treatment. We also remain open to having this discussion with participants at any point during their participation.

THERAPEUTIC EQUIPOISE

Ms. Allison has called for information after seeing an advertisement regarding your clinical trial. Over the telephone, you describe this randomized clinical trial comparing CBT to an SSRI for social anxiety disorder in children. Ms. Allison asks you about your professional credentials. You inform her that you are an associate professor of psychology and licensed clinical psychologist, at which point she asks, “So, if you’re a psychologist, you must believe the talk therapy is the best treatment, right? If this was your daughter, is that the treatment you would seek for her?” You believe that the talk therapy may be a superior treatment, and though there are data to support the efficacy of both treatments with stronger effect sizes for the talk therapy, no direct comparison studies have been conducted to date.

Therapeutic equipoise is an ethical standard which suggests that, for an RCT to be truly ethical, genuine doubt must exist with regard to the superiority of treatments under comparison (Freedman, 1987). This standard arises from the ethical principles of beneficence and nonmaleficence, two primary ethical principles requiring that medical professionals aspire to do good (i.e., what is in the best interest of a patient) and avoid harm (Beauchamp & Childress, 2001). Historically, two forms of equipoise have been conceptualized: one in which an individual clinician or researcher must have uncertainty regarding the optimal treatment (Fried, 1974), and the second in which the professional community of clinicians and/or researchers must be in disagreement or doubt with regard to treatment of choice (Freedman, 1987). If equipoise is not present, the ethical mandate is to make a direct, appropriate treatment recommendation.

The notion of therapeutic equipoise has been the source of considerable debate, with some scholars espousing strong support for the notion that researchers as medical professionals are obligated to provide the best available treatment (e.g., Lilford & Jackson, 1995), and others arguing that this notion conflates the otherwise important difference between professional as researcher and professional as clinician (e.g., Miller & Brody, 2003). This latter viewpoint holds that the ethical conduct of RCTs does not require equipoise and should be governed by other relevant, comprehensive guiding principles such as scientific validity and value, informed consent, and favorable risk–benefit ratio, and that the division between therapy and research actually serves to protect research participants from exploitation (Miller & Brody, 2003).

The concept of therapeutic equipoise is complex in the context of psychotherapy versus pharmacotherapy treatment trials. Such trials are often initiated to determine relative

efficacy after each treatment has demonstrated efficaciousness in previous trials (Elkin et al., 1988). One must wonder, with regard to therapeutic equipoise, whether head-to-head trials are always necessary to determine treatment superiority given that effect size data from efficacy studies may be able to provide some indication of how the treatments compare. If psychotherapy versus pharmacological treatment trials are comparing treatments that have demonstrated efficacy, and clinical equipoise requires that a trial be conducted only if no superior treatment is obvious, isn't it also reasonable for trial participants to have an expectation of therapeutic benefit? Researchers must also grapple with the question of who must "hold the equipoise." In other words, is it enough for an individual researcher to genuinely doubt the superiority of any one treatment over the other, or does the research community at large need to be in equipoise? Must this equipoise have roots in empirical data or is belief or theory enough? Certainly, one could assume that the differential training and experience of psychologists and psychiatrists may lead to dissimilar belief sets regarding therapeutic action and mechanisms of change that might influence the degree to which they favor one treatment approach compared to another.

In the case of Ms. Allison, should this situation arise we would use this as an opportunity to remind her that although we may have hypotheses about relative efficacy of treatments, we do not know which treatment is best, and that is why we are carrying out the study. Similarly, it would also be important to remind her assignment to treatment in a research study is not akin to making individualized treatment recommendations but rather evaluating her daughter's appropriateness for the study and assigning her to treatment without regard for her specific characteristics. It should also be made clear to her that even when treatments work on average, not all people who receive them benefit.

STRUCTURE AND BURDEN OF TREATMENTS

Ms. Walsh is a single mother of three children who works a full-time day job and part-time evening job. She has brought her son to your office for an evaluation after learning about your RCT comparing a cognitive-behavioral intervention to a mood stabilizer for bipolar disorder in children. Ms. Walsh reports that she is desperate for treatment for her son and is particularly concerned about her son's well-being because her own mother has been diagnosed with bipolar disorder. However, given the nature of her difficult work schedule, she has limited availability to bring her son for appointments. Ms. Walsh reports that she does not receive medical insurance through her employer and the family is not eligible for state-assisted insurance because her income is too high.

A well-designed efficacy trial comparing psychotherapy to pharmacological treatment will consider the standardization of the treatments under comparison in the trial with regard to variables such as length of treatment, number and frequency of sessions, and use of manuals to guide interventions (Elkin et al., 1988). To provide adequate time for delivery of each treatment while maintaining consistency between different treatment modalities, some interventions may have to be extended in session length or duration in clinical trials (Elkin et al., 1988). For example, in treatment-as-usual, a family seeking treatment for their child's ADHD may not see his or her psychiatrist every week for medication checks, yet if this child were enrolled in and receiving treatment as part of an RCT, it is quite likely that they would be asked to attend several sessions during consecutive weeks. This design issue can become an important ethical consideration when the demands placed on participants are perceived as excessive.

The previous case illustrates the importance of being explicit very early on with potential RCT participants with regard to the demands of participation in the trial and how such demands compare to treatment that may be received outside of the study. In the case of a

psychosocial versus pharmacological treatment trial, it is quite likely that, particularly for those in the medication condition, participation will require significantly greater involvement in time and effort than if they were to receive treatment from an outside provider. Such a burden should be clearly articulated and presented with the potential benefits (i.e., knowledge for greater community) that are associated as well. It would be a disservice, and potentially an ethical problem, to minimize the differences between treatments received through study participation compared to usual clinical care.

Informed consent also requires a discussion of treatment availability outside the realm of the RCT, which becomes a complicated ethical issue when these treatments under investigation are otherwise unavailable. Although this has been discussed widely in the cancer literature (e.g., Levi, Marsick, Drotar, & Kodish, 2000), few scholars have discussed this notion as it applies to the treatment of psychopathology. The movement toward dissemination of empirically supported psychotherapies is in its infancy, and it remains to be seen whether children are actually receiving treatments that have empirical support (Herschell, McNeil, & McNeil, 2004; Hoagwood, Burns, Kiser, Ringeisen, & Schoenwald, 2001). It is quite possible that there are communities in which the standard of care is not optimal and, despite best efforts to provide appropriate referrals, empirically supported interventions are simply unavailable. In these cases, children and parents may feel pressure to participate in RCTs because of lack of availability of treatments in the community. In a related way, researchers must be careful to avoid coercion in cases where families report having limited access to medical care, including lack of health insurance (Pace, Miller, & Danis, 2003).

In the previous case, it would be important for the researchers to be aware of treatment options available in the community in order to allow Ms. Walsh to consider possibilities before providing consent for her son's participation. Even for those with no insurance, treatment options typically exist. Free clinics, residency programs, community health centers, and clinics with sliding scale fees may be appropriate community referrals. In addition, researchers should be very clear at the outset with the expectations for time and other commitments required during study participations. This means that in the consent form and during the consent process, a researcher must be explicit about how much time, how many visits, and how long the study lasts. This should be clear for each intervention in the study. For example, a consent form may describe, "The CBT program that you may be randomized to in this study requires one in-person visit each week. Each visit will last approximately 1 hour. One parent is expected to accompany their child to each visit. These visits will occur for 12 weeks. This is a total of 12 hours of treatment over 3 months. ..."

The practical burden of treatment, and how it compares to the burden of treatment as usual, is an important consideration for decisions about whether to participate in research.

BALANCING RISK VERSUS BENEFITS

Mr. and Mrs. Johnson have given permission for their teenage son, Jason, to receive treatment for depression as part of your clinical trial comparing CBT to fluoxetine, and Jason has provided assent. They arrive at your office for Jason's first treatment session after he was randomized to receive medication. They have expressed concern over the recent media reports concerning the risks associated with antidepressant use in adolescents.

Balancing potential benefits with associated risks is a critical researcher responsibility and an important priority for Institutional Review Boards that maintain oversight of human participants protection. One critical component of the informed consent process is an overview of the risks and benefits associated with clinical trial participation. Unfortunately, despite efforts to provide informed consent, data suggest that parents and children have difficulty identifying stated risks associated with RCT participation after the consent process

and may inaccurately believe that risks are limited (Harth & Thong, 1995; Snowden, Elbourne, & Garcia, 2006).

This risk–benefit analysis extends beyond the study design and informed consent phases of research. In recent years, the Food and Drug Administration has issued several warnings with regard to the use of various psychopharmacological treatments in children and adolescents. Researchers should be aware that these warnings may necessitate additional contact with current, and potentially former, research participants to ensure they are aware of changes in risks associated with the treatment condition.

In psychosocial versus pharmacological treatment trials, though the potential benefits may be similar, the risks associated with each approach are inherently quite different. This can pose a complicated ethical concern when discussing these risks with potential participants. On one hand, it is of critical importance that researchers fully disclose any and all risks associated with the treatments. However, if risks in one treatment condition are perceived to outweigh the risks associated with the other condition, rates of refusal may be inflated which could bias study results. Obviously, the importance of disclosure outweighs the concern of enrollment from an ethical perspective; however, this issue is nonetheless an important one for researchers to consider.

If this situation presented in the previous vignette were to arise, it would be important to present the parents with factual data that includes up-to-date information regarding risks associated with the treatments under comparison in the study and to answer any questions the parents may have truthfully. If information regarding the risk of treatments were to change over the course of a study (e.g., the recent black box warning for antidepressants), contact (e.g., letter, phone call) should be made with all participants already enrolled, with an explanation of the change in risk and an invitation to discuss this information with study staff. The consent form would need to be modified to include the new risks, and anyone in the study and still receiving active treatment would need to be approached for a discussion of the change in risk and would need to be reconsented to continue in the trial.

RESEARCH-RELATED RECOMMENDATIONS

The primary purpose of our article is to highlight some of the ethical concerns present in clinical trials comparing psychosocial and pharmacological interventions for childhood psychopathology. Dilemmas such as treatment preference, ensuring equipoise and balance across treatments, and avoiding coercion are critical ones for researchers to struggle with at the design phase of RCT work but also throughout the implementation of RCTs.

These issues are not restricted to these types of comparison trials, nor are they mutually exclusive of one another, but rather they are interwoven in a complex way. Although our suggestions to researchers for limiting the impact of these ethical concerns are not novel, they should serve as a useful reminder of core ethical concerns, the significance of clearly understanding the dual role of professionals as researcher and clinician and being able to articulate and separate those roles as appropriate, and the importance of maintaining integrity in research.

We propose the following research-related recommendations that may help to resolve some of these ethical issues in psychotherapy versus psychopharmacological treatment trials among children and adolescents:

1. Research should continue to focus on children's and parents' understanding of information provided during informed consent, and methods for enhancing learning.

2. Research should examine children's preferences for treatment modalities across a range of psychopathology and any impact these preferences may have on treatment outcome and study enrollment and retention.
3. Research should examine decision making around the participation in treatment trials. How are parents making these decisions with their children? How do they weigh risk and benefit? How do children make decisions about providing assent?
4. Research should examine the *process* of consent, not just the content.

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