Research Knowledge Among Parents of Children Participating in a Randomized Clinical Trial

BENEDETTO VITIELLO, M.D., MICHAEL G. AMAN, Ph.D., LAWRENCE SCAHILL, Ph.D., JAMES T. MCCracken, M.D., CHRISTOPHER J. McDOUGLE, M.D., ELAINE Tierney, M.D., MARK DAVIES, M.P.H., AND L. EUGENE ARNOLD, M.D.

ABSTRACT

Objective: Parental permission is required for child research, but parents’ understanding of research aims and procedures has not been well documented. Parental research knowledge was assessed during a clinical trial in autism. Method: Parents of 101 children (age 5–17 years) with autism participating in a placebo-controlled trial of risperidone were given a questionnaire at the end of the study. Results: Of the 95 parents completing the questionnaire, 99% knew of possible placebo assignment and that testing the medication efficacy was the main purpose of the investigators; 96% to 98% knew that research involved both risks and potential benefits, identified the study medication, and knew of their right to withdraw at any time; 90% to 95% knew of the medication’s main side effects; 87% reported having been informed of possible alternatives to research participation; and 72% were aware that treatment was randomly assigned (whereas 27% reported that treatment was chosen based on individual needs to ensure best care). Parents with a college degree were more likely to recognize the random nature of treatment assignment. Conclusions: Overall, parents were highly knowledgeable of the main research components. About one fourth, however, seemed unaware that treatment was randomly determined and not personalized, suggesting that therapeutic misconception may affect some otherwise well-informed parents. J. Am. Acad. Child Adolesc. Psychiatry, 2005;44(2):145–149. Key Words: ethics, clinical trials.

Randomized, controlled clinical trials are research activities designed to test specific experimental hypotheses with the purpose of acquiring generalizable knowledge about therapeutic interventions and thus informing future clinical practice. For a child to participate in research, parental informed permission is typically required. The three essential components of a valid permission for clinical research are information, understanding, and voluntary agreement (U.S. Department of Health and Human Services, 2001).

The federal Common Rule specifies the information elements that must be included in the consent process, such as a statement that the activity is research, purpose of the research, description of the study procedures, potential risk and discomfort, alternatives, and voluntary participation. The process of informing prospective research...
Subjects plays a critical role from both an ethical and legal standpoint. It informs not only about research procedures, potential benefits, and risks, but also on the rights of the participants, such as that of withdrawing from the study.

Parents usually receive information about study participation through verbal interaction with the investigators and written consent forms. Although much attention and effort are devoted by investigators and ethics committees to ensure that research subjects and, in the case of pediatric studies, parents are accurately and thoroughly informed, limited information is available on the effectiveness of this process in mental health research (Lavori et al., 1999). Comprehension of informed consent by adult subjects with schizophrenia was found to be adequate when appropriate procedures were followed (Wirshing et al., 1998). Surveys of adults with cancer or cardiovascular disease participating in clinical trials have reported variable and often deficient levels of understanding of research aims and procedures (Agard et al., 2001; Joffe et al., 2001).

In particular, it appears that many research subjects fail to appreciate the difference between research and individualized clinical care, a phenomenon often referred to as the therapeutic misconception (Bergler et al., 1980; Lidz and Appelbaum, 2002; Miller and Rosenstein, 2003). The primary purpose of usual medical practice is to treat each patient by providing optimal care that is based on individual characteristics, needs, and preferences. The primary aim of research, on the other hand, is to inform on how to treat an entire category of patients suffering from a certain disorder through an experiment that controls, and therefore limits, treatment options for the research participants. In fact, within ethically acceptable limits, investigators are restricted by the research protocol in the range of care that study subjects can receive.

Little is known about the level of research understanding of parents whose children participate in psychiatric research. Parental understanding of research aims and procedures were examined in pediatric oncology, neonatology, and other medical and surgical conditions (Mason and Allmark, 2000; Tait et al., 2003; van Stuijvenberg et al., 1998). Among parents of children with asthma participating in a clinical trial, most failed to appreciate the risk of adverse events and only one third seemed aware of their right to unconditionally withdraw consent to research participation (Harth and Thong, 1995). During enrollment in a randomized trial for children with leukemia, half of the parents were found not to understand the meaning of randomization in spite of extensive oral and written explanations (Kodish et al., 2004).

We assessed parental knowledge of critical aspects of research participation at the end of a placebo-controlled, randomized clinical trial of a medication for children with autism. The intent of this investigation was descriptive. On the one hand, because much attention to properly informing parents was paid by experienced investigators in the risperidone clinical trial, under the supervision of five institutional review boards and a centralized data and safety monitoring board, it was expected that parents would show a good general level of understanding of the research aims and procedures. On the other hand, based on existing literature, it was anticipated that certain aspects, such as the probability of receiving placebo and the double-blind and experimental nature of the clinical trial, would be less well appreciated.

**METHOD**

**Subjects and Description of the Clinical Trial**

Parents of children completing a randomized clinical trial were asked to answer a questionnaire inquiring about critical aspects of participation in a clinical trial. The clinical trial was a multisite, 8-week, double-blind, placebo-controlled, randomized study of risperidone in autism whose main results have been already reported (RUPP Autism Network, 2002). Briefly, 101 outpatients, aged 5 to 17 years (mean ± SD 8.8 ± 0.7), suffering from autism-associated serious behavioral disturbances such as aggression, self-injury, and severe tantrums, were randomized to receive either risperidone or placebo. Sixty-six percent were white, 11% African American, 7% Latino, 8% Asian, and 8% of other racial/ethnic groups. Parents were required to be fluent in English to complete the study assessments. Of the children, 73% were cognitively impaired, with an IQ in the mild to profound mental retardation range. Of the parents, 50% reported an annual income above $40,000; 34% had no more than a high school education, 31% had attended some college or trade school but without achieving a degree, and 35% had a university college degree (15% also had an advanced degree). The clinical trial protocol, consent form, and all assessment forms, including the After Study Knowledge (ASK) questionnaire that provided the data reported here, were approved by each institutional review board at the five study sites. No separate consent form for completing the ASK questionnaire was used. Active medication (risperidone) was found to be superior to placebo on the efficacy outcomes, with a response rate of 69% on risperidone versus 12% on placebo ($p < .001$) (RUPP Autism Network, 2002).

**Procedures**

To enter the randomized trial, parental informed permission was required. For those children capable of understanding, verbal assent was also obtained. A written consent form was signed by the parent or other legal guardian. The seven-page consent form included...
This study has been designed as a placebo-controlled, double-blind study. The terms placebo-controlled and double-blind mean that neither you nor the investigators will know if your child is receiving risperidone or an inactive placebo. Subjects will be randomly assigned to either the active medication or the placebo. This means that your child has a 50% chance of getting risperidone and a 50% chance of getting placebo (like the flip of a coin). Designing the study this way (double-blind with random assignment) helps us evaluate each subject’s progress in the study in a fair and careful way.

The consent form also included a list of possible adverse events associated with risperidone, such as increased appetite, weight gain, sedation, muscle stiffness, abnormal movements, increased heart rate, and neuroleptic malignant syndrome, according to the official labeling of this drug.

Typically, an initial description of the clinical trial was provided verbally to the parent by the study coordinator (a research assistant with college degree who was familiar with the main aspects of the trials), followed by a meeting in person with the clinical investigator during which the parent was given a copy of the consent form. The investigator then reviewed the contents of the consent form, paragraph by paragraph, answering any questions that the parents might have. Two copies of the consent form were signed both by the parent and the investigator, and the parent retained one copy.

At the end of the randomized trial, as part of the end-of-study assessments, the parent who had given written informed permission was asked to complete an ASK questionnaire that inquired about their understanding of the following aspects of research participation: main purpose of the study, requirement of parental permission for research participation, right to withdraw at any time, specific medication being tested, main possible side effects, possibility of being assigned to placebo, random treatment assignment, double-blind nature of the study, and alternatives to research participation. For each item of the questionnaire, parents were asked to select one of multiple possible answers. The ASK questionnaire is available via the Article Plus feature on the Journal Web site at www.jaacap.com.

Data Analysis

Descriptive statistics were used. Group differences were tested using nonparametric tests, such as the $\chi^2$ test. All reported $p$ values are two-tailed.

RESULTS

Ninety-five parents/guardians (95% of total randomized sample) completed the questionnaire. In most cases, the informant was the mother (72%), followed by the father (19%) and other guardian (9%). Of the 95 responders:

- 99% reported having given written permission for their child’s participation after receiving adequate information, knew of the possibility of their child being assigned to placebo, and correctly identified testing the medication efficacy as the main aim of the clinical trial.
- 98% correctly identified the study medication.
- 97% were aware that research participation involved both risks and potential benefits.
- 96% knew of the right to withdraw from the clinical trial at any time.
- 95% knew of the medication’s possible main side effects.
- 93% identified the exact probability of receiving placebo (i.e., 50%).
- 91% were aware of the double-blind nature of the clinical trial.
- 87% reported having been briefed on possible alternatives to research participation before giving permission.
- 72% were aware that treatment assignment was made randomly, whereas 27% reported that treatment choice was based on individual needs of each child to ensure that he or she received the best possible treatment (Table 1).

Responses to this last item were further investigated by examining the possible association with parental education, race/ethnicity, preresearch treatment relationship with the investigators, improvement status at the end of the trial, and type of informant. Eighty-three percent of the parents with a college degree versus 60% of parents without a college degree indicated that treatment was randomly assigned ($\chi^2 = 6.59, df = 1, p = .01$). Seventy-seven percent of white parents indicated that treatment was randomly assigned versus 59% of nonwhite ($\chi^2 = 3.4, df = 1, p = .06$). Only seven of the 95 children had been under the care of the investigators before entering into the trial; for six of them (86%), the

<table>
<thead>
<tr>
<th>Item of the After Study Knowledge Questionnaire</th>
<th>Response Rates ($N = 95$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment assignment was decided:</td>
<td></td>
</tr>
<tr>
<td>a. Randomly (i.e., by the toss of a coin)</td>
<td>72%</td>
</tr>
<tr>
<td>b. By the child</td>
<td>1%</td>
</tr>
<tr>
<td>c. Based on the individual needs of each child</td>
<td>27%</td>
</tr>
<tr>
<td>to ensure that each child received the best</td>
<td></td>
</tr>
<tr>
<td>possible treatment for his or her condition</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 1
parents indicated that treatment assignment was random. Seventy-four percent of the parents whose children were clinically improved at the end of the randomized trial indicated that treatment assignment was randomly determined versus 70% of the parents whose children were not improved. The type of informant completing the questionnaire (mother, father, or other guardian) did not significantly affect the answer to this item.

DISCUSSION

These data indicate that the parents of the children participating in this randomized trial of risperidone were well informed of the research procedures and research subject rights. These parents were assessed at the end of the experimental treatment, which was about 8 weeks after giving written informed permission for their children to enter into the clinical trial. Almost all the parents correctly identified the medication being investigated and its side effects and knew of the presence of a placebo and the exact probability of receiving it. Ninety-one percent understood the concept of double-blind. Ninety-six percent were aware of their basic right to withdraw from the study unconditionally and at any time. However, only 72% of the parents indicated that treatment received was decided randomly, whereas 27% apparently believed that treatment decision was driven by the individual needs of the child to ensure optimal treatment.

On the whole, these data provide a more reassuring scenario of the ability of research subjects to understand the essential features of clinical trials than previously reported in both adults and pediatric studies (Agard et al., 2001; Harth and Thong, 1995; Joffe et al., 2001; Kodish et al., 2004). In this study, almost all the parents understood the concept of double-blind. Ninety-one percent were aware of their basic right to withdraw from the study unconditionally and at any time. However, only 72% of the parents indicated that treatment received was decided randomly, whereas 27% apparently believed that treatment decision was driven by the individual needs of the child to ensure optimal treatment.

In spite of the overall excellent level of understanding, it is remarkable that the only area where a substantial proportion of parents apparently showed a misunderstanding was that about treatment assignment being randomly determined (Table 1). More than one fourth of the parents answered that “the study treatment that each child received was decided based on individual needs of each child to ensure that each child received the best possible treatment for his/her condition” rather than “randomly (that is by the toss of a coin)”. Level of education moderated this result, with better educated parents being more aware of the random assignment than less educated parents.

This finding is consistent with previous reports of therapeutic misconception among research participants (Bergler et al., 1980; Lidz and Appelbaum 2002; Miller and Rosenstein, 2003). This misconception can occur also among otherwise well-informed subjects. Indeed, failure to appreciate the experimental nature of therapeutic clinical trials may well be the most difficult aspect of clinical research for research participants to grasp (Kodish et al., 2004).

A therapeutic misconception can be expected to be more likely when a therapeutic relationship between patient and clinical investigator has preexisted participation in research. In this study, only seven children had been treated by the investigators before the clinical trial, and among their parents, the rate of response suggestive of therapeutic misconception (14%) was not greater than that in the overall sample (27%).

The therapeutic misconception has relevance from both an ethical and experimental perspective. Participation in a research protocol implies acceptance of certain limitations to the treatment options that are available during usual individualized care. Thus, it is problematic that participants or their families fail to appreciate such a difference (Miller and Rosenstein, 2003). In addition, an incorrect expectation of receiving optimal individualized care may contribute to higher rates of placebo response.

It must be pointed out, however, that alternative explanations, other than the therapeutic misconception,
can also apply, including a possible misunderstanding of the meaning of the question by the nearly one fourth of the respondents. For instance, some parents might have understood “study treatment” to mean that the active drug of the study was the best possible treatment choice for their child. This explanation seems, however, less likely given the choice of possible answers being offered (Table 1). On the other hand, the relatively poor rate of correct response to this particular question stands in contrast with the excellent level of understanding shown on the other questions. Because of the word “received” rather than “assigned” in the stem of the question (Table 1), it is possible that some parents were thinking of individual titration within the assigned treatment arm. Future research should focus on understanding of random assignment and try to assess it using more detailed and precisely worded questions.

Limitations

Although the questionnaire was completely self-administered by the parents, the survey was conducted by the investigational team as part of the clinical trial end-of-treatment assessments. It would have been preferable that a separate team, completely independent of the clinical trial, had conducted this survey.

This report informs on the level of knowledge of parents at the end of research participation rather than at study entry. Because the questionnaire was completed at the end of the 8-week trial, rather than soon after signing the informed consent form, the level of knowledge displayed by these parents cannot necessarily be ascribed to the informed consent process that took place before entering the trial. It is well possible the results reflect knowledge acquired during their child’s participation in the trial. Likewise, finding knowledge gaps at the end of study does not rule out that correct understanding was present at time of enrollment but then lost during the following 8 weeks.

Clinical Implications

These findings are primarily relevant to clinicians involved in treatment research. The data indicate that parents of children participating in research can be adequately informed about all the main components and procedures of clinical trials and understand their basic rights as research participants. The results also suggest that the process of informing parents about research can be further improved by clarifying the meaning of randomization and of the distinction between research activities and personalized care.

Disclosure: Dr. Aman has received research funding from and/or served as paid consultant and speaker for Janssen Pharmaceutica and Eli Lilly. Dr. Scibill has received research funding from Janssen Pharmaceutica and served as a paid consultant or speaker for Janssen Pharmaceutica, Pfizer, and Bristol-Myers Squibb. Dr. McCracken has received research funding from and/or served as a consultant or speaker for Bristol-Myers Squibb, Eli Lilly, Glaxo, Janssen Pharmaceutica, McNeil, Noven, Pfizer, and Shire. Dr. McDougle has received research funding from and/or served as a paid consultant or speaker for Janssen Pharmaceutica, Pfizer, PediaMed, Bristol-Myers Squibb, Repligen, and Eli Lilly. Mr. Davies owns stock in the following pharmaceutical companies: Aven, Bard, Bristol-Myers Squibb, Elan, GlaxoSmithKline, Lilly, Johnson & Johnson, Merck, Pfizer, and Wyeth. Dr. Arnold has received research funding and/or served as a paid consultant or speaker for Eli Lilly, McNeil, Novartis, Noven, PTM, Shire, Sigma Tau, and Targacept. The other authors have no financial relationships to disclose.

REFERENCES

Kodish E, Eder M, Noll RB et al. (2004), Communication of randomization and of the distinction between research activities and personalized care.