Treatment for ADHD: Is More Complex Treatment Cost-Effective for More Complex Cases?

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**Abstract (250 words)**

**Background:** Attention-deficit/hyperactivity disorder (ADHD) is among the most common emotional and behavioral disorders affecting children and youth. Little, however, is known about the relative cost-effectiveness of proven treatments, such as behavioral therapy and psycho-stimulant medication.

**Objective:** To determine the cost-effectiveness of alternative high-quality treatments and whether cost-effectiveness varies with the presence of comorbid disorders.

**Research Design:** Data are taken from a large clinical trial that randomized participants to one of four arms: routine community care; medication management; behavioral treatment, and a combination of behavioral treatment and medication.

**Subjects:** 579 children ages 7-9 with diagnosed ADHD at six sites.

**Measures:** Parent and teacher reports of the child's symptoms, parental reports of psychosocial functioning and diagnosis, and records of service use.

**Results:** The preferred cost-effective treatment varies as a function of the child's comorbidity and of the policy-maker's willingness to pay. For pure (no comorbidity) ADHD, high-quality medication management (MedMgt) appears likely to be cost-effective at all levels of willingness to pay. In contrast, for some comorbid children, willingness to pay is critical: the policy-maker with low willingness to pay likely will judge MedMgt most cost-effective. On the other hand, a policy maker willing to pay more now to avert future costs (involving, for example, juvenile justice), may recognize that the most cost effective choice for comorbid children likely involves behavior therapy, with or without medication.

**Conclusions:** Analyses of costs and effectiveness of treatment for ADHD must consider the role
of comorbidities.

Keywords: cost-effectiveness, adhd, conduct disorder, anxiety, children
Attention problems are among the most common of mental/emotional/behavioral disorders among children and youth\textsuperscript{1}. Youth with attention-deficit/hyperactivity disorder (ADHD) are more likely to be involved in a variety of costly behaviors including substance use and abuse\textsuperscript{2,3} and delinquency\textsuperscript{4} as well as to receive costly services. Because attentional problems interfere with learning, such children require costly special education services and nevertheless often fail in school over time.

Fortunately, effective treatments are available, notably psychosocial treatment and medication, including psychostimulants. A key issue in the field involves the degree to which these two broad categories of treatment are complements or substitutes for each other\textsuperscript{5} – i.e., whether each is more (or less) effective and cost-effective when combined with the other.

Assessment of ADHD treatment effectiveness is complicated by the common occurrence of comorbidities, including both externalizing problems such as conduct and oppositional-defiant disorder and internalizing problems, such as anxiety. Comorbidities amplify the link between attention problems and service use\textsuperscript{6} and raise the risk for poor long-term outcomes, such violence and substance abuse\textsuperscript{7}. The link between attention problems and these comorbidities is receiving increasing attention, both in terms of nosology and effective treatment\textsuperscript{8}.

In contrast to the evidence on efficacy and effectiveness, little is known about the cost-effectiveness of alternative treatments, either separately or in combination. To address this issue, we use data from one of the largest and most influential studies in the field, the Multimodal Treatment Study of Children with ADHD (MTA)\textsuperscript{9,10}. The MTA was designed to compare the effectiveness of psychosocial treatment versus medication, and determine whether the two
modalities are more effective when delivered together.

An earlier cost-effectiveness analysis of MTA data focused on the relative cost-effectiveness in reducing the core attention-related symptoms in the whole sample (Jensen et al., in press)\textsuperscript{11}. The analyses presented here extend that earlier work in three ways. First, we examine a broader measure of social functioning by focusing on a key measure of functioning, the Columbia Impairment Scale (CIS). While the study did not collect a measure of health-related quality of life (HRQoL), the CIS represents an overall measure of well-being that is consistent with the spirit of HRQoL. Second, we examine differential cost-effectiveness of the treatments in key sub-groups of participants. A focus of these moderator analyses involves common comorbidities. Earlier results suggest that more comprehensive treatments are more effective for these complex cases. Third, we employ the latest methodology for examining cost-effectiveness of treatments, the cost-effectiveness acceptability curve\textsuperscript{12-14}. An advantage of this method is that it facilitates moderator analyses.

**PRIOR RESEARCH**

Two areas of prior work inform this research: that on the cost-effectiveness of treatment for ADHD and earlier research on MTA.

**Prior research on cost-effectiveness of treatment for ADHD.** In addition to the Jensen et al. analyses (discussed below), economic evaluations of ADHD treatment have been published for Canada and the United Kingdom (UK). In a report commissioned by the Canadian Coordinating Office for Health Technology Assessment, Miller and colleagues compared six treatments: methylphenidate, dexamphetamine, pemoline (high-dose and low-dose), non-drug therapy, combined therapy, and no treatment\textsuperscript{15}. The study considers costs and outcomes over a
one-year period; the study's perspective is that of third-party payers. Based on a systematic review of the literature\textsuperscript{16}, treatment effects were determined using a measure of symptoms, the Conners Teacher Rating Scale (CTRS). The methylphenidate strategy was found to dominate its alternatives, with a cost of 498 CAN-$ per 6-point (or one standard deviation) improvement of the CTRS score. Some of these estimates were quite imprecise because of small sample sizes: the data for the psychological/behavioral and the combination strategies involved fewer than 20 patients each.

In the United Kingdom, Gilmore and Milne\textsuperscript{17} examined the cost-effectiveness of different medications from the perspective of the UK National Health Service (NHS). From that perspective, methylphenidate was cost-effective in children with hyperkinetic disorder according to ICD-10 criteria. This study considered neither behavioral nor combined treatment strategies, however. The UK National Institute of Clinical Excellence (NICE) estimated the cost per quality-adjusted life year (QALY) gained by methylphenidate at £9,200 to £14,600\textsuperscript{18}. In a further study from the perspective of the UK NHS, a once-daily modified-release preparation of methylphenidate showed extended dominance over immediate-release methylphenidate (both combined with behavioral treatment) over a wide range of assumptions. Like the Canadian evaluation, all UK analyses to date employed a one-year time horizon.

While international studies are interesting, their cost-effectiveness data may not be applicable to the United States health care context, what has been called the "portability" problem.

Prior research on MTA. The MTA study has been the subject of substantial research and some debate.\textsuperscript{9,10,19,20} The study involved a randomized controlled study of 579 children at six
sites. Participants were ages 7 to 9 at baseline and were randomized to one of four treatment arms: assessment and referral to community care (CC); medication management (MedMgt); behavioral treatment (Beh) and a combination of behavioral treatment and medications (Comb). The MTA-administered interventions were high quality. In the case of MedMgt, dosage was carefully titrated, and participants met with their physician monthly. The physician consulted with the child's teacher regarding his or her performance in the classroom. Beh treatment was multicomponent and targeted multiple aspects of the child's life. It consisted of three major components: Parent Training, a two-part School Intervention component, and a child treatment component anchored in an intensive Summer Treatment Program. Each of the treatments continued for 14 months, although Beh was faded to monthly parent group sessions over the last 3-5 months.

Results indicated that for ADHD symptoms, children in the Comb or MedMgt groups showed significantly greater improvement than those given community care or Beh treatment alone. Much debate focused on the question of whether the study really implied that medication (only) was the ideal treatment. Preliminary reports in the media seemed to suggest this. However, the actual findings were more nuanced. The most dramatic findings focused on symptoms, but analyses of broader outcomes, such as social skills, parent-child relationship, and academic performance), generally suggested that the combination therapy was modestly superior to medication alone\textsuperscript{21-23}. Additional analyses reveal that the optimal treatment varies not only depending on the outcome considered but also by sub-groups of participants. One key finding involves comorbidity.\textsuperscript{9,10,19,24} For children with comorbid anxiety, or anxiety accompanied by conduct or
oppositional-defiant disorder, better outcomes were achieved through different treatment options depending on the type of comorbidity. Similarly, treatment outcomes were moderated by other risk factors, including subclinical maternal depression, higher degrees of ADHD symptomatology, lower IQ, and ethnicity. Thus, the MTA study offers an excellent opportunity to examine the cost-effectiveness of different treatment modalities for children with ADHD, with and without various comorbidities and/or risk factors.

METHODS

The methodology for this study involves cost-effectiveness acceptability curves using information on costs and interview data collected as part of the MTA. We discuss each of these in turn.

**Data.** The MTA study collected a comprehensive battery of tests, and our analyses focused on several key measures: the Columbia Impairment Scale (a comprehensive measure of child functioning), the Services for Children and Adolescents, Parent Interview (SCA-PI, a measure of service use), the Beck Depression Scale (a measure of parental depressive symptomatology), a standardized intelligence test (Wechsler Intelligence Scale – Children, Wechsler, 1991), and the Diagnostic Interview Schedule for Children used to assess the presence of DSM-IV diagnoses, including ADHD, oppositional defiant disorder, conduct disorder, major depression, and anxiety disorders.

The Columbia Impairment Scale is a structured questionnaire completed by parents and measures impairments in four areas: interpersonal relations, broad psychopathology domains (for example, depression, anxiety, or behavior problems), schoolwork, and use of leisure time. The analyses below focus on the change in impairment between baseline and the 14-month treatment
The revised Services for Children and Adolescents, Parent Interview (SCAPI) was used by research staff to assess utilization of mental health services across multiple service systems for all four treatment groups. This measure was given at 3-month intervals during treatment, and asked the families to report on the use of any medical and school services, community mental health services, or juvenile justice services. This measure allowed us to determine the specific amounts and types of services used, medication costs, and costs associated with primary care and specialty mental health services across all 4 randomly assigned groups. Reliability and validity of this scale are excellent.\textsuperscript{29-30}

**Comorbidity Subgroups.** Following procedures outlined in Jensen et al. (in press)\textsuperscript{11}, we defined 4 comorbidity subgroups, given previous evidence that the presence of comorbidity can exert a substantial effect on costs and that MTA subjects showed differential treatment effects as a function of comorbidity patterns\textsuperscript{19}. Thus, children were categorized into one of 4 comorbidity profiles based on diagnoses generated by the DISC: ADHD-only (31.8%, n=184) ADHD + internalizing comorbidities only (anxiety or depression) (14.0%, n=81), ADHD + externalizing comorbidities only (conduct or oppositional defiant disorder) (29.5%, n=171) and ADHD + both comorbidities (24.7%, n=143).

**Costs of Treatment.** The costs of the different treatment arms were measured from a payor perspective. These costs were calculated in accordance with economic principles and include the direct costs associated with providing each treatment arm. All costs were included regardless of whether they were paid for by a patient, an ensurer, or any other third party. All the costs associated with a given service were assumed to be the same across sites despite the
regional differences in cost of living or in actual billing charges for a specific service. All costs were adjusted for inflation to year 2000 dollars using the Consumer Price Index to insure that the results of the study can be understood in terms of current dollar amounts. This process is described in more detail in Jensen et al., in press\textsuperscript{11}.

Statistical Methods: Cost-Effectiveness Acceptability Curve. Traditional methods of cost-effectiveness analysis revolve around incremental cost-effectiveness ratios (ICER)\textsuperscript{33-34}. One limitation of those methods involves the determination and presentation of statistical uncertainty. Until relatively recently, ICERs were often provided with no sense of the precision of the estimates. Addressing this problem, however, turned out to be easier said than done, largely because of the strange statistical properties of ratios. A variety of solutions have been proposed involving the delta method, Feiler’s method, and bootstrapping\textsuperscript{34-35}.

Even if a satisfactory confidence interval of sorts could be developed, conceptual problems remain. In particular, regions of the confidence interval that are negative are difficult to interpret. A negative ICER may mean that a new treatment is more costly and less effective than the old or that it is less costly and more effective. Clearly, the implications for the decision-maker are different (indeed, completely opposite).

For that reason, two related alternatives have been proposed: net benefits and the closely related net health benefits. While both involve manipulating the familiar cost-effectiveness ratio, we employ the former here\textsuperscript{12-14}.

The key question in cost-effectiveness is whether the ICER of a new treatment relative to an existing one exceeds a policy maker’s or society’s willingness to pay ($\delta_c$) for the outcome of interest. This outcome is measured in non-monetary terms. If the ICER is less than $\delta_c$, then the
new technology or treatment is desirable–i.e.,

\[ 1) \frac{\overline{C}_{New\text{Tx}} - \overline{C}_{Usual\text{Tx}}}{\overline{E}_{New\text{Tx}} - \overline{E}_{Usual\text{Tx}}} < \lambda_c. \]

Because of sampling error, this statement is probabilistic, and thus confidence intervals for the ICER are needed. As mentioned above, the bounds of this interval can be difficult to calculate and/or interpret. For that reason, one can manipulate (1) into the following:

\[ 2) \lambda_c * (\overline{E}_{New\text{Tx}} - \overline{E}_{Usual\text{Tx}}) - (\overline{C}_{New\text{Tx}} - \overline{C}_{Usual\text{Tx}}) > 0 \]

A positive value of NB clearly indicates that the new treatment is preferred. A key feature of equation (2) is that it no longer involves a ratio and that one can calculate the P(NB>0) at alternative values of \( \lambda \), and these values can be plotted, generating the so-called cost-effectiveness acceptability curve (CEAC). The CEAC provides the policy maker with the information he or she needs–what is the probability the new treatment is cost-effective at alternative values of the outcome of interest (or levels of willingness to pay). The policy maker might have varying degrees of tolerance for different treatment decisions, and the CEAC provides the necessary information for an informed decision under uncertainty\(^3\).

**RESULTS**

Table 1 describes the sample and key variables across the four treatment arms. These figures are provided for all sample members and for the four comorbidity sub-groups. Three features of table 1 stand out. First, one can see that the average individual improved, regardless of the comorbidity sub-group or treatment arm. (Improvement corresponds to negative values of the CIS variable (row 1) (reduced functional impairment) and positive values of the
normalization variable (row 2). Second, for a given comorbidity subgroup, costs and outcomes vary across the four treatment arms in nearly every instance. (See the p-values in the last column.) The two exceptions involve functioning for the ADHD (only) sub-group and for the conduct-disordered sub-group. Third, within a treatment arm, outcomes and costs vary a good deal less across comorbidity sub-groups. (See the last three rows.) The variation in costs is not significant for any of the four arms. To some extent, outcomes do vary. For three of the four arms, variation across sub-groups is significant at the .05 level. For symptomatology, variation across comorbidity subgroups is significant only for community care.

Table 1 about here --

Figure 1 provides the CEAC for the analyses in Jensen et al.(in press)\textsuperscript{11}. As mentioned above, the specific outcome in that study involved the reduction of core ADD symptoms (as reported by parents and teachers) below a clinically significant threshold. This figure and the ones that follow were generated using STATA\textsuperscript{37}. For each value of lambda, the net health benefits were calculated for each individual. This tabulation involved a simple function of the improvement they experienced multiplied by lambda, and from this figure, costs were subtracted. Then using bootstrapping (with 500 replications) the probability that a given treatment had the highest net benefits was calculated for each arm.

Figure 1 about here --

One can see that at very low levels of willingness to pay, assessment and referral is the best option. This finding makes sense—in an extreme case, where the policy maker does not value the outcome at all, the best option is the least costly. In this case, assessment and referral represented community care involving medication treatments delivered at fairly low doses with
little follow-up or coordination of care\textsuperscript{10}. One can see that at a modest level of willingness to pay, the more intensive MedMgt strategy is the best option. Finally, as Jensen et al. (in press)\textsuperscript{11} report, at higher levels of willingness to pay, the combination treatment is the treatment arm with the highest probability of being cost-effective. (The Beh treatment alone is never cost-effective (at the 14-month treatment endpoint). This finding is consistent with that treatment being “dominated”—other treatments are more effective and less costly.\textsuperscript{38})

The CEAC, however, adds insights that are not apparent in the original, ratio-based cost-effectiveness analysis. For example, in a traditional ICER framework, whether the policy maker’s WTP is $20,000 or $40,000 matters relatively little—in either case, the best choice is medication management. However, the CEAC reveals that the amount of uncertainty is substantially greater in the later case—indeed, the data provide no real basis for choosing between combination therapy and medication management.

Figure 2 shows the CEAC for the CIS for all study participants. The outcome in this case is a continuous variable—the WTP figures correspond to a one standard deviation improvement in functioning. This figure is quite consistent with figure 1. At modest levels of willingness to pay, MedMgt is nearly certain to be cost-effective. At somewhat higher levels of willingness to pay, Comb therapy becomes cost-effective. Beh therapy alone is again dominated.

– Figure 2 about here --

Neither figure 1 nor 2 accounts for the variation in outcomes (and costs) across co-morbid sub-groups. Figure 3, however, provides CIS CEAC across the four sub-groups. One can see striking differences across the four sub-groups. While MedMgt appears cost-effective at all levels of willingness to pay for ADHD-only children, the picture changes for ADHD-Anx
children: Beh may be cost-effective choice at higher levels of willingness to pay. Likewise, for youth with ADHD and comorbid CD/ODD-only, MedMgt may be cost-effective choice at low levels of willingness to pay, but Comb may be the more likely cost-effective choice at higher levels of willingness to pay. And for ADHD+CD/Anx youth, medication management is the only treatment arm with a reasonable probability of being cost-effective but that occurs only at very low levels of willingness to pay.

– Figure 3 about here --

DISCUSSION

These analyses generate several important insights into the choices that a policy maker may face when deciding how to use scarce health care dollars to improve health outcomes for children with ADHD. First, note that a simple comparison of the CEAC analyses in Figure 1 based on a composite symptom scores yields very similar findings to a measure of overall functioning (figure 2). While the Columbia Impairment Scale is not a measure of quality of life per se, it does take into account the parents’ perceptions of the child’s functioning across all major areas of the child’s life—home, school, and peer functioning—likely to be salient and meaningful to parents/consumers.

Second, our analyses showed the cost-effective treatment varies as a function of the child’s comorbidity and of the policy-maker’s willingness to pay. For “pure” (no comorbidity) ADHD high-quality medication care (MedMgt) appears certain to be cost-effective at all levels of willingness to pay. In contrast, for comorbid children, willingness to pay is critical: the policy-maker who is willing to pay only a little likely will judge Med Mgt cost-effective. On the other hand, a policy maker willing to pay more now to avert future costs (involving, for example,
juvenile justice), may recognize that the most cost effective choice likely involves behavior therapy, either with or without medications (depending on the comorbidity – cf. Fig. 3).

These analyses also indicate that in instances of doubly comorbid ADHD (with both anxiety-depression and conduct/oppositional disorders), the policy-maker faces considerable uncertainty. For these complex cases, the likelihood of making a cost-effective choice falls dramatically: a policy-maker willing to pay $30,000 or more has at best a 50-50 chance of making a cost-effective choice when opting for Comb interventions. Alternatively, for the policy-maker willing to pay $10,000 for high quality medication management (MedMgt), the likelihood of making a cost-effective choice is high (above 80%), but this probability falls dramatically if the policymaker is hoping for cost-savings greater than that.

Similar to the findings of the original report by Jensen et al., these findings suggest that under many (but not all) circumstances, high quality medication management offers the policy maker a reasonable chance of making a cost-effective choice, but in instances of specific comorbidities and at higher levels of willingness to pay, intensive behavior therapy (for ADHD/Anx children) and combined treatments (for ADHD with CD/ODD) may be cost-effective. Our findings demonstrate that high costs alone do not rule out cost-effectiveness; however, such treatments may be more likely to be cost-effective when carefully targeted. Future studies must address whether these findings apply to longer-term follow-up periods, other types of outcomes, or other patient subgroups or risk profiles.
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Figure 1. Cases Normalized (Symptomatology)

MTA data
Figure 2. Improved Functioning

Policy Maker’s Willingness To Pay

% Chance Best option

MTA data
Figure 3. Improved Functioning by Comorbidity Status

Graphs by comorbidity
References


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All data were collected under the approval of the Institutional Review Boards for the Institutions involved.