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REVIEW

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Beyond the question of placebo controls: ethical issues in psychopharmacological drug studies

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Abstract *Rationale:* There is a broad range of complex ethical issues in the conduct of psychopharmacological drug studies that go beyond the question of the ethics of placebo controls. However, our empirical knowledge with respect to these issues is very limited. This review, although not exhaustive, highlights an array of ethical issues that arose from discussions within the NIMH Human Subjects Research Council Workgroup. *Objectives:* To delineate issues in psychopharmacological drug studies that require debate and would benefit from research leading to the development of empirically-supported guidelines. *Methods:* Information included in this report was drawn from the first author's participation as chair of the NIMH Human Subjects Research Council Workgroup, guidelines for the ethical conduct of research proposed by professional organizations to which the first and third author belong, and relevant research literature. *Results:* We have focused on general issues relating to informed consent, research with special populations, and long-term treatment studies. Additionally, we raise issues relevant to large research-oriented institutions. *Conclusions:* The essential ethical challenge in psychopharmacological trials is to balance risks and benefits in the context of the needs and capacities of individual research subjects. The IRB system must become evidence-based and not rely on unproven assumptions. Specific research studies should be undertaken to address many of the issues of informed consent and research ethics postulated in this paper.

Keywords Research ethics · Informed consent · Guidelines · Psychopharmacology · Special populations

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Introduction

When Dr. Steven Hyman decided that it would be beneficial for a subset of NIMH grant applications to receive an additional, intensive look at questions relating to the use of human subjects in research that would not ordinarily be provided in the context of Initial Review Group or National Advisory Council peer review, he formed the NIMH Human Subjects Research Council Workgroup. The purview of this group was originally to be limited to studies involving symptom challenge or drug discontinuation. Over the course of the two years that the first author chaired this group, however, a broad range of complex ethical issues in the conduct of psychopharmacological drug studies came to the Workgroup's attention. Many of these issues had been addressed in statements of various professional organizations including the American College of Neuropsychopharmacology (2001), but many had not. Indeed, the group found itself on a novel and interesting journey in their ongoing effort to find the point at which meaningful science and ethical treatment of human subjects are balanced.

In the process, the Workgroup had numerous, interesting discussions leading to a conceptual framework that involved both general ethical issues in psychopharmacologic drug research and special issues that are of import for specific clinical populations. The general issues might be further subdivided into issues that have to do with informed consent and issues that have to do with the ethical conduct of trials.

The one issue the workgroup did not take up, and which will not be taken up in this report, but rather in another report in this issue of Psychopharmacology, is the question of placebo control. What we found, however, is that there are many important ethical issues in psychopharmacologic drug studies that go beyond the question of the ethics of placebo controls. In preparing this report, the authors have found, however, that our empirical knowledge with respect to these issues is very limited indeed (Foucar 2001) and provides few guidelines for the ethicist or clinical researcher. In this report, we

delineate a series of ethical issues in psychopharmacological drug studies that do not involve the question of placebo controls and define a research agenda in this area.

General issues relating to informed consent

For consent to be informed and non-coercive, and to maintain the ethical integrity of research, the exchange of goods or services between researchers and subjects must be cooperative. The national guidelines (e.g. Food and Drug Administration, Office for Human Research Protection, National Institutes of Health) governing informed consent and research practice allow considerable leeway for local Institutional Review Boards (IRBs) to determine their own policies. However, the arena of liability and lawsuits in which research institutes have recently found themselves (Grahnke 1999; Kaplan and Brownlee 1999), coupled with the Department of Human Services' call for the ultimate responsibility for protecting human subjects to be borne by the institutions that perform the research (Shalala 2000), have led local IRBs not only to adopt the national guidelines as steadfast rules, but also to expand upon them considerably.

Over and above IRB's uniform rules about informed consent, there are many outstanding issues, including coercion, explaining randomization and alternative treatments to subjects, the role of physicians as investigators, and informed consent for special populations that have not been joined to any great extent at the institutional level.

Coercion

IRBs and national guidelines prohibit creating a coercive climate for potential research subjects. Most often, excessive incentives for participation are conceptualized as monetary contributions that are not commensurate with subjects' contributions (Roberts et al. 2001a). Yet, can a coercive climate be created when a treatment is offered to a subject that he or she would have found difficult to obtain either for financial reasons or because of limited availability? Will subjects make judgments that are in their own best interest when one aspect of a study involves receiving treatment that they desperately want, but also requires that they accept the possibility of receiving a treatment they do not want or do not believe is in their best interest? Certainly, the importance of this issue increases exponentially as the risks associated with study participation increase.

Additionally, we should not only be attentive to how subjects' decisional capacity is affected by incentives, but also by their psychiatric disorder (NIMH 2002; D'Souza and Krystal 2001). The limited research in this area is conflicting. Some researchers have found that the pathophysiology of some disorders, specifically schizophrenia (Appelbaum and Grisso 1995; National Bioethics Advisory Commission 2001), hampers the cognitive and information-driven dimensions of decisional capacity (Roberts et al. 2000, 2001a). However, other studies show that decision-making is not as easily affected by psychiatric symptoms as once thought (Applebaum et al. 1999; Carpenter et al. 2000; Roberts et al. 2003). The waxing and waning course of many psychiatric illnesses may cause decisional capacity to fluctuate with the illness, allowing full comprehension of consent forms and the associated risks and benefits of research participation only at specific points during an illness (Roberts et al. 2001a). As a solution to this problem, current guidelines suggest proxy informed consent of acutely ill individuals. Yet, when such proxies are used, should researchers reconsent subjects when they are less symptomatic?

Explaining randomization to research subjects

Often, investigators have a strong belief that one treatment in a randomized controlled trial (RCT) is somehow superior to another (Avins 1998). However, a fundamental scientific assumption of the RCT is that, prior to the completion of the trial, the treatments are presumed to be equal by the broader scientific community. Thus, it is essential that the investigator present random assignment in that light. However, exactly how this fine distinction can be explained in terms a layperson can understand is not always obvious. Many IRBs prefer an explanation that relates random assignment to "the toss of a coin," but is this really the best way to explain this procedure to potential subjects? Does the terminology or the analogy need to change depending on the level of sophistication of the subject? How do we explain to subjects who will be randomly assigned that they are not consenting to receive a given treatment, but rather to receive a probability of receiving a given treatment (Avins 1998)?

Discussion of alternative treatments with potential research subjects

Virtually all IRBs now require that a researcher consenting a subject to a treatment study discuss alternatives to the treatments offered within the research protocol. Usually, such information is handled in a rather perfunctory manner. We are unaware of any guidelines that suggest how extensive this discussion should be for fully informed consent. Should it include names and/or descriptions, associated costs and/or availability, and risks and/or benefits of other treatments? While these are entirely researchable questions, we were unable to locate any studies directly or even indirectly addressing them. Clearly, the extent and content of the information provided, especially in high-risk RCTs, may determine how truly informed the consenting individual's decision about research participation actually is.

The role of treating physicians as researchers

One of the thorniest issues in the area of ethics in psychopharmacological drug studies is the question of whether, when the treating clinician is also a research clinician, he or she should be allowed to recruit patients of his or her own for research study (Schaefer 1982; Spiro 1986; Kantor 1994; Daugherty et al. 1995). Indeed, Katz (1997) argues that the most difficult task for physician-investigators is recognizing that their agendas may not be the same as or in the best interest of their subject-patients. Nowhere was this issue more pointed or poignantly portrayed than in the stage play and movie, "Wit," involving a not-truly-oriented-to-the-real-world English professor suffering from metastatic cancer and a group of overzealous, if sometimes well-meaning group of research clinicians. On the one hand, the treating clinician may have the best appreciation of the subject's particular treatment needs and suitability for a given research protocol. On the other hand, this same clinician may not be in a position to be objective about the risks and benefits of the study for the patient. We do not really know whether patients can see their doctors as research investigators when necessary (Katz 1997). Again, however, this is a researchable question.

The simplest solution to this dilemma, and one taken by many IRBs, is that the treating clinician should never be in a position to recruit a patient for his or her own research study. We can, however, imagine circumstances in which it would almost be unethical not to do this. Consider, for example, the case in which the clinician has actually been motivated to study a new compound or psychotherapy by virtue of the fact that many of his or her patients are highly intolerant of or unresponsive to all existing treatments for the condition in question. To exclude the very patients who motivated the work in the first place and who perhaps most need to be involved in the testing of the new compound could, in quite another way, be considered unethical. Is the best approach, for the researcher to ask another clinician to recruit his or her patients for the study? This solution has been taken in some cases.

Finally, there is the question of a treating clinician's role in supporting or dissuading a patient from participation in a study that involves monetary compensation. If the treating clinician is familiar with the patient's economic circumstances, he or she may be swayed by an economically imposed differential in the risk to benefit ratio for that particular patient.

When multiple protocols are ongoing for the same disorder at the same location

In large research-oriented institutions, it is not unusual for there to be multiple ongoing protocols examining various treatments of the same condition. What is the best way to inform potential research subjects about these alternatives? One option is to inform potential research subjects of all research studies currently being conducted at the site. If this is done, should the potential subject be left to decide among the alternatives on his or her own or should the subject be provided with an opinion as to which study would be best for him or her? If the latter, who is to provide that opinion? In many institutions today, potential subjects must give consent to a specific study before an evaluation can even take place. It is not clear how the subject is best informed of alternative protocol options under such requirements. Another approach is for the institution to develop an allotment scheme based on the needs and timelines of the various ongoing studies. In that case, how much information should the potential subject be given about alternative treatment trials and alternative treatments available outside of treatment trials? This raises the question of whether there is such a thing as providing too much information to the subjects. Many of us who study depressive illness, for example, and are governed by IRBs that require consent forms that now go to nine or ten single-spaced pages in length fail to understand how the average depressed subject can possibly concentrate long enough to understand all of the information provided in an informed consent document (Annas 2001; Wendler 2000). This would only be compounded if subjects were expected to choose among several different studies as presented in these lengthy consent documents. How do we find the balance between adequately informing potential research subjects and providing so much detail that the most relevant information for their decision-making is lost in documents intended primarily to protect institutions and investigators?

Consenting subjects to long-term maintenance studies

By far the majority of psychopharmacological drug studies and psychotherapy trials conducted both in the United States and abroad have been short-term studies. The longer-term continuation and maintenance treatment studies that have been carried out to date represent a small fraction of all completed psychopharmacologic studies. Thus, relatively little attention has been given to whether there should be a special type of consent process for longer-term studies. In many of these phased studies, random assignment does not actually take place until the end of the acute treatment phase. Some investigators and ethicists are now of the opinion that the potential subject should be asked to give consent to the entire study at the outset, but then re-consented at the point of randomization to the (experimental) continuation or maintenance portion of the trial. Indeed, in particularly long maintenance trials (e.g. 2–3 years in length), consideration could be given to re-consenting the subject again at the end of each year of the maintenance phase.

Presentation of relapse risk in long-term treatment study consents

In short-term treatment studies, the primary risk is that the subject will not get better; however, in long-term maintenance studies there is, in a sense, a double risk involved. While the subject must consider whether or not the acute phase of the trial offers an acceptable probability of getting better, he or she must also consider whether the continuation and/or maintenance phase offers an unacceptable risk of relapse. There are few generally agreed-upon guidelines for how to explain the risk of relapse in an informed consent document. Now that some long-term studies have been done in several of the major psychiatric disorders (e.g. schizophrenia, recurrent depression, bipolar disorder, panic disorder), researchers often have a reasonable idea at the outset of the trial that the risk of relapse may not be equal in all conditions. Just as investigators typically expect in an acute study that response or remission is more likely in an active treatment than in a placebo or treatment-as-usual control condition, the same is generally true for maintenance studies. To what extent are researchers bound to explain the differential probabilities of relapse under the different conditions of the study based on data, for example, from another age group or diagnostic subtype? How specific can or should such explanations be?

Another issue raised with respect to relapse risk in psychopharmacological drug studies is whether, if a research subject experiences a relapse, the investigator is obligated to provide open treatment to the subject and, if so, for how long? Furthermore, there are no guidelines as to whether that obligation is greater if the relapse has been associated (i.e. the subject has been assigned) to a condition that involves a change in the treatment that brought about the remission.

Treatment studies involving biological assessments

Today many treatment trials are conducted in which the investigators are attempting to examine biological moderators or mediators of treatment response. These investigations raise the question of whether subjects should be consented separately for the treatment trial and the biological assessments (US Congress 1994). Given a trial in which the whole purpose is to uncover significant moderators or mediators of response to diverse treatments, and there is no question of the efficacy of the treatments, should the subjects have the right to refuse the biological assessments, but still have the right to participate in the treatment trial? In such studies, researchers appear to be under an obligation to state explicitly which procedures and assessments are for research purposes and which are simply for clinical monitoring and optimization of the subject's care.

Particularly in studies that involve burdensome biological assessments, the question of subject compensation frequently comes up. Specifically, in the United States where medication and adequate treatment are difficult for many individuals to access, is free treatment adequate compensation or should subjects be compensated monetarily for participation in those procedures that are simply for the purpose of research?

Pharmacogenetic studies, aimed at understanding the molecular genetics of drug response, raise other issues. Under law, individuals have the right to withdraw their DNA sample at any time during or after the conclusion of research participation (National Research Council 1997). If the provision of free treatment is the compensation for completing biological assessments, what should be done if subjects withdraw their samples prior to the completion of treatment?

Psychopharmacological studies of special populations

National guidelines require that IRBs specifically delineate the protection of particularly vulnerable research subjects including children and adolescents, pregnant women, and elderly men and women. For researchers, the study of these populations presents some of the most difficult ethical challenges. Although these are areas where empirical data specific to the group is sorely needed, the costs to the health of some of the individual study participants of obtaining such data may be substantial. Additionally, the dilemmas of informed consent discussed in the beginning of this paper are exacerbated in vulnerable populations.

Children and adolescents

We clearly need more information about the effects of psychopharmacological drugs in children and adolescents; however, the relatively small numbers of children who present with disorders other than those exclusive to childhood has meant that we have very little empirical data on the effects of medications for many of the "adult" disorders that present in childhood. On the other hand, we know, for example, that with respect to mood disorders, it is the very individuals with the earliest onset who have the highest risk of recurrence (Weissman et al. 2001). This means that it would be extremely important to know something about the long-term effects of mood disorder medications on children. The ethical issues surrounding the study of long-term treatment strategies in children and adolescents are numerous (Gaylin 1982; Munir and Earls 1992). We know essentially nothing about the effects of psychopharmacologic compounds over the course of development and, particularly, in the transition from pre-puberty to puberty. While these drugs are perfectly safe during childhood and once an individual has completed the pubertal transition, they may have unanticipated negative effects over the course of the pubertal transition; perhaps, analogous to in utero drug exposure, in which teratogenic effects of SSRIs increase during

specific fetal development periods (Wisner and Perel 1988; Altshuler et al. 1998). This raises the question of whether animal, and particularly primate development studies, should be required before long-term maintenance studies are done in children crossing the pubertal transition.

Our lack of systematic knowledge constitutes a clear rationale against conducting long-term drug trials in children and adolescents. However, the seriousness of their illness, and the developmental loss they experience with prolonged episodes or multiple recurrences, means that clinicians feel pressured to prescribe long-term medication without empirical data supporting a low-risk safety profile. Thus, the countervailing rationale is that we must have information about the safety and efficacy of practices that are already occurring. The need to avert risks associated with drug trials must be weighed against the risks of continuing to neglect this important area of research.

Studies of children and adolescents also raise the contentious topic of consent versus assent, especially in the case of relatively mature adolescents. Guidelines suggest that when children or minors are involved in research, minimally, the assent of the child or minor and the permission of at least one guardian be obtained, although some IRBs waive the requirement of assent. Should a child participate in a study to which the parent has consented and the child assented, but the child's assent appears to have been forced upon him or her by the parents? Although we were unable to find data specific to participation in research trials, Paul et al. (2000) have reported that one in five children receives treatment against his or her wishes.

Furthermore, we do not know at what age children and minors can decide what is best for them. Children's desire to ingratiate and please adults may stand in the way of truly informed assent. In a small pilot study, researchers found that although all 18 children acknowledged their ability and right to withdraw from a study once it was started, the majority felt that the investigator would be mad or unhappy with them if they did this (Ondrusek et al. 1998). Adolescents may be more susceptible to outside and social pressures, including fear of being stigmatized. Thus, even if they are able to assent/consent, can they make an informed and objective decision?

Finally, studies of children and adolescents raise difficult issues with respect to the confidentiality of information about research subjects who are minors. While the law is clear about the researcher's obligation with respect to sexual or physical abuse of the child or potential for physical self-harm or the harm of others, it is not at all clear what a researcher's obligation is with respect to informing parents of at-risk behavior such as hypersexuality in hypomanic or manic adolescents. This is exacerbated by the variability in state laws governing minors' access to contraceptives and abortion services without the consent of a parent or guardian.

Women of childbearing potential

In 1993, the Food and Drug Administration withdrew the 1977 regulation that forbade the inclusion of women of childbearing potential or pregnant women in early clinical pharmacology studies. Briefly, their decision was based on the lack of studies conducted on the effects of such female physiology as the menstrual cycle, menopause, and pregnancy on drug action and pharmacokinetics (FDA 1993; Office of Human Research Protection 2002). Furthermore, they feared that the 1977 regulation had led to a more general lack of participation of women in drug studies, thus leaving us with little information about the effects of drugs in women. The 1993 guideline suggests that all drug development studies include subjects of both genders, "analyses of clinical data by gender, assessment of potential pharmacokinetic differences between genders, and where appropriate, assessment of pharmacodynamic differences and the conduct of specific additional studies in women" (FDA 1993). The FDA concluded that assessment of the risk of research participation is most properly left to the woman and her physician, local IRBs, and sponsors. The guidelines require that women receive adequate counseling about the short-term and long-term reproduction risks associated with research participation and the importance of precautions against becoming pregnant when appropriate. The guideline suggests that all subjects (male and female) be informed of the potential risk and the need for precautions. However, the FDA's policy does not require the adoption of these policies. Thus, IRBs may impose restrictions—and many do—on the research participation of women, even if it is simply to decrease liability.

Pregnant women

The position of many IRBs is that pregnant women should never be included in a psychopharmacological drug study (Grush and Cohen 1998), even though national guidelines state that the needs of a pregnant woman generally take precedence over those of a developing fetus. Restrictions imposed by many IRBs on the participation of pregnant women in drug studies, including requiring consent of the father when the research holds out the prospect of direct benefit solely to the fetus, continues to contribute, despite the FDA's efforts, to an atmosphere of neglect of the mental health needs of pregnant women and a clear lack of systematic knowledge about the safe and effective treatment of psychiatric illness in this population (Llewellyn et al. 1997; Viguera et al. 2000; Altshuler et al. 2001; Heath and Yonkers 2001).

Pregnant women pose a distinct ethical challenge as research subjects since we are ethically bound to minimize subjects' risks in drug trials (Quitkin 1999). Participating in research may confer benefits (Roberts et al. 2001b) even for this population, and thus blanket exclusion appears unethical. For example, when we consider the emerging literature on the negative effects

of maternal depression on a developing fetus (Fowles 1998; Weissman and Jensen 2000; Wisner et al. 2000), we must ask the question of whether women who become pregnant should be allowed to continue in a protocol or enter a protocol if a full discussion of the risks and benefits leads to the conclusion on her part (and on the part of her obstetrician/gynecologist) that continued participation would be beneficial (APA 1993; Wisner et al. 2000). Obviously, this is not an issue for studies of new compounds about which no knowledge exists with respect to teratogenesis in humans, but many research trials are being conducted on compounds for which there is an abundance of data on (the lack of) teratogenic effects (Masand and Gupta 1999; Misri et al. 2000). Again, we see the automatic exclusion of pregnant subjects as possibly more related to protecting the institution and investigator (from liability) than the subject or her unborn fetus (from possible harm). While a more nuanced and thoughtful approach to this problem greatly increases the burden on IRBs and investigators, the effort may well be worth the new knowledge to be gained.

Another set of issues arises when a woman becomes pregnant during a trial. What is the researcher's obligation in terms of explaining the teratogenicity of the compound under study? Should this be detailed ahead of time in the consent form? If not, what is the appropriate time to inform subjects on the teratogenic effects of compounds? All of these questions, other than the potentially teratogenic effects of having a depressed mother, also apply to males, with some IRBs insisting on statements regarding double-barrier contraception for both males and females. What does this say about the institution's duty to inform partners of male study subjects? Can institutions require that a partner be informed without violating the subject's rights of confidentiality and personal choice to disclose their study participation to others?

Elderly

While there may be few special ethical issues in research with those now termed the "young old," some of the "old old" may lack the capacity to fully comprehend what is being asked of them in a modern research protocol simply because the contexts of medical practice and of research have changed so dramatically in the last quarter of the twentieth century. Of course, the seriously demented elderly fall fully into the category of those who have impaired capacity to consent. In the case of the non-demented "old old" research participant, it may be desirable to have a family member or other legally authorized representative aid in research participation decisions. In the latter case, such an individual is an essential part of the consent process. Whenever such a person is involved in the original recruitment and consent of the patient, that individual should be kept informed about the patient's progress through the study and must be informed in the case of any major changes in the research protocol or the investigator's view of the risk/benefit ratio.

In cases of clear diminished capacity among elderly research participants, investigators should obtain the participant's assent whenever possible. As with children, the investigator assumes additional ethical responsibilities for such patients. More problematic are the moderately "confused" elderly potential participants who fall into a gray zone somewhere between frankly demented and clearly competent. Such confusion may result from the strangeness of the surroundings in which research recruitment takes place, from the sheer amount of information potential research participants are now expected to take in the process of providing informed consent, or from hypersensitivity to drugs that may already have been given as part of their medical care for their psychiatric or another medical condition. At this point, we have no research to guide us as to what constitutes full capacity in this population, but this is clearly a researchable question.

A final special concern with respect to the participation of the elderly in clinical trials is the extent to which the risk/benefit ratio must be adjusted when the individual participant or expected group of participants is suffering from multiple complicating medical conditions and is taking multiple, possibly interacting, medications to treat those conditions. Investigators are obliged to consider such issues in evaluating the risks to the patient(s) who they recruit.

Conduct of study issues

A number of ethical issues relate to safeguards within studies that relate to the safety of human subjects. Two examples of such safeguards are rescue strategies for patients who either are not improving or are deteriorating and study stopping rules.

Rescue strategies within protocols

Some of the greatest need for knowledge in psychopharmacological drug research comes in the area of disorders that have the capacity to deteriorate rapidly and in which that deterioration presents serious risks for physical or social self-harm, particularly manic-depressive illness and schizophrenia. In order to improve treatments for these conditions, we must find compounds or treatment strategies that are clearly superior to those that we have now. However, proving superiority often requires that we allow subjects to worsen sufficiently that a definitive outcome is obtained. This raises the question of how long worsening should be permitted to continue without intervention, what kind of monitoring should be in place under the general conditions of the study and, most important, what kind of monitoring should be in place under conditions suggesting the beginning deterioration (Schaefer 1982)? Such studies undoubtedly require well-defined, ongoing

monitoring and carefully thought out and well articulated rescue protocols. On the one hand, one could argue that it is unethical for researchers to withhold intervention until a full-blown relapse occurs rather than at the first signs of a relapse. On the other hand, particularly in the case of manic-depressive illness where waxing and waning of symptomatology is the rule rather than the exception, one could argue that failing to withhold additional treatment until a full syndromal relapse is observed could invalidate the outcome of the trial. In the end, this would mean that subjects were asked to participate in a trial from which nothing can be learned.

In addition to monitoring for the emergence of general symptomatology, a discussion of rescue strategies also raises the question of the specific monitoring for suicide. How is this best accomplished? To what extent should significant others be involved in the monitoring process? Are there studies in which a subject should not be entered unless there is a collateral who can report on the subject's condition? All of these are questions that are difficult to address through experimental research; however, retrospective review of methods in studies in which various levels of suicidality were observed might yield important information.

Although often considered in relation to the ethical dilemmas of placebo use, pathophysiological consequences of untreated symptoms should be considered in all kinds of trials. For instance, some researchers argue that there is a relationship between the number of past manic episodes and increased risk of relapse and a poorer prognosis (Angst and Sellero 2000). By allowing subjects to become symptomatic again, is the investigation placing them at increased subsequent risk? On the other hand, drug-free periods or symptomatic-periods have yet to be proven detrimental and, in fact, may be psychologically and physically beneficial (Roberts et al. 2001b). For instance, few individuals are immediately accepting of the need for maintenance medications in the absence of symptoms without a drug-free trial period. If, via experimental research, we allow such periods to occur within the context of a study, the subject should have the advantage of adequate clinical monitoring, and rapid intervention once the study endpoint is achieved. Quitkin (1999) argues that symptomatic periods are acceptable when long-term harm from these symptomatic periods is unsubstantiated and the disorder in question is characterized by a fluctuating course.

Stopping rules

Research methodologists have long argued that all randomized controlled trials should have a stopping rule such that when it becomes clear one arm is significantly superior to or more dangerous than another arm, the study should be stopped even though the originally projected number of subjects has not been recruited. Such questions need to be addressed statistically so that the stopping rule is based on power and effect size considerations. Stopping rules have been used extensively in other areas of medicine where the outcome of interest is death or metastasis; however, to our knowledge, stopping rules have rarely been established or invoked in psychopharmacological drug studies. Given the new emphasis on Data Safety and Monitoring Boards (DSMBs), it would seem that it is incumbent on the investigator and DSMB to agree upon a stopping rule for each trial. Another question is whether, given the presence of DSMBs, there should also be stopping rules for trials that appear, after a reasonable period of time, to have only the slightest probability of being able to show a difference between the treatments even if the projected number of subjects is recruited.

Research agenda

In 1982, Meisel urged researchers and IRB boards to seek empirical support with respect to elements of informed consent and research ethics. Yet, 20 years later, although there has been an explosion of debate, research in this area has not increased substantially. The essential ethical challenge in psychopharmacological trials is to balance risks and benefits in the context of the needs and capacities of individual research subjects (Roberts et al. 2001a). We must place emphasis on the substance of the consent form rather than the language and document; informed consent needs to be a process, not a form (National Bioethics Advisory Commission 2001). The consent form and process must be in the best interest of educating and informing the research subject, and not serve as a legal document to protect the institution. Research review and monitoring should reflect the risk and complexity of the research, and emphasize the protection of ethical standards and subjects (National Bioethics Advisory Commission 2001). Often, however, it seems that IRBs are moving inexorably away from this stance. The IRB system must become evidence-based and not rely on unproven assumptions (Foucar 2002). If that is to happen, the pace of research in this area must increase dramatically. Research studies should be undertaken that address many of the questions postulated in this paper, as well as others not discussed here. Informed consent and research ethics must be guided by fruitful debate and consensus, empirical research, and standards of good clinical practice (Shalala 2000).

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