Ethics of Placebo Use in Pediatric Clinical Trials
The Case of Antihypertensive Drug Studies
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Abstract—Industry-sponsored pediatric clinical trials of antihypertensive medications have greatly increased in number since passage of the Food and Drug Modernization Act of 1997. This development should ultimately benefit the treatment of hypertensive children by increasing the amount of scientific knowledge regarding the efficacy and safety of antihypertensive agents in children. However, the designs of many of these trials raise ethical questions related to the inclusion of placebo controls, a practice that has largely been abandoned in trials of antihypertensives in adults because of the well-known adverse consequences of untreated hypertension. This is an especially important issue in pediatric hypertension, as many hypertensive children have either secondary forms of hypertension or hypertension-induced target organ damage, potentially increasing the risk of harm during exposure to placebo. Against this background, and with a strong emphasis on protection of this vulnerable patient population, a strict set of conditions for use of placebos in pediatric antihypertensive trials is proposed. (Hypertension. 2003;42:	329–333.)

Key Words: ethics ■ hypertension, secondary ■ antihypertensive agents ■ clinical trials ■ placebo

Since the passage of the Food and Drug Modernization Act (FDAMA) of 1997,1 written requests for pediatric studies of more than 200 compounds have been issued by that agency, and more than 100 industry-sponsored pediatric clinical trials have been completed.2,3 This increase in industry-sponsored pediatric trials has led to a renewed interest in the ethical implications of such research. Issues that have received recent attention in the literature include the following:

• the possibility of increased risk to both healthy research subjects and subjects with disease;
• the need to obtain “informed assent” from older children and adolescents;
• the possibility that research risks will be unequally distributed across the pediatric population (and the related issue that only a small number of children will have the opportunity to participate in research); and
• how to recruit and compensate pediatric subjects without coercion.4–6

An additional ethical issue that has not received much attention in the literature is placebo use in pediatric clinical trials. Although guidelines issued by the American Academy of Pediatrics several years ago endorsed the use of placebo in limited circumstances in pediatric clinical trials,7 these guidelines were issued before the recent increase in pediatric clinical trials, which has greatly increased the numbers of children with chronic illnesses involved in such research. Indeed, the ethics of placebo use in pediatric trials, especially those involving subjects with potentially significant illness, have recently been questioned.8

Of all of the medications that the FDA has requested be studied in children as a result of the FDAMA, one of the largest categories is cardiovascular medications, particularly antihypertensives.2 As of March 2003, at least 20 written requests have been issued by the FDA for studies of antihypertensive compounds in children, and manufacturers have responded to these requests with at least 15 pediatric clinical trials. Many of these industry-sponsored studies of antihypertensive agents have incorporated placebo controls to establish efficacy. These studies are being conducted at the same time that some investigators have called for the end of placebo use in adult hypertension research because of the well-known cardiovascular consequences of untreated hypertension in adults.9 However, placebo use in pediatric antihypertensive trials has not been addressed, despite the issuance of guidelines for optimal conduct of such trials.10 In this article, the ethical issues raised by the use of placebos in pediatric hypertension research will be examined, with the goal of proposing a set of ethical guidelines to be followed in the design of future pediatric antihypertensive trials.

Ethics of Clinical Research in Children
It is unfortunate but true that children have not benefited from advances in drug development to the same extent as adults.11,12 Until recently, with the exception of certain

Hypertension is available at http://www.hypertensionaha.org

Received June 16, 2003; first decision July 8, 2003; revision accepted September 4, 2003.
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DOI: 10.1161/01.HYP.0000095616.91352.2E
classes of drugs such as antibiotics or antiasthmatics, few new drugs were studied in children because of the pharmaceutical industry’s reluctance to conduct clinical trials in children. As a consequence, few drugs have FDA-approved indications for use in children. In the case of antihypertensives, as recently as 2000, the Physicians Drug Reference (PDR) contained pediatric indications and/or manufacturer’s dosing recommendations in the prescribing information for fewer than one third of the most commonly prescribed agents. As a result, pediatricians are left with the option of prescribing medications for their patients that have been studied only in adults, an example of so-called “off-label” prescribing. Although such off-label use is common in pediatrics, in effect it means that each prescription written is literally an experiment with potential untoward consequences.

The importance of pediatric labeling cannot be underestimated. Children may absorb and metabolize medications differently than adults, making pharmacokinetic parameters derived from adult studies useless for predicting clinical efficacy in children. Adverse reactions may occur with significantly greater or significantly lower frequency in children than in adults, or unique adverse reactions may occur in children, making it difficult at best to predict the tolerability of a specific drug in children. Granting of pediatric labeling by the FDA means that the results of well-designed studies have been submitted to the agency and have received its approval. Medications with pediatric labeling can be judged safe to use in children and can be confidently prescribed.

Thus, a clear need exists for children to participate in clinical trials, especially when the agent being studied has a potential health benefit in children. However, although the need for increased participation of children in drug trials is clearly recognized, children are considered to be a vulnerable population in need of special protection from the potential harms of such research.

In adults, protection from research risks has traditionally been accomplished through review of proposed research by a qualified ethics committee/Institutional Review Board (IRB) and through the informed consent process. Children, however, are considered to be a vulnerable population and therefore require additional protection from the risks of participation in research. These additional protections have generally been incorporated into the IRB review of research proposals for several reasons, among them concerns that parents and guardians may not have the child’s best interests at heart when providing informed consent. In the United States, these protections were originally developed by the Federal government as regulations delineating the types of research involving children that could be approved to receive Federal funding. These are listed in the Table. Subsequently, these regulations have been adopted by IRBs to guide the review of all research protocols involving children. Similar rules have been adopted in other countries. They help to ensure that necessary clinical research involving children can be conducted in a manner that protects them from unwarranted risk.

Ethics of Placebo Use in Clinical Research

Placebo-controlled trials are typically held to be the “gold standard” for assessing efficacy of a new drug or even of a surgical procedure. This belief is not only held by many researchers but also is embedded in some aspects of FDA regulations governing new drug approvals. The FDA’s insistence on incorporation of placebo controls flies in the face of recent revisions to the Declaration of Helsinki mandating that placebo controls be abandoned in randomized clinical trials when an effective therapy exists. Arguments used to support this belief range from those that are purely utilitarian (use of placebo allows the trial to be conducted with a smaller number of subjects than an equivalency study, making the study easier and less expensive to conduct) to those that are scientifically indisputable (use of placebo may be necessary if the disease being studied has a high rate of placebo response).

However, these arguments in favor of the continued use of placebo controls have been strongly criticized. Among the most important criticisms of the continued use of placebos is that placebo use may subject the study participant to increased risk from not receiving active therapy. Use of placebo is especially suspect if an accepted treatment exists for a given condition and the potential subject is to be withdrawn from or denied active treatment in order to be enrolled in the study. Two recent asthma treatment studies, one conducted in adults and the other conducted in children, have come under criticism on these grounds. In both studies, a significant number of subjects who were randomly assigned to placebo had worsening of their symptoms, which necessitated withdrawal from the study. Although the case could be made that the subjects were protected by the option to withdraw, the stronger argument is that the subjects were subjected to an unnecessary risk of harm, therefore making the study designs unethical.

On the other hand, if there were no effective treatments for the condition under study, then placebo use would certainly be ethical, at least for the initial studies of the proposed new treatment. Once a new treatment is shown to have some benefit, however, further use of placebo in subsequent trials would not be acceptable. Placebo use could also be ethical if placebos were used as an “add-on” to current treatment or if currently available treatments were themselves risky to the
subject. Additionally, the case could be made that placebo use could be ethical if the potential subjects were untreated before entry into the study. However, this argument is difficult to accept, especially when it is known that the subject would clearly benefit from receiving standard therapy and could be harmed by omitting it. As discussed below, this last scenario is especially pertinent to clinical hypertension research.

Hypertension and the Risks of Nontreatment

Hypertension is a common condition in adults, with well-known adverse consequences, most notably increased morbidity and mortality rates from cardiovascular disease. Even patients with mild blood pressure elevation have been shown to have a significantly increased risk of adverse cardiovascular events. Treatment with antihypertensive agents clearly reduces these risks. Therefore, use of placebos in clinical hypertension research has come under criticism.

However, such criticisms are valid only if it is true that participation in a placebo-controlled trial will actually harm the subject. Many industry-sponsored trials designed to examine the efficacy of antihypertensive agents actually include only very short periods (generally less than 8 to 12 weeks) of placebo “treatment.” This raises the possibility that placebo use may be justifiable because the period of time that the subject will be receiving placebo is too short to substantially increase the risk of adverse cardiovascular events. Furthermore, a recent meta-analysis of short-term hypertension trials demonstrated that short-term exposure to placebo actually did not appear to result in increased risk to subjects. This finding was true for studies of short duration with the following characteristics:

- subjects had mild-to-moderate hypertension;
- complicating conditions such as history of myocardial infarction or stroke were excluded; and
- subjects were closely monitored during the study.

When a new treatment is tested for a condition for which no effective treatment is known, there is usually no ethical problem with a study comparing the new treatment to placebo. Use of a placebo control may raise problems of ethics, acceptability, and feasibility, however, when an effective treatment is available for the condition under study in a proposed trial. In cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control. There are occasional exceptions, however, such as cases in which standard therapy has proven toxic so severe that many patients have refused to receive it.

Are Placebos Justifiable in Pediatric Antihypertensive Drug Trials?

One of the difficulties in assessing the risks of placebo use in pediatric antihypertensive trials is that the long-term consequences of untreated hypertension have not been well studied in children. Although it is clear from tracking studies that elevated blood pressure in childhood is predictive of the development of hypertension in early adulthood, it is not clear that elevated childhood blood pressure will lead to increased morbidity or mortality rates from cardiovascular disease. Given this, one could make the argument that placebo use could be acceptable in pediatric antihypertensive trials because there are no data that such use would result in serious harm to the study subjects.

Another potential justification for placebo use in pediatric antihypertensive trials is that many children with mild-to-moderate uncomplicated hypertension receive nonpharmacological treatment before starting drug therapy. This practice is based on numerous studies that have demonstrated significant blood pressure reduction in hypertensive children with various nonpharmacological measures. In the context of this widely accepted practice, a relatively brief period of placebo use in a clinical trial would clearly be ethical, since it would not vary from accepted standards of care.

Placebos may also be not only ethical but actually necessary in pediatric antihypertensive efficacy trials because of the placebo effect. Until recently, although children were known to have labile blood pressure, it was unknown whether they would demonstrate a significant placebo effect—this was yet another consequence of the lack of pediatric clinical trials. However, now that several of the first pediatric antihypertensive trials have been completed, there are published data demonstrating that hypertensive children enrolled in clinical trials do indeed demonstrate a significant placebo effect. Thus, there appear to be several ethical justifications for placebo use in clinical trials of antihypertensive agents in children.
On the other hand, it is clear that even “uncomplicated” primary hypertension in childhood will result in hypertensive target-organ damage in a significant number of children: approximately 25% of children with primary hypertension have left ventricular hypertrophy at the time of initial evaluation.\textsuperscript{28,29} It is generally accepted that children with target-organ damage from hypertension should receive pharmacological therapy.\textsuperscript{26} Therefore, randomly assigning such children to placebo could be deemed unethical, not only because it goes against standard practice but also because they could have target-organ damage that might be improved by treatment with active drug.

Furthermore, in a large percentage of children, especially in the young, hypertension is secondary in origin, usually caused by underlying renal disease.\textsuperscript{36,30} Although clinical trials examining the effects of blood pressure control in children with renal disease have not yet been conducted, given the known benefits of blood pressure control in adults with renal disease, it is reasonable to assume that most pediatric nephrologists would choose to treat hypertension in children with underlying renal disease. This would add another category of hypertensive children to the category of those in whom placebo use should be considered unethical.

The above arguments lead to the following set of proposed guidelines for the ethical use of placebo controls in clinical trials of antihypertensive drugs in children:

Placebo use can be considered ethical if the following conditions are met:
1. The potential subjects have asymptomatic, mild-to-moderate primary hypertension;
2. The potential subjects do not have hypertension-related target organ damage;
3. Placebo treatment will be of short duration (generally <4–8 weeks);
4. No standard of care exists in the community or it is common practice not to initiate drug therapy immediately after diagnosis; and
5. The subjects will be monitored closely for deterioration and can be exited from the study for worsening hypertension and/or the development of symptoms.

Placebo use should be considered unethical if any of the following conditions apply:
1. The potential subjects have secondary hypertension; or
2. The potential subjects have hypertension-related target organ damage.

Both of these restrictions on placebo use are based on the ethical principle noted above that participation in a clinical trial should not expose subjects to potential harm when an accepted treatment exists.

Some of the criteria set forth above clearly would require discussion among a group of experts in the field of pediatric hypertension before they could be widely adopted. For example, unlike in adults, there is no generally accepted definition of what constitutes mild-to-moderate hypertension in children; a consensus definition would need to be developed. Similarly, an acceptable frequency of study visits and characterization of what would constitute deterioration during a trial would have to be specified. With such refinements, these guidelines could ensure that hypertensive children enrolled in clinical trials would be protected from unnecessary harm.

**Perspectives**

The FDAMA has had the desired effect of increasing the number of drugs that have been studied in children and offers the hope that children will be “therapeutic orphans”\textsuperscript{11} no longer. However, it is incumbent on researchers to develop research procedures that will not only answer the scientific questions of interest but also protect this vulnerable patient population from harm. Although the guidelines proposed in this article are specific to hypertension research, the ethical principles underlying them can be applied to almost any branch of pediatric medicine. It is hoped that publication of this article will stimulate further debate regarding placebo use in clinical research involving children and will contribute to the enhancement of research protections for all children involved in clinical research.

**Acknowledgments**

The author thanks Dr Ruth Macklin for her guidance during the preparation of this manuscript.

**References**


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Hypertension. published online September 22, 2003;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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