Double-blind Methylphenidate Trials

Practical, Useful, and Highly Endorsed by Families

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**Objective:** To evaluate a 3-week, randomized, double-blind, methylphenidate placebo-controlled trial (MPT) in routine practice for children with attention-deficit disorder.

**Patients and Methods:** School-aged children with attention-deficit/hyperactivity disorder (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria) who enrolled an “N of 1” trial at a pediatric tertiary care center were eligible. Families (n = 50) with a child eligible for the MPT were given 3 bottles of identical capsules. The capsules contained, in random order: placebo of the prescribed dose of methylphenidate (Ritalin) hydrochloride (0.3 mg/kg or 0.6 mg/kg). Families gave the child 1 capsule at 8 AM and 1 capsule at noon. The family, teacher, and physician were blinded for the order of medication. Conners questionnaires (Conners Parent Questionnaire and Conners Teacher Questionnaire) and written comments were completed by parents and teachers at baseline and at the end of each week. Once MPT results were known and following discussion with the physician, families decided whether to continue methylphenidate therapy. Families were interviewed by telephone 14 to 21 months after the MPT.

**Results:** Forty-three (86%) of the 50 eligible children (mean age, 129 months) were contacted. No family found the MPT difficult, but 6 trials were incomplete, usually because of side effects. All families used the MPT to decide if methylphenidate was the correct treatment choice for their child and 68% (34 of 50 families) used the results exclusively. The remaining 16 families believed the MPT was helpful. Overall, 31 (72%) of the 43 children had a good response to methylphenidate treatment—20 (47%) continued to use it for longer than 12 months and 8 (26%) for 2 to 12 months; 3 responders chose not to use it after the MPT. Nine of the 43 families chose not to use methylphenidate treatment; however, all indicated that participating in the MPT helped them to make that decision. In follow-up interviews, the same proportion of methylphenidate users and nonusers reported improvement in many areas of function including significantly less time spent doing homework. Users reported reduced aggression ($P < .001$) and fewer discipline problems ($P < .01$) compared with nonusers.

**Conclusions:** An “N of 1” MPT was easily performed and permitted families to decide whether to use methylphenidate for long-term treatment of attention-deficit disorder or attention-deficit/hyperactivity disorder. Regardless of methylphenidate use or lack of use, the condition of all of these children was improved at follow-up.


**Editor’s Note:** What a wonderful way to use true experimental design to help the parents and the physicians determine medication effectiveness. Bravo!

Catherine D. DeAngelis, MD

Three percent to 10% of school-aged children exhibit symptoms of attention-deficit disorder (ADD). These children are often referred to pediatricians, pediatric neurologists, and developmental specialists for evaluation and management of their condition. The diagnosis of ADD may lead to a recommendation for daily treatment with methylphenidate (Ritalin) hydrochloride. It is estimated that about 4% to 5% of US schoolchildren receive methylphenidate treatment—about 50% of those who have ADD. The number of prescriptions has increased markedly, more than doubling between 1990 and 1993 although many children do not appear to receive the prescribed medication for long periods. Nevertheless, we encounter many parents who are reluctant to consider medication. The decision to try medication is often accompanied by the hope that the lowest possible dosage will be effective, with few or no side effects.

In our routine clinical practice, we have offered families a 3-week, random-
PATIENTS AND METHODS

PATIENTS AND CASE FINDING

The IWK Grace Health Center is the only pediatric hospital in Nova Scotia, serving a population of 1.6 million for tertiary care and 0.4 million for secondary care. All pediatric subspecialists in the province work from this center.

The children enrolled in this study received a diagnosis of attention-deficit/hyperactivity disorder, based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria, by us between September 1, 1995, and April 30, 1996. Each child subsequently underwent a 3-week, randomized, double-blind, placebo-controlled MPT. If the results of the MPT suggested a favorable response, the family was offered a prescription for methylphenidate. If there was no evidence of response, continued methylphenidate treatment was not suggested.

Inclusion criteria required that the children were between 4 and 14 years of age, were English- or French-speaking, and were living with caretakers with whom they had lived for longer than 6 months. Each of the eligible children had a teacher who could evaluate him or her in a classroom. Exclusion criteria included the following: a history of significant developmental delay, a previous diagnosis of pervasive developmental disorder, or the unwillingness of parents and/or school personnel to meet the MPT requirements.

THE METHYLPHENIDATE PLACEBO-CONTROLLED TRIAL

The MPT was conducted with only those families who consented to the study. Once enrolled in the MPT, the nonblindened hospital pharmacist randomly assigned each child to a particular dosing schedule. Study medication consisted of the same capsules filled with either an inert white powder (placebo) or the prescribed dose of methylphenidate hydrochloride (0.3 or 0.6 mg/kg) as an intact pill plus sufficient inert white powder to fill the capsule. Each trial was conducted over 3 weeks: 1 week of placebo, 1 week of methylphenidate hydrochloride, 0.3 mg/kg per dose, and 1 week of methylphenidate hydrochloride, 0.6 mg/kg per dose. Similar protocols have been well described in recent literature.

Each day, one capsule was administered at 8 AM and another at noon although it is understood that this particular regimen results in only partial coverage throughout the day. Each 7-day block was started on a Saturday to allow the primary caretaker to evaluate the child, especially for side effects. As methylphenidate has a short half-life, no washout period was used between medication weeks.

The Conners Parent Questionnaire and the Conners Teacher Questionnaire were completed by each child’s caretaker and teacher, respectively, at baseline and on the last day of each week of the MPT. When the child had multiple teachers, such as in junior high school, the child and family selected 2 teachers whom they thought would know the child well and would be likely to cooperate. In addition, each child’s parents and teacher were encouraged to provide weekly descriptions of the child’s activities, behavior, mood, attention span, and possible side effects.

At the end of each trial, the code was broken. The physician evaluated this information and made a clinical inference about the degree of response each week. A decision was made whether to recommend daily use of methylphenidate, and if so, at which dose. The empiric decision to recommend medication use generally required an improvement of at least 1 SD on the hyperactivity subscale of the Conners questionnaires plus positive statements from the family/school. The physician conveyed this information to the family, usually by telephone. If the family’s decision was to use methylphenidate, a prescription for morning and midday medication was given for 1 month and the child was reexamined in person then. Those not choosing medication came for an appointment approximately 1 month after the MPT. This group included those who responded favorably to methylphenidate treatment, but whose family decided against regular use and those who did not respond.

LONG-TERM OUTCOME OF METHYLPHENIDATE TREATMENT

All 50 children who received a prescription for the MPT between September 1, 1995, and April 30, 1996, were eligible for this follow-up study, independent of their completion of the 3-week trial. Seven children were lost to follow-up. A 30-minute, semistructured, follow-up interview was conducted in June or July 1997 (at least 12 months after the completion of the original MPT). The 9 possible outcomes are shown in the Figure. We were unable to document how many families were offered the MPT and decided not to try it.

For this study, methylphenidate users were identified as those individuals in groups 3, 6, and 9 (Figure). Epi-sodic users of methylphenidate (groups 2, 5, and 8) and nonusers of methylphenidate (groups 1, 4, and 7) were classified as nonusers.

The follow-up interview elicited information from the caretaker regarding the utility of the double-blind trial, subsequent use of methylphenidate, and the child’s present home, school, and social function. Responses to questions in these areas were categorized and coded. Data analysis was performed with a commercially available software program.

The Research Ethics Board of the IWK Grace Health Centre approved this protocol.

ized, double-blind, placebo-controlled methylphenidate trial (MPT) rather than an open prescription. This approach seems to make the assessment of medication effects and side effects objective and allows evaluation of the effect of different doses of medication. This article outlines our method for these trials and documents their influence and use on longer term management in a variety of family situations.
age were 2.5 years older than the group of children contacted. An interview was conducted with at least 1 parent or guardian for the remaining 43 children. The duration of follow-up ranged from 14 to 21 months at an average age of 129 months (age range, 77-187 months). Sixty percent of the participants were in grade 4 or lower, 16% were in grades 5 or 6, and 24% were in grades 7 through 9. Twenty-four (49%) of the 50 children had failed a grade, but 72% of the parents were happy with the educational placement of their child.

Overall, 37 completed the MPT; 31 patients (84%) were classified as responders. Twenty-eight (92%) of the responders chose to continue with daily medication. Of these 28 families, the dose was discussed with the physician and 50% chose the lower dose (0.3 mg/kg per dose) and 50% the higher dose (0.6 mg/kg per dose). As seen in the Figure, 20 (65%) of 31 responders continued to receive methylphenidate treatment at the time of follow-up. However, 8 (26%) discontinued use of methylphenidate after less than 1 year of treatment. One year later, the dose had been changed in 17 usually upward—the same proportion in the initial low- and high-dose groups.

Twenty-six (53%) of the 50 patients were from a rural, 9 (18%) from a suburban, and 14 (28%) from an urban area. The living arrangements of these children were diverse—21 (42%) live with 1 biological parent, 24 (49%) live with both biological parents, and 4 (9%) live with adoptive parents or guardians. Fifteen (30%) live in households that have a family income below the Canadian poverty line (<$20,000/y).

Of the families interviewed, 28% (14/50) of mothers and 28% (14/50) of fathers have less than a grade 12 education, while 37% (18/50) of mothers and 28% (14/50) of fathers have at least an undergraduate university degree.

At the time of the MPT, a variety of comorbid diagnoses were noted (Table 1). Of the 43 children with comorbid diagnoses, 68% (23 children) cited improvement in many areas of function (Table 2). In addition, families reported that both groups spent significantly less time doing homework in the year(s) fol-

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**Table 1. Prevalence of Comorbid Diagnoses in the MPT**

<table>
<thead>
<tr>
<th>Characteristic of Methylphenidate Hydrochloride Group</th>
<th>Status of Condition</th>
<th>Total Study Group (n = 43)</th>
<th>Methylphenidate Hydrochloride (n = 20)</th>
<th>Nonusers (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td>Users</td>
<td>Nonusers</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td>37</td>
<td>25</td>
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<tr>
<td>Learning disability</td>
<td></td>
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<td>Initiation</td>
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<td></td>
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<td>4</td>
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<td>Psychiatric disorder</td>
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<td>2</td>
<td>0</td>
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<tr>
<td>Tourette syndrome</td>
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<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td>23</td>
<td>20</td>
</tr>
</tbody>
</table>

* MPT indicates 3-week, randomized, double-blind, placebo-controlled methylphenidate trial. All values are expressed as percentages. All P values by χ² test were not statistically significant.
following the MPT compared with before the MPT. (Total group: before the MPT, 23% [12 of 50 children] spent <60 minutes per day vs 67% [34 of 50] at follow-up; methylphenidate users group: 10% [5 children] spent <60 minutes per day vs 65% [33 children] at follow-up). Methylphenidate users reported reduced aggression (P < .001) and fewer discipline problems (P < .01) as compared with the nonusers. Thirty-four families (68%) reported that they had used the MPT to decide whether methylphenidate was the correct treatment choice for their child. This included all of the methylphenidate treatment users. The 9 families who chose not to continue methylphenidate after the MPT found the trial helpful as it allowed them to discover that methylphenidate was not the appropriate treatment choice for their child. An additional 8 of 43 families believed the MPT was helpful, but it was only 1 factor in their decision about the use of methylphenidate. The degree of extended family support and their agreement or disagreement with the use of methylphenidate did not affect the family’s eventual decision.

We found the MPT to be helpful, practical, and definitive for families of children with attention-deficit/hyperactivity disorder to making a decision about medication use. The results of the 3-week trial were generally predictive of whether the child would continue methylphenidate treatment for 1 year or longer. Regardless of the outcome, it was important for families to complete the MPT to understand, for their own child, the effect of methylphenidate on the child’s behavior and the presence of any side effects. For some children the MPT was inconclusive and yet they continued to use methylphenidate for a short period; however, all eventually stopped.

The “N of 1” method is a powerful and objective technique for assessing an individual’s unique response to a given treatment. It is of special value when the severity of the given disorder varies between individuals. Blinded randomization removes important sources of bias when considering each patient’s response to a given treatment. Randomization of dosage schedules helps to identify the lowest effective dose for each patient and side effects may be recognized objectively. The length of the treatment intervals in MPT is controversial. Some authors have suggested very short intervals, 1 to 3 days, and others have used 1 week. We selected a full week for 3 reasons. First, the initial 2 weekend days allowed parents to be comfortable that there were no serious side effects before sending the child to school with a new medication—given the ups and downs of life with a child with ADD, 1 day might have been insufficient. Second, 1 week allows for a full range of school activities. Weeks with holidays and special events such as school trips were avoided. Third, we were unsure how cooperative school officials would have been if requested to make more frequent reports. This issue should be addressed with a randomized trial.

The MPT can be accomplished in a variety of family situations and in patients with varying degrees of attention difficulties. Thirty percent of families interviewed lived below the Canadian poverty line and an equal number of parents had less than a grade 12 education. Only 49% of the children lived with both of their biological parents. A comorbid diagnosis of anxiety, depression, Tourette syndrome, conduct disorder, or a psychiatric disorder was present in almost 40% of the subjects at the time of the MPT. No family found the MPT too difficult to complete. We found teachers to be willing to assist with the MPT. For junior high school students who have multiple teachers, we asked the parents and children to designate the appropriate teachers to participate in the MTP. We did not use standard side effect questionnaires with the MPT, because we believed that the increased complexity might make the trial more difficult. Before the institution of the MPT we routinely asked families to report mood, appetite, or sleep problems. We conclude that the MPT may be carried out in even the most complicated family settings with a spectrum of very difficult children.

The MPT quickly supplies the results of therapy and most families believed this information was pivotal in their decision. Thirty-four families (68%) used the MPT exclusively; whereas the remaining 16 families found the result helpful, but used additional factors to aid their decision making. By using 2 dosages of methylphenidate hydrochloride (0.3 and 0.6 mg/kg), the lowest effective dose, in association with the fewest side effects, could be determined for each child responder.

We found that many symptoms improved during follow-up, both in children who received methylphenidate and those who did not. In our study, methylphenidate use was associated with a statistically significant decrease in reported aggressive behavior and discipline problems in both short- and long-term evaluations (P < .001). This finding is supported by a recent study by Gadow et al8 who concluded that both noncompliant and aggressive behaviors decreased with methylphenidate therapy and the degree of response was independent of dose. It is impossible to know how these children would have fared without methylphenidate therapy. There is evidence suggesting that as young adults, children with ADD who received long-term methylphenidate treatment exhibit more aggression than their normal aged, normal IQ, socioeconomically matched peers. However, those treated with methylphenidate have fewer difficulties than their untreated peers with ADD.9,10

Double-blind, placebo-controlled protocols for the use of methylphenidate have been reported previously.11-19 These studies, in which groups of children with ADD were randomized to 1 of 2 study treatment arms, were designed to compare the efficacy of placebo and of methylphenidate. Occasionally, additional treatment arms were employed to establish dose-related outcome measures. The results of these trials have consistently indicated that approximately 75% of children with attention-deficit/hyperactivity disorder enrolled in studies respond to methylphenidate treatment and there is an increasing behavioral response and rate of side effects as the dose was increased. This study design is a powerful way to show group treatment differences but does not yield specific information for an individual child. Single-subject, double-blind, crossover trials have also been reported. Ahmann et al12 employed a study design similar to ours. Their 4-week randomized design included 2 medication blocks of placebo or methylphenidate hydrochloride at spe-
cific dosages of 0.3 mg/kg per dose and 0.5 mg/kg per dose. Each was compared with a randomly ordered week of placebo. Capsules were administered 3 times daily with the outcome measures determined by weekly parent and teacher Conners scale scores. It was concluded that randomized placebo-controlled trials are an efficient and effective method to aid the physician in selection of the optimal dose for the given patient.

Pelham et al. used single-subject, double-blind, crossover trials to demonstrate individual response to several drugs for attention-deficit/hyperactivity disorder—methylphenidate, dextroamphetamine, and pemoline. The study design was more complicated and used daily switching of medication except for 3-day blocks for pemoline which may have a more delayed effect. Twenty-two children were evaluated over a 2-week baseline and 6-week blind treatment phase. Short-term efficacy of the medication was obtained for the individual child as well as for the group. All of the medications evaluated were equivalent in efficacy. Information concerning the presence of side effects was immediately available for the child and for the group.

The excellent individual, double-blind crossover study of McBride was similar to our own in many aspects. She only evaluated 1 dosage of methylphenidate. The trial consisted of a treatment block of 2-weeks’ duration and a placebo block of 2-weeks’ duration. Short-term outcome measures included the Conners Parent and Teacher questionnaires and an attempt to obtain a sense of the quality and quantity of academic work brought home each week. Follow-up information was available for 41 of 45 methylphenidate responders 1 to 5 years after the initial study. During follow-up 14 of the initial responders discontinued methylphenidate use or switched to another behavior-modifying medication.

In conclusion, the 3-week, double-blind, placebo-controlled MPT is practical and can be carried out in an office or clinic. Our method of preparation for blinded medication or placebo can be carried out by any willing community pharmacist. Lack of extended family support, socioeconomic or educational status, or comorbid diagnoses do not adversely affect the MPT outcome. Children who receive methylphenidate seem to have the long-term benefit of reduced aggression and increased self-discipline. We have demonstrated that the MPT is a useful tool and feasible in routine clinical practice. Given the current concern about overuse of methylphenidate, this technique ensures the practitioner and family that the drug has a desirable effect without serious side effects.

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