Pharmacotherapies for Attention-Deficit/Hyperactivity Disorder: Expected-Cost Analysis

Albert Marchetti, MD,[1] Raf Magar, BSc,[1] Helen Lau, MS,[1] Erin L. Murphy, MS,[1] Peter S. Jensen, MD,[2] C. Keith Conners, PhD,[3] Robert Findling, MD,[4] Elliot Wineburg, MD,[5] Isabel Carotenuto, MD,[6] Thomas R. Einarson, PhD,[7] and Michael Iskedjian, MSc[8]

[1]Health Economics Research, Secaucus, New Jersey, [2]Department of Child Psychiatry, Columbia University, Center for the Advancement of Children's Mental Health, New York, New York, [3]Department of Psychiatry, Duke University Medical Center, Durham, North Carolina, [4]Department of Psychiatry, Case Western Reserve University, Cleveland, Ohio, [5]Private Practice, New York, New York, [6]Department of Pediatrics, University of Medicine and Dentistry of New Jersey, Newark, New Jersey, [7]Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada, and [8]Pharmaceutical Regulatory Affairs Program, Seneca College, Toronto, Ontario, Canada

ABSTRACT

Background: Attention-deficit/hyperactivity disorder (ADHD) is a common childhood neurobehavioral disorder characterized by inattention, hyperactivity, and impulsivity. Prevalence estimates in elementary school children generally range from 3% to 8%. ADHD is frequently treated with psychostimulant medications, which have been shown to improve both cognitive and behavioral outcomes for most children.

Objective: The goal of this study was to estimate the total expected costs for the treatment and management of school-age children with ADHD using 6 commonly prescribed pharmacotherapies: methylphenidate immediate-release/extended-release (MPH IR/ER), methylphenidate immediate-release (MPH IR), Metadate® CD (branded MPH IR/ER), Concerta™ (branded MPH ER), Ritalin® (branded MPH IR), and Adderall® (a combination of dextroamphetamine and amphetamine salts).

Methods: A literature review and clinical assessment using a 27-question survey instrument were used to capture information on the clinical characteristics of ADHD, including common treatment regimens, clinical management of patients, pathways of care, and components of care. A meta-analysis provided response rates for 3 commonly used pharmacotherapies: Metadate CD, MPH IR, and Adderall. Information from the clinical assessment and the meta-analysis were used to populate a decision-analytic model to compute total expected cost for each comparator.

Presented in part at the 13th Annual Academy of Managed Care Meeting, Tampa, Florida, April 18–21, 2001.

Accepted for publication September 18, 2001.

0149-2918/01/$19.00

Results: The average total annual expected cost per patient was $1487 for Metadate CD, $1631 for Concerta, $1792 for MPH IR/ER, $1845 for MPH IR, $2080 for Ritalin, and $2232 for Adderall.

Conclusions: Metadate CD had the lowest total expected cost and Adderall had the highest total expected cost among the ADHD pharmacotherapies evaluated. The differences were attributable to differences in drug-acquisition costs and the need for in-school dosing of twice-daily and thrice-daily medications.

Key words: attention-deficit/hyperactivity disorder, psychostimulants, economic, methylphenidate, amphetamine. (*Clin Ther.* 2001;23:1904–1921)

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder and one of the most prevalent chronic health problems affecting school-age children in the United States. Symptoms include inattention, hyperactivity, and impulsivity.[1,2] Academic underachievement,[3] troublesome relationships with family members or peers,[4,5] and low self-esteem are noted often among children with ADHD. Symptoms that appear early in life may continue into adolescence[6] and adulthood[7]; however, with early recognition, assessment, and management, educational and psychosocial problems can be minimized for most children.[8,9]

Reported prevalence rates for ADHD vary considerably, possibly because of methodological differences among studies and changes in diagnostic criteria.[10–13] The use of formal criteria to diagnose ADHD (eg, the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [*DSM-IV*][13]) varies among primary care, psychiatry, and nonphysician mental health providers.[14] As a result, over the past 20 years, the reported prevalence of ADHD has ranged from 4% to 12%, or from 8% to 10%, if studies are pooled.[10–13] Prevalence rates are 9.2% (range, 5.8%–13.6%) in male populations and 2.9% (range, 1.9%–4.5%) in female populations[15–26]; or 6.9% (range, 5.5%–8.5%) in school populations and 10.3% (range, 8.2%–12.7%) in community settings.

Public awareness of ADHD has paralleled the media debate concerning diagnostic processes and the appropriateness of stimulant therapies.[27] The increase in stimulant prescriptions for children has been cited as evidence of potential overdiagnosis of ADHD.[28] In addition, surveys of pediatricians and family physicians reveal wide regional variations in the amount of stimulants prescribed and practice patterns for diagnosis.[29,30] However, a search of the MEDLINE, Embase, and Cochrane databases revealed few published studies on the economic burden of ADHD on parents or on the health care system in general.[31,32] These 2 economic studies[31,32] evaluated health care costs in general for children with ADHD, but not the costs of treatment for ADHD. The goal of this evaluation was to assess the direct costs associated with the pharmacologic treatment of school-age children with ADHD and not indirect costs such as parents' time lost from work or long-term costs to society. This health economic evaluation sought to identify and compare the total expected costs associated with 6 pharmacotherapies used for the management of ADHD: methylphenidate immediate-release/extended-release (MPH IR/ER), methylphenidate

immediate-release (MPH IR), Metadate®* CD (branded MPH IR/ER), Concerta™† (branded MPH ER), Ritalin®‡ (branded MPH IR), and Adderall®§ (a combination of dextroamphetamine and amphetamine salts). These therapies were chosen by virtue of their classification as currently available psychostimulants in the US formulary (generic and branded forms) of first-line medications approved by the US Food and Drug Administration (FDA) for the treatment of ADHD. Other medications used to treat ADHD (eg, pemoline, desipramine, bupropion) were not included because they are rarely used (National and Therapeutic Drug Index, IMS Health, 2000), are not considered first-line treatments for ADHD, and with the exception of pemoline, are not approved by the FDA for ADHD. The evaluation was conducted from the payer perspective. School-related costs were included based on results from a stakeholder survey of managed care organizations (MCOs) that indicated that payers were concerned with costs associated with dosing of medications at school.

MATERIALS AND METHODS

A stakeholder survey of MCOs was conducted to accurately identify attributes for model development. The telephone survey included questions about each plan's policies regarding generic use, formulary inclusion, coverage for mental health care professionals, and the plan's interest in educational/societal costs.

A 27-item survey created to assess clinical practice was sent to 5 recognized clinical experts (who regularly treat children with ADHD in their practices) for feedback on treatment pathways and the human and material resources dedicated to patient care. Responses were pooled and analyzed, and discrepancies were resolved through follow-up discussions with experts. Using survey results, a clinical algorithm for ADHD management was developed and returned to experts for face validation or modification (Figure 1). On approval by the experts, the algorithm was adopted as the analytic framework for an economic model to compute total expected costs.

Components of Care and Cost

Components of clinical care (office visits, laboratory tests, and therapeutic interventions) identified in the survey were each assigned a monetary value. Cost data for physician visits and laboratory tests were taken from the 2001 National Physician Fee Schedule and the 2001 Clinical Diagnostic Laboratory Fee Schedule, respectively (Table I). Drug-acquisition costs were based on average wholesale prices listed in the April *2001 Drug Topics® Red Book®*[33] (Table II). For Concerta and Metadate CD, weighted average daily dose in milligrams was computed based on clinical trial data (Table II).[34,35] Dosages for the other pharmacotherapies were based on information from the respective manufacturers' product package inserts.

Costs associated with dosing at school were derived from a telephone survey of 8 public elementary schools in 4 randomly

*Trademark: Metadate® CD (Celltech, Rochester, New York).

†Trademark: Concerta™ (Alza Pharmaceuticals, Mountain View, California).

‡Trademark: Ritalin® (Novartis Pharmaceuticals, East Hanover, New Jersey).

§Trademark: Adderall® (Shire US Inc, Florence, Kentucky).

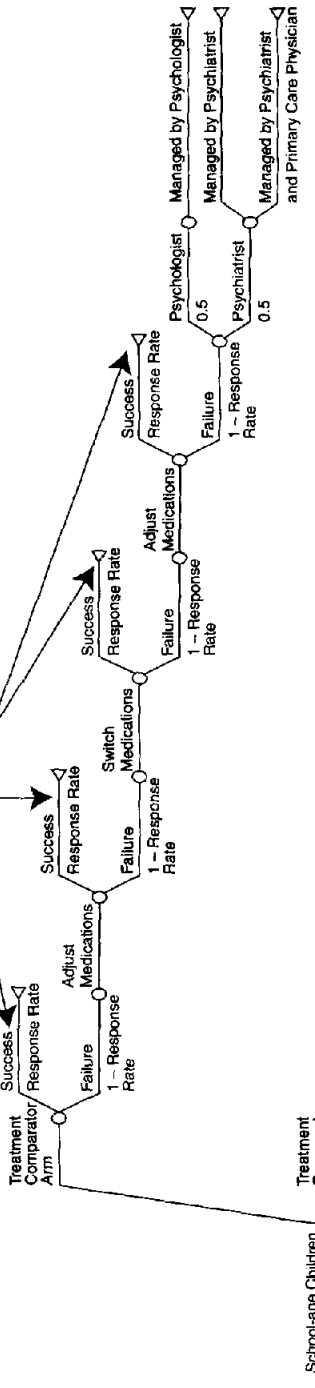

Figure 1. Economic model of pharmacologic treatment of attention-deficit/hyperactivity disorder. The economic model is depicted with 1 comparator treatment arm expanded as an example; all treatment comparator arms are identical.

Table I. Costs for medical contacts and laboratory tests.

	Cost of Initial Assessment*	Frequency	Cost of Follow-up Visits*	Frequency
Pediatrician	$167.57 $117.07 (second visit)	2 visits per month	$78.81	1 visit per 4 months
Psychiatrist	$151.50	2 visits in month after 4 failures	$100.62	1 visit per 4 months (if required)
Psychologist	$90.00	2 visits in month after 4 failures	$90.00	1 visit per 4 months (if required)
Laboratory tests†	$17.87	1 time with first visit	$17.87	1 time per year; 2 times if >4 failures

*Source: 2001 National Physician Fee Schedule.
†Source: 2001 Clinical Diagnostic Laboratory Fee Schedule.

Table II. Drug costs for commonly used pharmacotherapies for attention-deficit/hyperactivity disorder.

Drug Comparator	Manufacturer	Dose	Cost per 100 Tablets*	Cost per Day
Metadate CD	Celltech	40.8 mg† QD	$115.60‡	$2.36§
MPH IR/ER	Superior/Mallinckrodt	20 mg QD/20 mg QD	$63.53/$111.95	$1.75
MPH IR	Superior	20 mg TID	$63.53	$1.91
Concerta	Alza	39.6 mg† QD	$234.00‖	$2.77§
Ritalin	Novartis	20 mg TID	$85.78	$2.57
Adderall	Shire	20 mg BID	$154.20	$3.08

MPH = methylphenidate; IR = immediate-release; ER = extended-release.
*April *2001 Drug Topics® Red Book®*.[33]
†Weighted dose based on clinical trial data.[34,35]
‡Pricing of Metadate CD provided by Celltech.
§Weighted dose was multiplied by cost per milligram to yield cost per day.
‖*PriceAlert*, May 2001.

selected states (Idaho, Oregon, Utah, and Washington, 2 schools per state) and were included in the model for those pharmacotherapies requiring a midday dose. The schools were randomly selected based on their willingness to respond to survey questions. Respondents included school nurses or members of office staff for schools without a full-time nurse. Collected data included the number of students at each school, the number of children with ADHD requiring midday dosing of medication, and detailed information about the process each school uses to administer medication. These data were used to provide a per-child cost estimate for time spent by school personnel on tasks related to storage, preparation, paperwork, and actual administration of medication, as well as the training of personnel.

Literature Review

The initial literature search of the MEDLINE, Embase, and Cochrane databases yielded a total of 410 articles for consideration in the meta-analysis. Search terms included ADHD or attention-deficit/hyperactivity disorder, methylphenidate, amphetamine or dextroamphetamine, and trial or study. All 410 articles identified by the literature search were reviewed and assessed by 2 independent reviewers (T.R.E. and M.I.) for inclusion in the meta-analysis based on adherence to the following criteria: randomized controlled trial, confirmed diagnosis of ADHD, appropriate drug comparator, children and/or adolescent study participants, no comorbidities, and reported outcome measure. Discrepancies were settled through consensus.

Meta-Analysis

Probabilities of clinical success, failure, and related information were derived from a meta-analysis of the contemporary medical literature in the MEDLINE, Embase, and Cochrane databases. Data derived in the analysis were incorporated into the model to weight all outcomes and related costs and ultimately to compute a total per-patient expected cost for each comparator. Because the model required probability data expressed as the proportion of treated patients who responded to treatment, which is not normally reported in studies of ADHD, a stepped approach to data analysis and synthesis was employed.

First, an effect size (ie, Cohen's d)[36] for each outcome within each study was calculated by taking the group mean at end point for each outcome minus the corresponding mean for the placebo group at end point divided by the pooled standard deviation for those data. Second, Tukey's jackknife method[37] was used to calculate an overall effect size for each study. The mean of all effect sizes from all studies was calculated. This mean was then recalculated, omitting each study in turn, to give a set of individual effect sizes. These effect sizes were then weighted by the number of studies and subtracted from the overall mean, which provides an effect size that represents the true overall effect of the drug, regardless of outcome measure. Third, effect sizes were combined using a random-effects model to determine the area under the curve for each drug comparator, thereby providing an estimate of the underlying response rate. Such methods and analyses are widely accepted and commonly employed in similar circumstances.[38]

Economic Model

One comparator arm of the economic model is presented in Figure 1. Branches emanating from each comparator arm were identical for all comparators. Total expected cost for each comparator arm was derived by summing costs associated with each treatment branch (drug-acquisition cost, physician visits, laboratory tests, and in-school dosing costs for twice-daily and thrice-daily pharmacotherapies) and weighting that total by the probability (response rate) associated with that branch. The costs for each branch were then summed to give the total expected cost for treatment with that comparator. The number, frequency, and type of physician visit varied depending on the specific treatment branch (Table I).

RESULTS

Representatives of MCOs who were surveyed indicated that both the payer and the societal perspective were important in an economic model of treatments for ADHD, and that they would like to see an economic model that included costs associated with treatment at school.

Ten articles were deemed acceptable by reviewers for data extraction and analysis.[39–48] The principal reasons for excluding articles were inappropriate outcome measure, inappropriate study design, inappropriate disease condition, inappropriate patient population, and unextractable data. Computed response rates are presented in Table III. There were no statistically significant differences among response rates for any comparators, as indicated by overlapping 95% CIs. For 3 of the comparators, adequate trial data were not available for meta-analytic purposes; response rates for these 3 comparators were derived from existing data to provide a relative estimate of the total expected cost for all commonly used pharmacotherapies. The response rates for Ritalin and MPH IR/ER were assumed to be similar to those for MPH IR (78.7% as computed in the meta-analysis). To estimate the response rate for Concerta, the mean of response rates for Metadate CD, Adderall, and MPH IR were used.

Table III. Response rates with drugs for attention-deficit/hyperactivity disorder.*

Drug	Metadate CD†	MPH IR‡	Adderall‡
No. of patients	119	965	21
No. of studies	1	13	1
Mean response rate	80.6%	78.7%	82.7%
95% CI	73.5%–87.7%	74.7%–82.4%	66.5%–98.9%
SD	4.44	2.50	10.13
Variance	19.69	6.25	102.52

MPH IR = methylphenidate immediate-release.
*Includes only those drugs for which response rates could be determined from the meta-analysis.
†Data derived from Celltech Trial M-0014.[35]
‡Estimated based on meta-analysis.

The clinical assessment survey provided information on the nature, frequency, and duration of medical contacts, the nature and frequency of laboratory testing, and the pathways of care in clinical practice. Although practice patterns vary widely,[30] the clinical assessment provided an estimate of the frequency of medical contacts. For example, once a diagnosis of ADHD is confirmed, a treating physician may see a juvenile patient twice during the first month and once every 4 months thereafter, if the child is controlled with the prescribed medication. More frequent follow-up is required if adequate control is not achieved or adverse events occur, and the dosage must be adjusted. Alternatively, if a child continuously fails to respond to medication, contact with a psychologist and/or psychiatrist is likely. The economic model applies frequency of medical contacts equally across all comparators.

Response rates computed by meta-analysis were based on clinical trials with varying lengths of treatment and evaluation. The evaluation period chosen for the model was 4 weeks, based on expert input for the average time used to evaluate response to medications. Children who responded adequately to medication by the end of 4 weeks were considered treatment responders. An assumption of the model was that if children who responded to treatment continued on the medication, they would continue to respond for the 1-year period. If a child did not respond by the end of 4 weeks (or experienced adverse events related to the medication), we assumed that the dose would be adjusted in clinical practice and the child would be reevaluated after 4 weeks. If once again the child did not respond, he or she would be reevaluated and the medication would be switched. If after 4 evaluations (1 evaluation period = 4 weeks) a child still had not responded, we assumed that he or she would require psychological and/or psychiatric interventions (Figure 1) in addition to primary ADHD care.

Based on these clinical scenarios (Figure 1) and the cost of consumed resources through all pathways of care (Tables I and II), the average total annual per-patient expected cost ranged from $1487 (Metadate CD) to $2232 (Adderall) (Table IV).

All comparators except Metadate CD and Concerta require a midday dose, which would normally be administered at school. Based on the in-school dosing survey, 88% of schools had an office staff member administer medication and 12% had a school nurse perform this task. The weighted average total annual cost for this

Table IV. Total annual, per-patient expected cost of pharmacotherapies for attention-deficit/hyperactivity disorder.*

Pharmacotherapy	Total Expected Cost
Metadate CD	$1487
Concerta	$1631
MPH IR/ER	$1792
MPH IR	$1845
Ritalin	$2080
Adderall	$2232
Medicaid†	$1795

MPH = methylphenidate; IR = immediate-release; ER = extended-release.

*These data were derived from the economic model, using response rates (Table III), costs associated with treatment (Table I), and drug-acquisition costs (Table II).

†Average reimbursement for total treatment costs (including medications) for a child with attention-deficit/hyperactivity disorder (Centers for Disease Control and Prevention Developmental Disabilities Branch, 1999).

task (including maintaining inventory and paperwork as well as preparation and administration of medication) was $531 per child, which includes a $35 training cost (Table V). This additional cost contributed to the total expected cost for all comparators except Metadate CD and Concerta, which are administered once daily.

Sensitivity Analyses

Rank-order sensitivity analyses were used to test the robustness of study findings and assess the impact of key variables on study results, specifically, the rank order of products according to their related expected costs. Because Metadate CD had the lowest total annual per-patient expected cost and the highest ranking among the 6 comparators, it was compared to MPH IR, which had the lowest drug-acquisition cost per tablet. Based on the sensitivity analysis, expected cost parity is achieved if the acquisition cost of MPH IR is reduced 54%, from $0.65 to $0.30 per tablet, which is unlikely (Figure 2). Consequently, the ranking of Metadate CD is considered to be stable in this regard. Another important variable for total expected cost is in-school dosing, which would have to decrease from $531 to $216, or 59%, before MPH IR/ER and Metadate CD reach parity in terms of total expected annual cost (Figure 3). The potential for this reduction is low, because the cost estimate used for in-school dosing in the analysis is already considered to be conservative. For example, in our model, the time allotted for in-school dosing was 12 minutes per day. However,

Table V. Cost estimate for in-school dosing of medication for attention-deficit/hyperactivity disorder (ADHD).

Cost	Proportion of Children*	Annual Cost per Child†	Weighted Cost‡
School nurse	0.12	$875	$105
Office staff	0.88	$444	$391
Training cost§	NA	$35	NA
Total cost‖	NA	$531	NA

*Of the 8 schools surveyed to evaluate how medication is dispensed, 12% used nurses to dispense ADHD medication, and 88% used office staff members.

†Based on the survey, the tasks involved with in-school dosing of ADHD medication include medication inventory, paperwork, communication with parents/physician, state-required locked storage of medication, dispensing medication, and finding the child if he/she forgets to come for the medication. On average, the person dispensing the medication spends ~1 hr/wk per child multiplied by the total number of weeks in a school year (36 weeks). The annual cost per child is based on the individual's compensation (annual salary for nurse [$35,000]) and an hourly rate for an office staff person ($12/hr) multiplied by the total time spent per child.

‡Weighted cost is the annual cost per child, weighted by the proportion of schools using a nurse versus an office staff member for dispensing medication.

§Training costs are based on the salary of the district nurse ($50,000 annually), for 2 days ($555) of training per school. Costs for training materials are not included. Dividing this total by the mean number of children with ADHD per school (16) yields a per-child training cost of $35.

‖The total cost of in-school dosing per child equals the weighted average cost of personnel salary ($105 + $391) plus the per-child training cost ($35), for a total of $531.

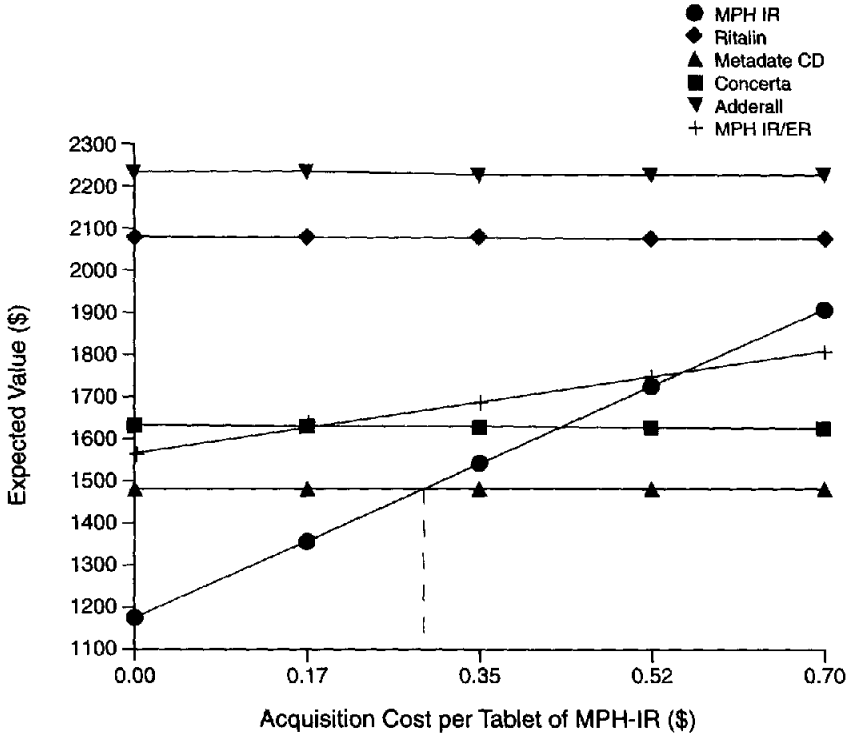

Figure 2. Sensitivity analyses for methylphenidate immediate-release (MPH IR) and Metadate CD. Expected values are shown for each comparator if the acquisition cost of MPH IR is varied. The total expected cost of MPH IR would reach parity with Metadate CD if its acquisition cost were reduced from $0.65 to $0.30 per pill (vertical dashed line), a 54% reduction. MPH = methylphenidate; IR = immediate-release; ER = extended-release.

based on the school survey, in-school dosing of ADHD pharmacotherapy involved not only administration of the drug but also various other tasks, including finding the child in the school, taking inventory of the drugs, keeping the drugs secured at all times (as required for a class II substance), notifying parents about the need for refills, and completing paperwork. These tasks are likely to require >12 minutes per day. In addition, based on survey results, only 12% of children were administered these drugs by a school nurse. A recent report from the US General Accounting Office[49] indicates that nationwide, 60% of schools use a school nurse to administer ADHD medications and 40% use an office staff member. If nationwide, the proportion of schools using a nurse is >12%, then the contribution of their higher salaries to the total cost of ADHD treatment would increase.

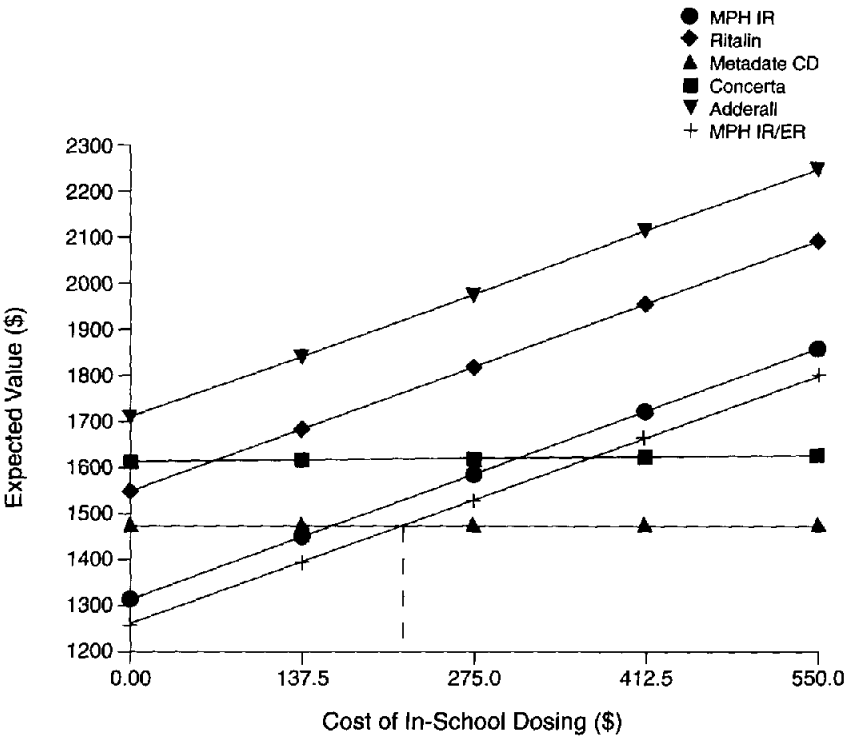

Figure 3. Sensitivity analyses for in-school dosing. Expected values are shown for all comparators if the cost of in-school dosing is varied. Metadate CD retains its ranking as the comparator with the lowest expected cost until the cost of in-school dosing is reduced from $531 to $216 (vertical dashed line), a 59% reduction. MPH = methylphenidate; IR = immediate-release; ER = extended-release.

Table VI indicates the reductions in drug-acquisition cost required for each comparator to reach parity with Metadate CD. In terms of effectiveness, all comparators were evaluated to estimate the change required to reach parity with Metadate CD. The results are presented in Table VII. Overall, the change in response rates would have to be substantial for Metadate CD to lose its ranking. For example, the response rate of Metadate CD must be reduced from 80.6% to 58.9% (a decrease of 21.7%) for the drug to drop in rank order for the lowest expected cost.

When the total per-patient expected annual costs reported in Table IV are applied to ADHD prevalence data, the total expected cost for all pediatric patients in the United States ranges from ~$2 billion to ~$11 billion (Table VIII).

Table VI. Threshold analyses for drug-acquisition costs.*

Drug Comparator	Cost per Day	Cost per Day Required to Reach Parity with Metadate CD	Reduction Required to Reach Parity with Metadate CD (%)
Concerta	$2.77	$2.40	13
MPH **IR**/ER†	$1.12	<0.00	>100
MPH IR/**ER**‡	$1.12	$0.25	77
MPH IR	$1.92	$0.90	53
Ritalin	$2.58	$0.90	65
Adderall	$3.08	$1.84	40

MPH = methylphenidate; IR = immediate-release; ER = extended-release.
*Threshold analyses indicate price point at which comparator reaches expected-cost parity with Metadate CD.
†IR drug-acquisition cost changed only.
‡ER drug-acquisition cost changed only.

DISCUSSION

Although an increase in stimulant use in children has been cited as evidence of overdiagnosis of ADHD,[50] epidemiologic research indicates that only ~12% of children diagnosed with ADHD are being treated with pharmacotherapies.[51,52] The increase in stimulant prescriptions is most likely due to an improved understanding of the disorder and its subtypes; therefore, more children are receiving appropriate diagnoses and treatment. If the long-term consequences of untreated ADHD could be prevented with efficacious treatment, the indirect costs to society might decrease. The total expected cost reported in this analysis is from the payer perspective. From the societal perspective, however, the current analysis likely underesti-

Table VII. Threshold analyses for response rates.*

Comparator	Increase in Response Rate Required to Reach Parity with Metadate CD (%)	Reduction in Response Rate Required for Metadate CD to Reach Parity with Comparators (%)
Metadate CD	0	0
Concerta	>100	–22
MPH IR/ER	>100	–38
MPH IR	>100	–42
Ritalin	>100	–59
Adderall	>100	–70

MPH = methylphenidate; IR = immediate-release; ER = extended-release.
*Threshold analyses indicate the percent change required for each comparator to reach expected-cost parity with Metadate CD.

Table VIII. Total expected cost of pharmacologic treatment of attention-deficit/hyperactivity disorder (ADHD) based on population estimates.

Pharmacotherapy	Expected Cost	No. of ADHD Patients (millions)*	Total Expected Cost (billions)†	Expected Incremental Spending (millions)‡
Metadate CD	$1487	1.8–4.9	$2.66–$7.29	$0
Concerta	$1631	1.8–4.9	$2.94–$7.99	$259–$706
MPH IR/ER	$1792	1.8–4.9	$3.23–$8.78	$549–$1494
MPH IR	$1845	1.8–4.9	$3.32–$9.04	$644–$1754
Ritalin	$2080	1.8–4.9	$3.74–$10.19	$1067–$2905
Adderall	$2232	1.8–4.9	$4.02–$10.94	$1341–$3650

MPH = methylphenidate; IR = immediate-release; ER = extended-release.
*Based on US Census 2000 data.[55]
†Computed by multiplying a conservative ADHD prevalence estimate of 3% to 8% by the number of children in the US population, according to US Census 2000 data.[55]
‡Computed by subtracting the range of total expected cost for each comparator from the range of total expected costs for Metadate CD.

mates the total cost of ADHD, because indirect costs such as time lost from work for parents, class disruption, and social problems related to drug abuse, alcohol abuse, and criminal activities were not included. The expected costs from the current analysis are consistent with Medicaid reimbursement claims (including drug costs) used to estimate annual direct costs for treatment of ADHD ($1795).[53]

In our analysis, the total expected cost of pharmacological treatment of ADHD ranged from ~$2 billion to ~$11 billion. Others have estimated these costs at $3 billion.[54] Thus, the differences in expected cost among products can lead to impressive cost savings or incremental spending at the national level. Between 1.8 and 4.9 million children[55] in the United States have ADHD and may require pharmacotherapy. By applying these numbers to the total expected costs for drug comparators in this study, incremental spending can be estimated. For example, according to our analysis, expected incremental spending related to generic MPH IR (acquisition cost of $1.91/d) compared with Metadate CD (acquisition cost of $2.36/d) would range from $259 million to $706 million. This expected incremental spending associated with generic MPH IR underscores the need to evaluate competitive interventions beyond their acquisition costs and to consider other resource consumption, clinical success rates, and compliance issues related to each alternative.

Although compliance was not included as a variable in the current expected cost analysis, previous research in other therapeutic areas has demonstrated that once-daily dosing has a compliance benefit over twice-daily or thrice-daily dosing.[56] To assess the possible impact of dosing schedule on compliance, 3 scenarios were evaluated for all comparators except Metadate CD and Concerta. For those pharmacotherapies requiring >1 dose per day, expected cost was recalculated, assuming that lowered compliance resulted in reduced efficacy. For example, if we assume that reduced compliance results in a 25%

reduction in efficacy, the total expected cost of treatment with Ritalin would increase from $2080 to $2190 per year, and the cost for MPH IR/ER would increase from $1792 to $1945 per year. This increased total expected cost is not observed with Metadate CD or Concerta, because compliance should be greater with drugs dosed once daily than with drugs dosed 2 or 3 times daily. These results suggest that although acquisition cost may be lower (eg, generic methylphenidate) and efficacy might be slightly higher (eg, Adderall), lack of compliance may result in higher total expected costs.

It should be noted that while school-related costs for management of ADHD are not borne by payers, we included them in our model based on input from payers who noted the importance of such factors and other quality-of-life variables that affect parents' and teachers' management of ADHD. The sensitivity analysis shown in Figure 3 reflects computations of total expected costs with and without the school-related expenses.

CONCLUSIONS

Among the 6 pharmacotherapies evaluated, Metadate CD had the lowest total expected cost, and Adderall had the highest total expected cost. These differences were attributable to differences in drug-acquisition costs and the necessity for in-school administration of pharmacotherapies that are dosed 2 or 3 times daily. Additional savings may be realized with a once-daily regimen versus a twice-daily or thrice-daily regimen because a midday dose is not required, potentially contributing to improved compliance. However, it should be noted that the costs for the treatment of ADHD, when accompanied by complex comorbidities, are likely to vary substantially from the costs computed herein for the management of a typical case. Elucidation of the impact of comorbid conditions on the costs of care must await future analyses.

Overall findings indicate that the likely true costs associated with the treatment of ADHD may be reduced by once-daily dosing regimens. Other factors, such as the need for parents to take time off from work to assist in the administration of medication at school, as is sometimes required, are not considered in our computed costs of treatment. If they were, such factors likely would further contribute to the differential cost-effectiveness of once-daily dosing regimens. Although beyond the scope of this report, issues such as parental convenience, preference, and other quality-of-life variables may be important additional considerations in the selection of cost-effective pharmacotherapy for ADHD in medication formularies.

ACKNOWLEDGMENTS

This study was supported by a research grant from Celltech, Rochester, New York. Research was conducted at Health Economics Research, Secaucus, New Jersey.

REFERENCES

1. Reiff MI, Banez GA, Culbert TP. Children who have attentional disorders: Diagnosis and evaluation. *Pediatr Rev.* 1993; 14:455–465.

2. Barkley R. *Attention Deficit Hyperactivity Disorder: A Handbook for Diagnosis and*

Treatment. 2nd ed. New York, NY: Guilford Press; 1996.

3. Zentall S. Research on the education implications of attention deficit hyperactivity disorder. *Exceptional Child.* 1993;60: 143–153.

4. Schachar R, Taylor E, Wieselberg M, et al. Changes in family function and relationships in children who respond to methylphenidate. *J Am Acad Child Adolesc Psychiatry.* 1987;26:728–732.

5. Almond B Jr, Tanner J, Goffman H. *The Family Is the Patient: Using Family Interviews in Children's Medical Care.* 2nd ed. Baltimore, Md: Williams & Wilkins; 1999.

6. Biederman J, Faraone S, Milberger S, et al. Predictors of persistence and remission of ADHD into adolescence: Results from a four-year prospective follow-up study. *J Am Acad Child Adolesc Psychiatry.* 1996;35:343–351.

7. Biederman J, Faraone SV, Spencer T, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *Am J Psychiatry.* 1993;150: 1792–1798.

8. Baumgaertel A, Copeland L, Wolraich M. Attention deficit hyperactivity disorder. In: *Disorders of Development and Learning: A Practical Guide to Assessment and Management.* 2nd ed. St. Louis, Mo: Mosby Yearbook, Inc; 1996:424–456.

9. Cantwell DP. Attention deficit disorder: A review of the past 10 years. *J Am Acad Child Adolesc Psychiatry.* 1996;35:978–987.

10. *Diagnostic and Statistical Manual of Mental Disorders, Second Edition.* Washington, DC: American Psychiatric Association; 1967.

11. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition.* Washington, DC: American Psychiatric Association; 1980.

12. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.* Washington, DC: American Psychiatric Association; 1987.

13. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.* Washington, DC: American Psychiatric Association; 1994.

14. Sloan M, Jensen P, Kettle L. Assessing services for children with ADHD: Gaps and opportunities. *J Attention Disorders.* 1999;3:13–29.

15. August GJ, Garfinkel BD. Behavioral and cognitive subtypes of ADHD. *J Am Acad Child Adolesc Psychiatry.* 1989;28:739–748.

16. August GJ, Realmuto GM, MacDonald AW III, et al. Prevalence of ADHD and comorbid disorders among elementary school children screened for disruptive behavior. *J Abnorm Child Psychol.* 1996;24: 571–595.

17. Bird HR, Canino G, Rubio-Stipec M, et al. Estimates of the prevalence of childhood maladjustment in a community survey in Puerto Rico. The use of combined measures. *Arch Gen Psychiatry.* 1988;45: 1120–1126.

18. Cohen P, Cohen J, Kasen S, et al. An epidemiological study of disorders in late childhood and adolescence—I. Age- and gender-specific prevalence. *J Child Psychol Psychiatry.* 1993;34:851–867.

19. King C, Young RD. Attentional deficits with and without hyperactivity: Teacher and peer perceptions. *J Abnorm Child Psychol.* 1982;10:483–495.

20. Kuperman S, Johnson B, Arndt S, et al. Quantitative EEG differences in a nonclinical sample of children with ADHD and undifferentiated ADD. *J Am Acad Child Adolesc Psychiatry.* 1996;35:1009–1017.

21. Newcorn JH, Halperin JM, Schwartz S, et al. Parent and teacher ratings of attention-deficit hyperactivity disorder symptoms: Implications for case identification. *J Dev Behav Pediatr.* 1994;15:86–91.

22. Shaffer D, Fisher P, Dulcan MK, et al. The NIMH Diagnostic Interview Schedule for Children Version 2.3 (DISC-2.3): Description, acceptability, prevalence rates, and performance in the MECA Study. Methods for the Epidemiology of Child and Adolescent Mental Disorders Study. *J Am Acad Child Adolesc Psychiatry.* 1996;35:865–877.

23. Shekim WO, Kashani J, Beck N, et al. The prevalence of attention deficit disorders in a rural midwestern community sample of nine-year-old children. *J Am Acad Child Psychiatry.* 1985;24:765–770.

24. Green M, Wong M, Atkins D, et al. *Diagnosis of Attention-Deficit/Hyperactivity Disorder: Technical Review 3.* Rockville, Md: US Dept of Health and Human Services, Agency for Health Care Policy and Research; 1999.

25. Wolraich ML, Hannah JN, Pinnock TY, et al. Comparison of diagnostic criteria for attention-deficit hyperactivity disorder in a county-wide sample. *J Am Acad Child Adolesc Psychiatry.* 1996;35:319–324.

26. Wolraich ML, Hannah JN, Baumgaertel A, Feurer ID. Examination of DSM-IV criteria for attention deficit/hyperactivity disorder in a county-wide sample. *J Dev Behav Pediatr.* 1998;19:162–168.

27. Gibbs N. The age of Ritalin. *Time.* 1998; 152:86–96.

28. Safer DJ, Zito JM, Fine EM. Increased methylphenidate usage for attention deficit disorder in the 1990s. *Pediatrics.* 1996;98: 1084–1088.

29. Rappley MD, Gardiner JC, Jetton JR, Houang RT. The use of methylphenidate in Michigan. *Arch Pediatr Adolesc Med.* 1995;149:675–679.

30. Wolraich ML, Lindgren S, Stromquist A, et al. Stimulant medication use by primary care physicians in the treatment of attention deficit hyperactivity disorder. *Pediatrics.* 1990;86:95–101.

31. Leibson CL, Katusic SK, Barbaresi WJ, et al. Use and costs of medical care for children and adolescents with and without attention-deficit/hyperactivity disorder. *JAMA.* 2001;285:60–66.

32. Guevara J, Lozano P, Wickizer T, et al. Utilization and cost of health care services for children with attention-deficit/hyperactivity disorder. *Pediatrics.* 2001;108:71–78.

33. *2001 Drug Topics® Red Book®.* Montvale, NJ: Medical Economics Company, Inc; 2001.

34. Pelham WE, Gnagy EM, Burrows-Maclean L, et al. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. *Pediatrics.* 2001;107:E105.

35. Greenhill L. Once-daily methylphenidate modified-release (MPH MR) treatment of attention-deficit/hyperactivity disorder (ADHD). Poster presented at: 47th Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 25–28, 2000; New York, NY.

36. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* Orlando, Fla: Academic Press Inc; 1977.

37. Mosteller F, Tukey J. Data analysis, including statistics. In: Lindzey G, Aronson

E, eds. *Handbook of Social Psychology.* 2nd ed. Reading, Mass: Addison-Wesley; 1968.

38. Efron B, Gong GA. A leisurely look at the bootstrap, the jackknife, and cross-validation. *Am Statistician.* 1983;37:36–48.

39. DuPaul GJ, Rapport MD. Does methylphenidate normalize the classroom performance of children with attention deficit disorder? *J Am Acad Child Adolesc Psychiatry.* 1993;32:190–198.

40. Douglas VI, Barr RG, O'Neill ME, Britton BG. Short term effects of methylphenidate on the cognitive, learning and academic performance of children with attention deficit disorder in the laboratory and the classroom. *J Child Psychol Psychiatry.* 1986;27:191–211.

41. Tirosh E, Elhasid R, Kamah S, Cohen A. Predictive value of placebo methylphenidate. *Pediatr Neurol.* 1993;9:131–133.

42. Douglas VI, Barr RG, Amin K, et al. Dosage effects and individual responsivity to methylphenidate in attention deficit disorder. *J Child Psychol Psychiatry.* 1988;29:453–475.

43. Barkley RA, McMurray MB, Edelbrock CS, Robbins K. The response of aggressive and nonaggressive ADHD children to two doses of methylphenidate. *J Am Acad Child Adolesc Psychiatry.* 1989;28:873–881.

44. Fischer M, Newby R. Assessment of stimulant response in ADHD children using a refined multimethod clinical protocol. *J Clin Child Psychol.* 1991;20:232–244.

45. Klorman R, Brumaghim JT, Salzman LF, et al. Comparative effects of methylphenidate on attention-deficit hyperactivity disorder with and without aggressive/noncompliant features. *Psychopharmacol Bull.* 1989;25:109–113.

46. Rapport M, Jones J, DuPaul G, et al. Attention deficit disorder and methylphenidate: Group and single-subject analyses of dose effects on attention in clinic and classroom settings. *J Clin Child Psychol.* 1987;16:329–338.

47. Brown RT, Sexson SB. A controlled trial of methylphenidate in black adolescents. Attentional, behavioral, and physiological effects. *Clin Pediatr (Phila).* 1988;27:74–81.

48. Pliszka SR, Browne RG, Olvera RL, Wynne SK. A double-blind, placebo-controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2000;39:619–626.

49. *Attention Disorder Drugs: September 2001.* Washington, DC: US General Accounting Office; 2001.

50. Diller LH. The Ritalin wars continue. *West J Med.* 2000;173:366–367.

51. MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Multimodal Treatment Study of Children with ADHD. *Arch Gen Psychiatry.* 1999;56:1073–1086.

52. Jensen P. Pediatric psychopharmacology in the United States: Issues and challenges in the diagnosis and treatment of ADHD. In: Greenhill L, Osman B, eds. *Ritalin: Theory and Practice.* 2nd ed. Larchmont, NY: Mary Ann Liebert, Inc; 2000:1–3.

53. Kelleher K, Childs G, Harman J. Healthcare costs for children with attention-deficit/hyperactivity disorder. *Econ Neurosci.* 2001;3:60–63.

54. Diagnosis and treatment of attention deficit hyperactivity disorder (ADHD). *NIH Consensus Statement.* 1998;16:1–37.

55. Profiles of General Demographic Characteristics: 2000. Washington, DC: US Bureau of the Census; 2000.

56. Iskedjian M. *The Relationship Between Daily Dose Frequency and Adherence to Antihypertensive Pharmacotherapy* [master's thesis]. Toronto: University of Toronto; 1998.

Address correspondence to: Raf Magar, BSc, Senior Manager, Health Economics Research, Division of Physicians World Thompson Healthcare, 400 Plaza Drive, Secaucus, NJ 07094. E-mail: rmagar@mail.pwcg.com