The New England Comparative Effectiveness Public Advisory Council

Public Meeting – June 1, 2012

Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-risk Preschoolers & Long-term Effectiveness in All Ages

Supplementary Data and Analyses to the Comparative Effectiveness Review of the Agency for Healthcare Research and Quality

Draft Report – May 11, 2012

Completed by:

The Institute for Clinical and Economic Review

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Introduction

To make informed healthcare decisions, patients, clinicians, and policymakers need to consider many different kinds of information. Rigorous evidence on the comparative clinical risks and benefits of alternative care options is always important; but along with this information, decision-makers must integrate other considerations. Patients and clinicians must weigh patients' values and individual clinical needs. Payers and other policymakers must integrate information about current patterns of utilization, and the impact of any new policy on access, equity, and the overall functioning of systems of care. All decision-makers, at one level or another, must also consider the costs of care, and make judgments about how to gain the best value for every healthcare dollar.

The goal of this initiative is to provide a forum in which all these different strands of evidence, information, and public and private values can be discussed together, in a public and transparent process. Initially funded by a three-year grant from the federal Agency for Healthcare Research and Quality (AHRQ), and backed by a consortium of New England state policymakers, the mission of the New England Comparative Effectiveness Public Advisory Council (CEPAC) is to provide objective, independent guidance on how information from supplemented AHRQ evidence reviews can best be used across New England to improve the quality and value of health care services. CEPAC is an independent body of 19 members, composed of clinicians and patient or public representatives from each New England state with skills in the interpretation and application of medical evidence in health care delivery. Representatives of state public health programs and of regional private payers are included as ex-officio members of CEPAC. The latest information on the project, including guidelines for submitting public comments, is available online: cepac.icer-review.org.

The Institute for Clinical and Economic Review (ICER) is managing CEPAC and is responsible for developing supplementary reports to AHRQ reviews for CEPAC consideration. ICER is an academic research group based at the Massachusetts General Hospital's Institute for Technology Assessment. ICER's mission is to lead innovation in comparative effectiveness research through methods that integrate evaluations of clinical benefit and economic value. By working collaboratively with patients, clinicians, manufacturers, insurers and other stakeholders, ICER develops tools to support patient decisions and medical policy that share the goals of empowering patients and improving the value of healthcare services. More information about ICER is available at www.icer-review.org.

ICER has produced this set of complementary analyses to provide CEPAC with information relevant to clinical and policy decision-makers in New England. This supplement is not meant to revisit the core findings and conclusions of the AHRQ review on "Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment" but is intended to supplement those findings with: 1) updated information on the patient management options for attention deficit hyperactivity disorder (ADHD) published since the AHRQ review; 2) regional and national data on utilization, existing clinical guidelines, and payer coverage policies; and 3) the results of budgetary impact and cost-effectiveness analyses developed to support discussion of the comparative value of different management options. This report is part of an experiment in enhancing the use of evidence in practice and policy, and comments and suggestions to improve the work are welcome.

1. Background

1.1 The Condition

Diagnoses of Attention Deficit Hyperactivity Disorder (ADHD) have risen in recent years, and ADHD is now regarded to be a common condition among children in the United States. While reported prevalence ranges widely between 6-16% depending on location and measurement technique (Pastor, 2008; Elder, 2010; Froehlich, 2007), it has been estimated that ADHD affects at least 5 million children aged 4-17 years in the U.S. (CDC, 2010). Over 2.5 times as many boys have a diagnosis of ADHD as girls (Froehlich, 2007; Pastor, 2008), and children from lower income families are at nearly double the risk of ADHD relative to those from higher income strata (Froehlich, 2007).

Presentation of ADHD symptoms is heterogeneous, and includes various subtypes as well as related psychiatric conditions. Subtypes are primarily defined as inattentive, hyperactive-impulsive, and a combination of the two (Elia, 2009). Other common and highly correlated disorders include oppositional defiant disorder (ODD), which involves disobedient, hostile, and defiant behavior toward authority figures (A.D.A.M. Medical Encyclopedia, 2012); and conduct disorders , which are often more serious and involve aggression toward people or animals, destruction of property, dishonesty, and other delinquent and/or criminal behavior (Lahey, 2000). These disorders are often grouped together as disruptive behavior disorders (DBD). In addition, children with ADHD often have substantial psychiatric comorbidity, including separation or other anxiety disorders, obsessive-compulsive disorder, and major depression (Ghanizadeh, 2009).

In the long term, a diagnosis of ADHD in children has been associated with poorer outcomes in social functioning (Hodgkins, 2012), academic performance (Galéra, 2009; Hodgkins, 2012), adolescent substance abuse (Hodgkins, 2012; Molina, 2007), and delinquent behavior (Hodgkins, 2012; Molina, 2007). The economic burden of ADHD has been estimated at over $30 billion dollars annually in the US, over 10% of which can be attributed to work loss of parents caring for affected children (Birnbaum, 2005).

Given the substantial burden of ADHD for children and their families, as well as the significant long-term implications that a diagnosis of ADHD carries, there is significant interest on the part of patients, clinicians, policymakers, and other stakeholders in exploring different management options for ADHD. This supplementary report builds on the conclusions of the AHRQ review by: describing recommendations and payer coverage policies for selected behavioral and medication-based management options for ADHD; identifying any new evidence on these options published since the AHRQ review; and finally, developing a simulation model to use findings from the AHRQ review to quantify the potential clinical and economic impact to the New England region of changes in the use of various therapeutic alternatives for ADHD.

1.2 Management Options for Children with ADHD

The primary aim of treatment for ADHD is to set specific goals for behavior correction, amelioration of target ADHD symptoms, and maintenance of behavior. Treatment can involve behavioral and psychosocial interventions as well as medications. The major management options for ADHD are described in further detail below.

Behavioral/Psychosocial Interventions

A range of behavioral and psychosocial interventions have been used to try to help patients with ADHD and their families. Approaches differ by provider type, clinical target, and setting, and include parent behavior training, school-based interventions, and individual psychotherapy.

Parent Behavior Training

Parent behavior training involves individual or group training sessions which typically track progress through a training manual. Sessions generally last 1-2 hours per week over a treatment course of 8-20 weeks. Overarching objectives include management of problem behaviors and fostering of positive and caring parent-child relationships. While available programs differ somewhat in their approach, all utilize rewards and other non-punitive tools to modify child behavior. Manual-based programs known by their brand names include the Triple P – Positive Parenting Program®, The Incredible Years® parenting program, and Parent-Child Interaction Therapy (see Appendix A for further details). Other programs exist, and may be delivered through interactive materials, individual or group-based sessions in a clinic setting, or telephone-based therapy discussions.

Other Forms of Therapy

Other forms of therapy may be used for children with ADHD, including behavioral and psychosocial approaches. Behavioral therapy is comprised of techniques designed to change the physical and social environment of a child with ADHD through utilization of reward systems for positive behaviors and consequences for undesirable behaviors (Subcommittee-AAP, 2011; Rader, 2009). Psychosocial therapy addresses the emotions and thought processes involved in destructive behaviors (Subcommittee-AAP, 2001), and may consist of individual psychotherapy, play therapy, or cognitive behavioral therapy (Pelham, 1998). These therapeutic approaches may be utilized alone or as part of a multimodal program that may also include parent training, social skills training, traditional psychotherapy, and school-based interventions (see below).

School-based Interventions

Multiple school-based interventions exist for ADHD, including classroom-based special education services, individualized student training, and specialized teacher training to develop strategies of behavior modification (Antshel, 2011). Specialized classroom environments utilize teachers and aides specially trained and supervised by child psychologists, employing behavioral methods and unique treatment curriculums (Barkley, 2000). Use of communication tools such as daily school

behavior report cards facilitates communication with parents regarding behavioral trends in children (Antshel, 2011). Positive reinforcement, peer-tutoring, and organizational skills training are other school-based approaches for children with ADHD (Antshel, 2011).

Medications

Stimulants

Several stimulants are used in children of all ages for the treatment of ADHD symptoms (see Appendix B for details). FDA-approved therapies evaluated in the AHRQ review include methylphenidate (e.g., Ritalin®), dextroamphetamine (e.g., Dexedrine®) and mixed amphetamine salts (Adderall®). Methylphenidate is the oldest available medication, gaining FDA approval in 1955, followed by mixed amphetamine salts in 1960 and dextroamphetamine in the 1970s. Stimulants work to improve symptoms such as inattention, impulsivity, and hyperactivity by increasing and balancing levels of neurotransmitters in the brain (Mayo Clinic, 2011).

Each of these stimulants is now available in both short-acting and extended-release formulations, as well as in alternate dosage forms such as chewable tablets and oral solutions. Recent examples include a transdermal patch formulation of methylphenidate (Daytrana®), approved in 2006 (Drugs@FDA, 2012), as well as lisdexamfetamine (Vyvanse®), approved in 2007, which is an extended-release formulation of dextroamphetamine that requires metabolism in the body to become "activated" (Antshel, 2011). In addition to potential improved adherence, use of extended-release formulations is felt by some to reduce stigmatization and to increase confidentiality within a school environment, as children would not require assistance from the school nurse for dosing (Pliszka, 2007). Patients are generally started on low doses with slow titration and careful monitoring for efficacy and emergence of side effects.

Adverse events commonly seen with stimulant therapy include decreased appetite, weight loss, insomnia, headache and abdominal pain; in addition, development of facial tics may be seen, although these are rare and tend to disappear with reductions in dose (Rader, 2009; Mayo Clinic, 2011). Other areas of concern that have been raised and debated include potential increased risks of serious cardiovascular events and decreases in growth rates (Vitiello, 2007; Cooper, 2011; Olfson [a], 2012). Guidelines recommend that clinicians evaluate patients to rule out any underlying heart disease before beginning stimulant therapy, and monitor height and weight changes while on therapy (Subcommittee-AAP, 2011; NICE, 2012).

Methylphenidate is the most widely-used stimulant for ADHD (Christensen, 2010), and its multiple formulations are approved for use in children ages 6 years and older. Extended-release formulations of mixed amphetamine salts and dextroamphetamine are also approved in children 6 and older; in contrast, immediate-release forms of these agents are approved for use beginning at age 3 (Micromedex® Healthcare Series, v. 2.0).

Non-stimulants

Other medications with FDA approval for use in ADHD include atomoxetine (Strattera®), a selective norepinephrine-reuptake inhibitor, and extended-release formulations of two alpha$_2$-agonists originally used as antihypertensive medications: guanfacine (Intuniv®) and clonidine (Kapvay™). Atomoxetine is widely considered to be a second-line agent following a trial of stimulant medication, but may be selected by parents choosing to avoid stimulant therapy or in patients with current substance abuse problems as well as those at risk for future abuse (Pliszka, 2007). It has been suggested that patients with comorbidities like ODD or anxiety may also experience better efficacy with atomoxetine (Dell'Agnello, 2009; Geller, 2007). While atomoxetine works by increasing the amount of the neurotransmitter norepinephrine, the exact mechanism of action in ADHD is unknown. Atomoxetine is dosed once or twice daily, and is approved for use in children age 6 and older, adolescents, and adults (Strattera®, package insert, 2011).

Common side effects of atomoxetine include nausea, sedation and fatigue. Importantly, this drug also carries a "black box" warning regarding the possibility of having suicidal thoughts (Rader, 2009). Other rarely reported but potentially serious side effects include liver injury, myocardial infarction, and stroke (Strattera® package insert, 2011).

Extended-release guanfacine and clonidine were approved in 2009 and 2010, respectively, for use in ADHD as monotherapy or in combination with a stimulant. Although the precise mechanism of their action in ADHD is unknown, these medications may stimulate receptors in the brain, working to improve concentration and control of impulsive behaviors (Scahill, 2009). Other populations that may respond to guanfacine and clonidine include children with a comorbid tic disorder and patients with predominant hyperactive/impulsive symptoms (Scahill, 2001; Biederman, 2008). Guanfacine is dosed once daily, and is approved for use in children and adolescents aged 6-17 years (Intuniv® package insert, 2011). Common adverse events are sedation, fatigue, and decreased blood pressure or heart rate (Scahill, 2001; Vaughan, 2012). Clonidine is available in a single dose (0.1 mg) and is dosed twice daily in children aged 6-17 years. The most pronounced side effect is sedation, along with depression, confusion and decreased blood pressure or heart rate (Biederman, 2008).

Duration of Pharmacotherapy

Regardless of the type of medication employed, guidelines recommend continuation of therapy while symptoms are present with concurrent monitoring for adverse events and continued efficacy (Pliszka, 2007). If patients have been on therapy for over a year, consideration of the need for sustained pharmacotherapy is warranted (Pliszka, 2007). For patients receiving stimulant therapy, if drug treatment is effective but there are treatment-related side effects, periodic drug holidays are recommended to try to alleviate these effects (Rader, 2009).

Other Medications

While not a focus of the AHRQ review, other medications are used to treat the symptoms of ADHD as well as common psychiatric comorbidities. For ADHD symptom treatment in patients refractory to first- and second-line therapies, alternative medications include antidepressants, medications

that promote wakefulness such as modafinil, and second-generation antipsychotics (Biederman, 2008; Antshel, 2011). Antidepressants evaluated in patients with ADHD include older agents such as imipramine, desipramine, and phenelzine, along with newer therapies such as bupropion and fluoxetine. However, the risks associated with these medications, including Stevens-Johnson syndrome with modanafil and metabolic syndrome with atypical antipsychotics, has limited their use in ADHD populations (Biederman, 2008; Weiss, 2009).

2. Clinical Guidelines

2.1 Preschool-aged Children

- **American Academy of Child and Adolescent Psychiatry (2007)**
  http://www.aacap.org/galleries/PracticeParameters/JAACAP_ADHD_2007.pdf

Behavioral/Psychosocial Interventions

If a child treated for ADHD shows full remission of symptoms and normative functions in response to medication, then it is not mandatory that behavior therapy be added to the regimen, although parental preferences should be considered. If a child has a less than optimal response to medication, has a co-morbid disorder, or experiences stressors in family life, then psychosocial treatments in conjunction with medications can be beneficial.

Behavior therapy alone may be recommended for children with ADHD if the patient's ADHD symptoms are mild with minimal impairment, the diagnosis of ADHD is uncertain, parents reject medication treatment, or there is marked disagreement about the diagnosis between parents or between parents and teachers.

When psychosocial interventions are applied, the frequency of sessions should be individualized to a patient's needs and parent preferences.

Medications

Methylphenidate (or any stimulant) is a treatment option for preschoolers, though the dose may be titrated more conservatively than for school-aged children, as lower mean doses may be effective.

- **American Academy of Pediatrics (2011)**
  http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654.full.pdf+html

Behavioral/Psychosocial Interventions

Primary care physicians should prescribe evidence-based parent- and/or teacher-administered behavior therapy as the first line of treatment. In areas where evidence-based behavioral treatments are unavailable, clinicians should weigh the risks of starting medication at an early age against the harm of delaying diagnosis and treatment.

Medications

It is recommended that ADHD treatment for preschoolers be initiated with behavioral therapy alone. Only preschool-aged children with ADHD who have moderate-to-severe dysfunction should be considered for medication, based on: a) symptoms that have persisted for at least 9 months; b)

dysfunction that is manifested in both the home and school or day care; and c) dysfunction that has not responded adequately to behavior therapy. Methylphenidate has the strongest evidence of safety and efficacy for this patient subgroup. If a preschooler is prescribed medication, it should be for a lower dose to start which can be increased in smaller increments.

- **National Institute for Health and Clinical Excellence (2009)**
  http://www.nice.org.uk/nicemedia/live/12061/42060/42060.pdf

Behavioral/Psychosocial Interventions

Health care professionals should refer parents or caregivers of preschool children with ADHD to an evidence based parent-training/education program as the first line of treatment, whether or not the child has a formal diagnosis of conduct disorder. Individual therapy should only be considered when group therapy is not possible or the family's needs are too complex.

Both group and individual based programs should be structured and incorporate a curriculum informed by principles of social learning theory; include relationship-enhancing strategies; offer a sufficient number of sessions, with an optimum of 8–12; enable parents to identify their own parenting objectives; incorporate role-play during sessions, as well as homework to be undertaken between sessions; be delivered by appropriately trained and skilled facilitators; and adhere to the program developer's manual**.**

Medications

Drug treatment is not recommended for preschoolers with ADHD.

2.2 School-aged Children and Adolescents

- **American Academy of Child and Adolescent Psychiatry (2007)**
  http://www.aacap.org/galleries/PracticeParameters/JAACAP_ADHD_2007.pdf

Behavioral/Psychosocial Interventions

If a child treated for ADHD shows full remission of symptoms and normative functions in response to medication, then it is not mandatory that behavior therapy be added to the treatment regimen, although parental preferences should be considered. If a child has a less than optimal response to medication, has a co-morbid disorder, or experiences stressors in family life, then psychosocial treatments in conjunction with medications can be beneficial.

Behavior therapy alone can be pursued in the treatment of ADHD in certain clinical situations. Behavioral interventions may be recommended as a first-line treatment if the patient's ADHD symptoms are mild with minimal impairment, the diagnosis of ADHD is uncertain, parents reject medication treatment, or there is marked disagreement about the diagnosis between parents or between parents and teachers.

When psychosocial interventions are applied, the frequency of sessions should be individualized to a patient's needs and parent preferences.

Medications

The initial psychopharmacological treatment of ADHD should be with an FDA-approved medication, including dextroamphetamine, methylphenidate, mixed amphetamine salts, and atomoxetine.

Stimulants have been recommended as a first-line treatment for ADHD, especially when no comorbidity is present. Physicians can prescribe either of the two stimulant types (methylphenidate or amphetamine), since evidence suggests they are equally efficacious for children and adolescents in the treatment of ADHD. Short-acting stimulants are often used as initial treatment in smaller children (<16 kg in weight), for whom there are no long-acting forms in a sufficiently low dose. Atomoxetine may be preferable for patients with substance abuse problems, comorbid anxiety, or tics. The choice of the agent should be individualized to the patient and physician preferences.

- **American Academy of Pediatrics (2011)**
  http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654.full.pdf+html

Behavioral/Psychosocial Interventions

For school-aged children, primary care physicians should prescribe evidence based parent– and/or teacher-administered behavior therapy as treatment for ADHD, preferably alongside FDA-approved medications for ADHD.

Medications

Primary care physicians should prescribe FDA-approved medications for ADHD, preferably alongside evidence based parent- and/or teacher-administered behavior therapy for school-aged children and adolescents. The greatest evidence exists for stimulant medications and is sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine. For children 12- 18 years of age, clinicians should assess if the patient has symptoms of substance abuse, and when there are signs of abuse or diversion, consider prescribing non-stimulant medications, such as those listed above.

School-based Interventions

The school environment, program, or placement should form part of any treatment plan. School programs can provide classroom adaptations, such as preferred seating, modified work assignments, and test modifications, as well as other behavior plans and special education programs. It is helpful for clinicians to be aware of the eligibility criteria in their state and school district to appropriately advise families of their options.

- **Institute for Clinical Systems Improvement (2012)**
  http://www.icsi.org/guidelines_and_more/gl_os_prot/behavioral_health/adhd/adhd_in_primary_care_for_children__adolescents__diagnosis_and_management_of_.html

Behavioral/Psychosocial Interventions

If medication is not tolerated or effective for the patient or parents reject medication after shared decision-making with the primary physician, family-focused strategies as well as child and school interventions should be emphasized. Nonpharmacological interventions, including social skills training, cognitive-behavioral therapy, study/organizational skills training, and parent/family focused strategies are recommended.

Medications

FDA-approved medications for ADHD, including psychostimulants and/or non-stimulants are options for school-aged children with ADHD. The choice of drug should incorporate comorbid conditions. If a patient fails with one stimulant, clinicians should attempt a second trial with a different stimulant. Atomoxetine is a good option for patients with comorbid anxiety, sleep initiation disorder, substance abuse, or tics, or if initially preferred by parents and/or physician.

School-based Interventions

Primary care providers for children with ADHD should advocate and advise parents in appropriate school programming, services, and supports. Educational accommodations/modifications in the classroom have been found to assist children with ADHD in coping with the condition and alleviating some of the academic and social difficulties associated with this disability.

If medication is not tolerated or effective for the patient, or rejected by the parents after shared decision-making with the primary physician, family-focused strategies as well as child and school interventions should be emphasized.

- **National Institute for Health and Clinical Excellence (2009)**
  http://www.nice.org.uk/nicemedia/live/12061/42060/42060.pdf

Behavioral/Psychosocial Interventions

For children with ADHD who have a moderate level of impairment, physicians should refer the parents or caregiver of the child to a group parent training/education program, either alone or combined with a group treatment program (CBT and/or social skills training) for the child as a first-line therapy. When using group treatment for the child or young person in conjunction with a parent-training/education program, particular emphasis should be given to targeting a range of areas, including social skills with peers, problem solving, self-control, listening skills and dealing with and expressing feelings. Active learning strategies should be used, and rewards given for achieving key elements of learning. For older adolescents with ADHD and moderate impairment, individual psychological interventions (such as CBT or social skills training) may be considered as they may be

more effective and acceptable than group parent-training/education programs or group CBT and/or social skills training.

Drug therapies can be superior treatment options for children and adolescents with severe ADHD, but group-based parent training/education programs should be offered to parents and caregivers of children and adolescents in this patient subgroup in combination with medication or in place of medication when the child or parents oppose drug therapy. Other psychological treatments (group CBT/other social skills training) can be offered if group parent-training/education is ineffective, and if drug treatment has been rejected.

Teachers who have received training in ADHD management should also provide behavioral interventions in the classroom to support students with ADHD. Parents of children with severe ADHD should also be offered group-based parent-training education programs.

Medications

Drug treatment is only indicated as the first-line treatment for school-age children and adolescents with severe ADHD. Children and adolescents with moderate levels of impairment should only receive medication if they have refused nonpharmacological interventions, or their symptoms have not responded sufficiently to parent-training/education programs or group psychological treatment.

Where drug treatment is considered appropriate, methylphenidate, atomoxetine, and dexamphetamine are options depending on co-morbidity, adverse effects, issues regarding compliance, potential for misuse or diversion, and patient and parent preferences. When prescribing methylphenidate, extended-release may help improve adherence, but immediate-release can be considered if more flexible dosing is required. Children on atomoxetine should be closely monitored for adverse side effects.

School-based Interventions

Teachers who have received training about ADHD and its management should provide behavioral interventions in the classroom to assist children and adolescents with ADHD. Following a diagnosis of ADHD, parents or healthcare professionals with the parents' or caregivers' consent should inform teachers of the patient's diagnosis, severity of symptoms and impairment, the care plan, and any special educational needs or considerations.

3. Medicaid, National and New England Private Insurer Coverage Policies

3.1 Behavioral/Psychosocial Interventions

Medicaid

Mental health services are always included as basic services in Medicaid plans across New England, though specific behavioral coverage policies for ADHD have not been published. Discussions with Medicaid representatives to CEPAC suggested that a significant number of children on Medicaid receive coverage for mental health services through community health clinics or primary care centers with access to fewer mental health visits and supportive psychotherapy services than the commercial population or children with access to specialty mental health clinics. Consequently, they believe that Medicaid patients are more likely to receive medication.

Regional Private Payers

No published policies on behavioral/psychosocial interventions specifically for ADHD were found. Discussions with private payer representatives to CEPAC suggested that most commercial insurers do not cover manual-based interventions that are considered to be primarily educational, personal coaching, or vocational in nature, but that these services are sometimes billed on a session-by-session basis as general outpatient psychotherapy. Some plans require prior authorization for outpatient psychotherapy, have limitations on the quantity of visits, and/or require that psychotherapy involve face-to-face visits *not* provided in the home or school setting.

National Private Payers

Aetna and CIGNA do not cover educational interventions (e.g. classroom environmental manipulation, academic skills training, parental training) and other interventions primarily related to improving academic or work performance, as they are not considered a medical benefit and are typically excluded from benefit plans. Psychotherapy services are generally covered for ADHD.

3.2 Medication

Medicaid

There are many similarities in Medicaid drug coverage policies across the six New England states (see Table 1 on page 16). Prior authorization is not required for generic stimulants and most branded stimulants that do not have generic equivalents. Differences in policy primarily involve non-stimulants (i.e., atomoxetine, extended-release guanfacine, extended-release clonidine), all of which are available as branded products only. All three agents require prior authorization and/or

step therapy in Massachusetts, New Hampshire, and Vermont; in other states, at least one of these agents is available without restriction. Maine, Massachusetts and Vermont also utilize dosing limits for several ADHD medications, and both Massachusetts and Vermont employ age restrictions (both minimums and maximums).

Regional Private Payers

ADHD drug policies among major regional private payers in New England are more variable (see Table 2 on page 17). All identified policies allow for unrestricted use of generic formulations; only Blue Cross Blue Shield of MA requires prior authorization for a few select therapies (e.g., extended-release dextroamphetamine). Blue Cross Blue Shield of MA and RI also apply dose limits to generic medications. If generic formulations are available, private payers place restrictions on the use of branded medications through non-coverage, dose limits, and/or prior authorization. Five of the six payer policies identified utilize step therapy and dose limits for many ADHD medications. The exception is Harvard Pilgrim Health Care, which restricts use only through tiered copayments. Medications without available generic formulations are generally covered, although dose limits are often applied. Tufts Health Plan requires step therapy for nearly all branded medications, regardless of generic availability.

National Private Payers

Like regional payers, national private payers generally do not place restrictions on use of generic formulations; only Aetna has dose limits in place. When generic formulations are available, private payers place restrictions on coverage through dose limits, non-coverage, and/or prior authorization for certain medications. CIGNA and Aetna require step therapy for ADHD medications, requiring patients to fail with a generic before receiving coverage for certain branded agents.

Table 1. Coverage Policies for ADHD-approved Medications: State Medicaid Agencies.

State	Stimulants Methylphenidate Dextroamphetamine Mixed amphetamine salts Lisdexamfetamine*	Non-stimulants Atomoxetine* Guanfacine, extended release* Clonidine, extended release*	Notes
Connecticut	• Generics and branded products without available generics: no PA required • Lisdexamfetamine: no PA required	• Atomoxetine, guanfacine, extended release: no PA required • Clonidine, extended release: PA required	• If generic formulation is available, PA required for use of brand
Maine	• Generics and most branded products without available generics: no PA required • Lisdexamfetamine: no PA required, but dose limits apply	• Guanfacine, extended release: no PA required • Atomoxetine, clonidine, extended release: step therapy, PA required	• If generic formulation is available, PA required for use of brand • Some extended release formulations without available generics require PA • Dosing limits apply to most available medications
Massachusetts	• Generics and most branded products without available generics: no PA required, but dose limits apply • Lisdexamfetamine: no PA required, but dose limits apply	• Atomoxetine, guanfacine, extended release, clonidine, extended release: PA required	• If generic formulation is available, PA required for use of brand • Some extended release formulations without available generics require PA • Age limits applied to medications
New Hampshire	• Generics and most branded products without available generics: no PA required • Lisdexamfetamine: no PA required	• Atomoxetine, guanfacine, extended release, clonidine, extended release: PA required	• If generic formulation is available, PA required for use of brand
Rhode Island	• Generics and most branded products without available generics: no PA required • Lisdexamfetamine: PA required	• Guanfacine, extended release, clonidine, extended release: PA required • Atomoxetine: no PA required	• If generic formulation is available, PA required for use of brand • Some extended release formulations without available generics require PA
Vermont	• Generics and branded products without available generics: no PA required, but some dose limits apply • Lisdexamfetamine: no PA required, but dose limits apply	• Atomoxetine, guanfacine, extended release, clonidine, extended release: PA required, dose limits apply	• If generic formulation is available, PA required for use of brand • Use of stimulants in children < 3 years requires PA

* Brand-only product, no generic available PA: prior authorization

Table 2. Coverage Policies for ADHD-approved Medications: Regional Private Payers.

Payer	**Stimulants** Methylphenidate Dextroamphetamine Mixed amphetamine salts Lisdexamfetamine*	**Non-stimulants** Atomoxetine* Guanfacine, extended release* Clonidine, extended release*	**Notes**
Blue Cross Blue Shield of Massachusetts	• Generics: some require PA, and some have dose limits • Branded products without available generics: most are covered, no PA required, but some dose limits apply	• Atomoxetine: PA required, dose limits apply • Guanfacine, extended release and clonidine, extended release: not covered, but no PA required	• If generic formulation is available, branded product is not covered, and some require PA for use • Formulary exceptions exist for some non-covered medications
Blue Cross Blue Shield of Rhode Island	• Generics and branded products without available generics: no PA required, some dose limits apply	• Atomoxetine: no PA required • Guanfacine, extended release and clonidine, extended release: not covered, but eligible for Medical Exception Process, dose limits apply	• If generic formulation is available, branded product is not part of preferred drug list, and dose limits apply
Blue Cross Blue Shield of Vermont	• Generics and branded products without available generics: no PA required • Lisdexamfetamine: PA required	• Atomoxetine and guanfacine, extended release: step-therapy required for use • Clonidine, extended release: no information provided	
Harvard Pilgrim Health Care	• No PA required for medication use	• No PA required for medication use	
Tufts Health Plan	• Generics: no PA required • Most branded products (with and without available generics): step therapy required for use	• Atomoxetine and guanfacine, extended release: no PA required, but dose limits apply • Clonidine, extended release: not covered	
ConnectiCare	• Generics and branded products without available generics: no PA required	• Atomoxetine: PA required • Guanfacine, extended release and clonidine, extended release: step-therapy required	• If generic formulation is available, branded product coverage is specific to individual provider plan

* Brand-only product, no generic available PA: prior authorization

4. New Evidence Following AHRQ Review

4.1 Updated Search

We conducted an updated systematic literature search of MEDLINE and PsycInfo utilizing the search criteria defined by the AHRQ review. The search timeframe spanned from January 1, 2010 to March 26, 2011, with 6,221 records identified. Any citations already considered in the AHRQ review were removed. The remaining abstracts were screened using parameters designated by the AHRQ review (i.e., study type, patient population, treatment intervention, and outcomes evaluated). Following removal of duplicate citations and initial screening, full-text review was performed on 203 retrieved articles. Most of these were excluded (n=188) for a variety of reasons, including inappropriate patient population (adults, children without specific ADHD/ODD diagnoses), and lack of long-term follow-up (12 months or more) in studies of school-aged children.

Fifteen articles were evaluated for new evidence (Appendix C) and are discussed in further detail in the sections that follow.

4.2 Management Options for Preschool-aged Children

Behavioral/Psychosocial Interventions

Six new studies evaluating the impact of parent behavior training in preschoolers were identified, including five RCTs and one cohort study (Appendix C, Table 1). Follow-up was variable, ranging from six weeks to 12 months. Interventions also varied, and included manual-based programs such as PCIT, Triple-P®, and IYPP, in addition to a telephone-based therapeutic intervention and a community-based program. Findings generally mirrored the results of the RCTs evaluated in the AHRQ report: compared to wait-list control or usual care, parent behavior training provided statistically-significant improvement in child disruptive behaviors, parent stress levels, and overreactive behaviors in parent-child interactions. Several studies were notable for their unique design features and interventions. A multi-center RCT evaluated an innovative telephone-based therapy delivery method in separate cohorts of children based on psychiatric diagnosis and age groups (McGrath, 2011). Following a 12-week therapeutic intervention, preschool children with ODD (mean age: 5 years) had greater success rates with treatment at 12 months as compared to usual care (Odds Ratio [OR]=2.13, 95% confidence interval [CI]=0.81,5.65). The primary study outcome was the decrease from baseline to follow-up in the percentage of patients diagnosed with ODD, an outcome that was not evaluated in the parent behavior training trials analyzed in the AHRQ report, thereby preventing explicit comparison of the treatment approaches.

In the one new study of IYPP, parent behavior training was coupled with a separate intervention for children designed to address social skills and behavioral symptoms (Webster-Stratton, 2011). Included in the evaluated outcomes were parent reports of child symptoms, along with teacher assessments of behavioral symptoms, and *independent* observation of parent-child interactions and

child-peer interactions at school. Use of objective observations to evaluate parent-child relationships is uncommon, as many previous studies utilized parent self-reported data (Webster-Stratton, 2011). Results of the trial included statistically-significant improvement in hyperactivity and inattentive behaviors ($p \leq 0.05$), along with high parent satisfaction with all interventions. Additionally, significant interventional impacts on externalizing behavior ($p \leq 0.05$) were reported by teachers, and significant improvement in peer social contact ($p \leq 0.01$) was observed.

Other studies evaluated the effects of parent behavior training programs in specific subpopulations. Compared to a wait-list control group, Bagner et al. (2010) found significant symptom improvement with PCIT in children born prematurely, a group at increased risk of behavioral problems. Lakes et al. (2011) evaluated the impact of a community-based, culturally-sensitive model of therapy in a predominantly Latino population of low socioeconomic status. Improvements in child symptoms and parent behaviors extended to one year following completion of the 10-week program (Lakes, 2011).

Medications

No studies have been published since the AHRQ review that provide significant new information about the impact of medication therapy on clinical, economic, and/or safety outcomes among children < 6 years of age with ADHD/ODD.

4.3 Management Options for School-aged Children

Behavioral/Psychosocial Interventions

In the multicenter RCT evaluating telephone-based parent behavior training as described above, a second cohort of school-aged children with ADHD was identified (McGrath, 2011) (Appendix C, Table 2). Following the 12-week therapeutic intervention, fewer patients in the parent behavior training group were diagnosed with ADHD at 240 ($p=0.03$) and 365 days ($p=0.04$) compared to usual care.

A collaborative care approach involving a care manager, the treating pediatrician, and a consulting psychiatrist was assessed in a prospective cohort of primarily Hispanic children with ADHD at two pediatric clinics (Myers, 2010). Patients were followed monthly, up to 14 months, and improvement, compared to baseline, was found in symptoms, academics, behavior and relationships ($p<0.05$), although a control group was not available.

Medications

No studies have been published since the AHRQ review that provide significant new information about the long-term efficacy of medication therapy among children ≥ 6 years of age with ADHD.

One RCT and two prospective controlled cohorts evaluated the effects of pharmacotherapy on growth rates in school-age children, with length of follow-up ranging from 1-4 years (Appendix C, Table 3). In an RCT of atomoxetine versus placebo, patients receiving atomoxetine had smaller mean increases in height and smaller mean increases in weight ($p<0.001$) as compared to placebo. In a controlled cohort

evaluating methylphenidate versus placebo, greater height gaps over time were seen with patients receiving methylphenidate ($p<0.001$), but no differences in weight changes were found (Zhang, 2010).

Four retrospective cohort studies examined the correlation of the use of stimulants and atomoxetine with the occurrence of cardiovascular and cerebrovascular adverse events in child and adult ADHD populations (Appendix C, Table 4). Similar to the findings of the AHRQ report, the use of these medications was not associated with increased risks of sudden cardiac death, acute myocardial infarction, or stroke.

School-based Interventions

Iseman and Naglieri (2011) investigated the impact of a planning-based cognitive strategy versus regular math instruction in an RCT of children with ADHD and learning disabilities (Appendix C, Table 2). Positive effects were seen immediately post-intervention on three measures of performance ($p<0.05$) versus control: math worksheets, the WJ-III ACH Math Fluency test and the WIAT-II Numerical Operations subtest. At one year, students were re-evaluated with the fluency test, and those in the intervention group demonstrated continued improvement (effect size = 0.85) over control (effect size = 0.09), although statistical significance was not reported.

4.4 Summary of Relevance of New Evidence

Preschool-aged children

Newly-identified studies evaluating parent behavior training supported the conclusions of the AHRQ review: such training is associated with statistically-significant improvements in problem behaviors, parent-child interactions, and parent stress levels relative to wait-list or usual care control. Alternative training approaches such as telephone-based therapy and inclusion of child-specific training also appear to be effective. In contrast, no new studies of medication therapy in preschool-aged children were identified, so the level of evidence remains low for medication use in this population.

School-aged children

Two newly published reports of behavioral/psychosocial interventions in school-aged children suggested benefit in this population, but were based on a subgroup analysis of an RCT in one instance and an uncontrolled study in the other. A separate RCT indicated beneficial effects of a school-based cognitive strategy intervention, but only in the domain of mathematics. We believe, therefore, that there should be no change in the AHRQ judgment that the strength of evidence is “insufficient” to judge the effectiveness of behavioral/psychosocial and academic interventions in school-aged children.

No new trials evaluating the long-term efficacy of medication in school-aged children were identified. Available safety reports confirm the findings of the AHRQ review that (a) ADHD medications are associated with minor and clinically insignificant decreases in growth rates; and (b) these medications do not appear to significantly increase the risk of major cardiovascular events.

5. Analysis of Comparative Value

5.1 Overview

An economic model was developed to evaluate the comparative value of multiple strategies for managing children at risk for, or diagnosed with, ADHD. The model framework considers the outcomes of two populations: preschool-aged children (0-5 years old) and school-aged children (6-18 years old). The comparative value of these strategies was considered by evaluating costs and clinical outcomes using two distinct approaches: the cost-effectiveness of a given management option vs. a relevant comparator(s), and the budget impact to the payer of changing coverage policy for selected strategies (and the associated distribution of management options utilized). All primary analyses adopted the perspective of a state Medicaid agency; as such, costs are represented by estimates of Medicaid payments for medications and services. Alternative analyses also were conducted using private-payer rates. Importantly, use of this perspective meant that we did not consider the broader social impacts of ADHD or its treatment such as caregiver work loss and school absence, nor did we consider costs not borne by the payer (e.g., school-based interventions, therapeutic summer camps).

Budget impact and cost-effectiveness analyses were evaluated using a short-term time horizon (1-2 years) to match the available comparative clinical data. Longer-term analyses were felt to be problematic because of the modifications to treatment that typically occur for children as they age, as well as the number of mediating factors that might affect long-term outcomes (e.g., comorbidity, family socioeconomic status).

As its primary measure of effectiveness, the AHRQ review focused on mean differences between treatment groups in the change from baseline on standardized parent/teacher evaluation scales. However, such measures of average outcomes do not provide information about whether or not this change is “clinically significant”, or meaningful to the child or family, nor is it known from these measures what proportion of children achieve such an improvement. In our modeling, therefore, we based our estimates of treatment effectiveness on the results of studies reporting outcomes in terms of the percent of children achieving a “clinically-significant” response.

Payments associated with each treatment strategy and routine care are presented as the total payment and by component for each strategy. It was assumed that both routine resource use and medication-related office visits would continue regardless of (a) the treatment received; and (b) response to treatment. No change in resource use was therefore assumed; costs for these services are nevertheless presented to provide a baseline for the annual costs of “usual care”. Cost-effectiveness results are presented as the cost per additional treatment response. The number needed to treat (NNT) is also presented, which represents the number of children who must be treated for one child to have a clinically-significant response to treatment. Quality adjusted life-years (QALYS) were not considered in these analyses given the short-term nature of the analyses and the paucity of data associating changes in clinical measures over the short term with long-term quality-of-life implications.

Methods are described in more detail separately by age group in the sections that follow.

5.2 Methods: Preschool-aged Population

Budget Impact Analysis

Both the AHRQ review and our supplementary analyses indicated that parent behavior training was associated with statistically- and clinically-significant improvement in a variety of measures of parent-child interaction as well as parent stress. Also, as noted in Section 3 of this document, manual-based programs are not currently covered by most public and private payers in the region. However, as also noted in Section 3, anecdotal information from payers suggests that some parents may already be receiving these services billed under general codes for individual or group therapy. Because baseline utilization of the portion of therapy codes that would relate to parent training would be problematic to estimate, evaluation of the potential economic impact of parent behavior training in this population was limited to cost-effectiveness analysis alone.

Cost-Effectiveness Analysis

Population

Cost-effectiveness was evaluated in a hypothetical cohort of 1,000 Medicaid patients less than 6 years old diagnosed with ADHD and considered the outcomes and Medicaid payments associated with each modeled management strategy.

Management Options

Our analyses of cost-effectiveness in preschool-aged children focused on three interventions of interest: parent behavior training, stimulant medication, and a combination of these two interventions. Because no studies were identified that involved direct comparisons of all of these interventions, analyses were based on findings from three studies reporting clinically significant response to management (Bor, 2002; Ghuman, 2009; Greenhill, 2006). Each study utilized a somewhat different measure of response, as described in further detail below. Because of this, analyses were conducted as three separate, pairwise comparisons of intervention to comparator based on the results of each individual study.

Parent behavior training alone vs. usual care. Standard or enhanced parent behavior training (based on the Triple P program) was compared to "usual care" (also based on wait-list control) using findings from a one-year study of 87 preschoolers diagnosed with co-occurring DBD and ADHD (Bor, 2002). Outcomes were essentially identical for enhanced and standard training; we therefore based model estimates on the standard program that is widely available. Improvement in this study was determined using the "reliable change index" (RCI) (Jacobson, 1991; Jacobson, 1999). The RCI is a standardized score which may be calculated from any number of measurement scales and is benchmarked to a threshold value. Standardized scores greater than the threshold indicate a clinically significant change. In this study, the RCI was derived using the Eyberg Child Behavior Inventory (ECBI), which is a measure of parent perceptions of disruptive behavior.

Medication only vs. usual care. Management with methylphenidate was compared to "usual care" (based on wait-list control) in a small study (n=14) of preschoolers diagnosed with developmental disorders including autistic disorder, Asperger disorder, or pervasive developmental disorder (Ghuman, 2009). Although representing a selected population, this study was one of the few that

represented a comparison of medication to usual care in preschoolers *and* reported clinically-significant response. In this case, response to treatment was estimated based on the percent of children achieving a 25% or greater reduction on the Connors Parent Rating Scale, ADHD subscale (CPRS-ADHD) *and* a rating of much improved or very much improved on the Clinical Global Impressions scale (CGI). The CPRS-ADHD scale is a measure designed to identify behavioral problems associated with ADHD, while the CGI is a measure that identifies global impairment or improvement.

Parent behavior training plus medication vs. usual care. The Preschool ADHD Treatment Study (PATS), funded by the NIMH, was used for the comparison of parent behavior training followed by methylphenidate to parent behavior training alone (Greenhill, 2006). This was a large (n=303), multi-center, randomized, controlled trial in which "excellent response" was determined based on a score of ≤1.0 on the Swanson, Nolan, and Pelham Scale (SNAP) composite score. The SNAP is a parent- and teacher-rated measure used to identify symptoms associated with ADHD, and a score ≤1.0 equates to what would be expected in a child without ADHD.

Estimates of clinically-significant improvement are presented in Table 1 below.

Table 1. Clinical effectiveness parameters used in modeling for the preschool-aged population.

	Behavioral Interventions only	Medication only	PBT followed by Medication	Usual Care	Treatment Period	Source
"Excellent Responder" (SNAP composite)	13%	—	22%	—	19 wks	Greenhill
25% reduction on CPRS-ADHD *and* CGI-I	—	50%	—	7%	4 wks	Ghuman
Reliable change index (ECBI-Intensity)	62%	—	—	23%	10 wks	Bor

CGI-I= Clinical Global Impression-Intensity subscale; CPRS-ADHD= Connors Parent Rating Scale-ADHD subscale; ECBI=Eyberg Child Behavior Inventory; PBT=Parent behavior training; SNAP=Swanson, Nolan, and Pelham composite score

Treatment-related Utilization and Payments

Preschool children in the parent behavior training strategy were assumed to receive a full course of Triple P therapy. The course of treatment was 10 weeks based on the "standard" program presented in the PATS and Bor studies. Children receiving medication were assumed to receive methylphenidate 5 mg three times daily. For patients receiving combination therapy, parent behavior training was assumed to be provided first, and medication did not commence until such training was completed. Neither noncompliance with treatment nor therapy switching was modeled, as no data were readily available to inform these assumptions. Since we assumed no change in the overall pattern of routine visits between different treatment options and "usual care", costs for all other health care utilization were assumed not to differ and the only marginal cost differences were assumed to be those directly related to the provision of behavioral therapy and ADHD medication.

Medicaid payment rates for ADHD-related services were not readily available. The average paid amount for each resource use item was derived from the LifeLink™ Health Plan Claims Database

(IMS Health, Danbury, CT), which is comprised of 79.4 million privately-insured individuals from 79 health plans nationwide and includes 6.7 billion medical and pharmacy claims generated from 2001 to the present. As these data represented payments by private insurers, we assumed lower levels of payment by Medicaid. In the absence of data on how payments for ADHD-related health services directly compare, these were assumed to be 60% of those made by private payers. Medication costs in the Medicaid population were determined using the estimated wholesale acquisition cost for ADHD medications as a proxy for actual Medicaid drug payments in this population.

Total estimated annual payments for each course of therapy in preschool children were approximately $844 for parent behavior training and $163 for medication therapy based on generic methylphenidate. Payments for usual care were estimated to total approximately $444 annually including outpatient care and other prescriptions.

All expenditures are reported in 2010 US dollars unless otherwise specified. Estimates from prior years were inflated to 2010 using the overall medical inflation component of the consumer price index for the Northeast U.S. (Bureau of Labor Statistics, 2010).

Table 2. Cost of treatment options.

Unit Item	Input/ Expenditure	Frequency	Total cost per year
Payment Items			
Medication			
Methylphenidate 5 mg - immediate release (generic)	$ 0.15	3 doses per day	$163
Parent Behavior Training			
Triple P (Positive Parenting Program)	$ 84.43	10 sessions	$844

Analyses

During the one-year time horizon, children may achieve a clinically-significant response to treatment. Effectiveness outcomes are presented for each strategy in terms of the numbers of patients with a clinically-significant response to treatment for each cohort. Payments associated with each treatment strategy and routine care are presented as the total payment and by component for each strategy. Cost-effectiveness results are presented as the cost per additional treatment response. The number needed to treat (NNT) is also presented, which represents the number of children who must be treated for one child to have a clinically-significant response to treatment.

5.3 Results: Preschool-aged Population

Parent Behavior Training versus Usual Care

The Positive Parenting Program (Triple-P) resulted in 62% of children with a clinically meaningful response, accounting for a 39% absolute increase in the percentage of children responding compared to those receiving usual care over one year (see Table 3 below). The estimated Medicaid payments associated with Triple-P were approximately $1,288 per child compared with $444 per child under usual care (i.e., no specific ADHD management). The NNT of 3 indicated that for every three children treated with Triple P rather than usual care, one child will have a clinically significant improvement. The cost per treatment response was estimated to be $2,165 relative to usual care.

Table 3. One-year cost-effectiveness of parent behavior training versus usual care for preschool-aged children with ADHD.

	Preschool Comparison ADHD at Risk for Conduct Problems*		
	Triple P	**Usual Care (Reference)**	**Net Difference**
Clinical Outcomes for 1000 Children with ADHD†			
Positive Treatment Response‡ (n)	620	230	390
Response Rate (%)	62%	23%	39%
Relative Risk Reduction (vs. Reference Therapy)			51%
NNT for 1 Additional Child with Improved Outcome			3
Cumulative Cost per Child with ADHD			
Behavioral/Psychosocial Therapy	$844	$0	$844
Other Resource Utilization	$444	$444	$0
Total Direct Medical Costs Over 1 Year	$1,288	$444	$844
Cost-Effectiveness			
Total Cost for Treating 1000 Children	$1,287,955	$443,635	$844,320
Cost/Additional Treatment Response			$2,165

*Bor et al., 2002; 81% of sample reported 5 or more risk factors out of 23 for conduct problems. This study was chosen as the results approximate the mean of all studies (n=3) reporting the same outcome measure - Reliable Change Index (RCI) based on the Eyberg Child Behavior Inventory (ECBI) - Intensity subscale.

†A negative net difference indicates that the comparator strategy is better than the reference strategy.

‡Positive treatment response reported as the RCI >1.96.

Triple P=Positive Parenting Program, a form of Parent Behavior Training (PBT); Usual Care refers to children on a "waitlist" for PBT

Medication versus Usual Care

Fifty percent of patients receiving methylphenidate had a clinically-significant response, accounting for a 43% absolute increase over usual care (i.e., no specific ADHD management) over one year (see Table 4 below). The estimated Medicaid payments associated with medication use were approximately $600 per child compared with $444 per child under usual care. The NNT was 2, indicating that for every two children treated with medication one child will have a clinically significant response to treatment. The cost per additional treatment response was estimated to be $380.

Table 4. One-year cost-effectiveness of medication only versus usual care for preschool-aged children with ADHD.

	Preschool Comparison ADHD with Developmental Disorders*		
	Medication	Usual Care (Reference)	Net Difference
Clinical Outcomes for 1000 Children with ADHD†			
Positive Treatment Response‡ (n)	500	71	429
Response Rate (%)	50%	7%	43%
Relative Risk Reduction (vs. Reference Therapy)			46%
NNT for 1 Additional Child with Improved Outcome			2
Cumulative Cost per Child with ADHD			
ADHD Medication (Immediate Release Methylphenidate)	$163	$0	$163
Other Resource Utilization	$444	$444	$0
Total Direct Medical Costs Over 1 Year	$607	$444	$163
Cost-Effectiveness			
Total Cost for Treating 1000 Children	$606,682	$443,635	$163,048
Cost/Additional Treatment Response			$380

*Ghuman et al., 2009: study of children with a diagnosis of ADHD *and* pervasive developmental disorder (PDD) or intellectual disability (ID).

†A negative net difference indicates that the comparator strategy is better than the reference strategy.

‡Positive treatment response reported as 25% or greater reduction on the CPRS-R-ADHD subscale *and* CGI-I rating of "much improved" or "very much improved"; (CGI-I=Clinical Global Impression-Global Improvement; CPRS-R=Conners' Parent Rating Scale-Revised).

Parent Behavior Training with Medication versus Parent Behavior Training Alone

Parent behavior training followed by methylphenidate use is associated with a 9% absolute increase in the number of positive treatment responses relative to parent behavior training alone over one year (see Table 5 below). The estimated Medicaid payments associated with parent behavior training followed by methylphenidate use are estimated to be $1,451 per child vs. $1,288. Medication was assumed to be generic immediate-release methylphenidate 5 mg three times daily, paid at Medicaid rates; therefore, the majority of costs for both strategies are associated with parent behavior training.

The number needed to treat (NNT) was 11, indicating that for every 11 children who add methylphenidate following parent behavior training, one additional child will have a clinically-significant response to treatment. The cost per additional treatment response was estimated to be $1,812.

Table 5. One-year cost-effectiveness of parent behavior training with medication versus parent behavior training alone for preschool-aged children with ADHD.

	Preschool Comparison Preschool ADHD Treatment Study (PATS)*		
	Training/ Medication	**Training Only (Reference)**	**Net Difference**
Clinical Outcomes for 1000 Children with ADHD†			
Positive Treatment Response‡ (n)	220	130	90
Response Rate (%)	22%	13%	9%
Relative Risk Reduction (vs. Reference Therapy)			10%
NNT for 1 Additional Child with Improved Outcome			11
Cumulative Cost per Child with ADHD			
ADHD Medication (Immediate Release Methylphenidate)	$163	$0	$163
Behavioral/Psychosocial Therapy	$844	$844	$0
Other Resource Utilization	$444	$444	$0
Total Direct Medical Costs Over 1 Year	$1,451	$1,288	$163
Cost-Effectiveness			
Total Cost for Treating 1000 Children	$1,451,002	$1,287,955	$163,048
Cost/Additional Treatment Response			$1,812

*Greenhill et al., 2006

†A negative net difference indicates that the comparator strategy is better than the reference strategy.

‡Positive treatment response reported % achieving an "excellent response" on the SNAP composite score (SNAP=Swanson, Nolan, and Pelham)

5.4 Methods: School-aged Population (Budget Impact)

One-Year Budget Impact Analysis

Because the AHRQ review concluded that there was insufficient evidence to distinguish the long-term effectiveness of different medication options for ADHD, our budget impact analysis evaluated varying scenarios of the percentage of children prescribed methylphenidate as first-line medication. The baseline distribution of the percentage of prescriptions for different medications was derived from a published retrospective claims analysis of medication use in children aged 6-12 years (Christensen, 2010). Budget impact was analyzed on a population basis and considered the impact of changes in coverage, resource utilization, and payment. The main population of interest was state Medicaid beneficiaries across New England. Alternative sensitivity analyses were conducted for private-payer beneficiaries. The results of alternative analyses are presented in Appendix D.

The patient population was estimated based on the number of children covered under Medicaid in each of the six New England states (see Table 6 on the following page). The total number of patients with ADHD was calculated using gender-specific prevalence for the Medicaid population. The age and gender distribution was assumed from data provided by the LifeLink claims database (IMS Health, Danbury, CT). Accordingly, 71% of children were assumed to be boys, and three-quarters were assumed to be school-aged. The overall prevalence of ADHD within this cohort was determined using data reported from a Centers for Disease Control and Prevention Vital Statistics report (Pastor, 2008). Estimates of prevalence were 11.8% for boys and 4.8% for girls irrespective of age group (Pastor, 2008). Prevalence was found to differ by payer type in this study; accordingly, estimates were higher for the Medicaid population (16.3% and 6.6% for boys and girls respectively).

As can be seen in Table 6, we estimate that there are approximately 95,000 school-age children with ADHD insured by Medicaid in New England.

Table 6. Estimated ADHD Medicaid population in children ≤ 19 years, by state.

	Medicaid*	
	N	%
New England State Distribution		
CT	190,100	20%
ME	109,500	11%
MA	461,600	48%
NH	53,500	6%
RI	87,200	9%
VT	54,800	6%
Covered Populations†‡		
Total membership (n)	956,700	
Prevalence of ADHD		
Preschool	33,883	3.5%
School-age	95,232	10.0%
Total	129,115	13.5%

*Kaiser Family Foundation, State health facts. Child covered lives with Medicaid 2009-2010.
†Note that uninsured patients are not represented in this analysis as there is no direct impact to a third party payer.
‡Some estimates do not add up due to rounding.

Treatment-related Utilization and Payments

Payments of interest included prescriptions associated with the use of methylphenidate and other ADHD medications as well as visits to clinicians related to ADHD medication use. The latter is based on analyses of the National Ambulatory Care Survey (NAMCS) which reported the annual rate of medication-related visits associated with stimulant drug use (Pincus, 1998): 1.5 for general practitioner visits, 0.5 for specialist visits, and 0.8 for other professional visits. Medication payments were based on wholesale acquisition costs for methylphenidate 10 mg three times daily, atomoxetine (Strattera®) once daily, or mixed amphetamine salts (Adderall®) once daily. Findings are reported on an annual basis. Note that, while payments for medication-related visits are presented, the frequency of these visits was not assumed to differ by medication type; accordingly, changes in the mix of medications used as first-line therapy did not affect visit payment levels.

Detailed methods for obtaining the major inputs and parameters are previously described. Those specific to analyses of both budget impact and cost-effectiveness of management in school-age children are shown in Table 7 on the following page. All expenditures are reported in 2010 US dollars unless otherwise specified.

Table 7. Payment input parameters: School-aged analyses.

Unit Item	Input/ Expenditure	Frequency	Total cost per year
Payment Items			
Medication (WAC)			
Methylphenidate 10 mg - immediate release	$0.24	3 doses per day	$262
Atomoxetine	$6.12	1 dose per day	$2,234
Mixed amphetamine salts	$3.83	1 dose per day	$1,400
School-age behavioral/psychosocial therapy			
Individual sessions	$84.43	8 sessions	$675
Group sessions	$43.07	27 sessions	$1,163

WAC=wholesale acquisition cost

5.5 Results: School-aged Population (Budget Impact)

Over the one-year time horizon, the budget impact analysis estimates the total number of patients with ADHD, the proportion treated with first-line medication using methylphenidate or other ADHD medications, and the corresponding resources consumed and associated payments. Payments are reported as total payments per patient with ADHD, annual plan payments for all patients with ADHD, and ADHD payments per member per month (PMPM) for all school-age members. As noted previously, rates of effectiveness with medication use were assumed to be equivalent for all ADHD medications, consistent with the findings reported in the AHRQ review.

Each scenario was specified as the percentage of children treated with methylphenidate as first-line therapy. Based on the source study (Christensen, 2010), the following distribution of first-line use was assumed at baseline:

- Methylphenidate: 51%
- Mixed amphetamine salts: 32%
- Atomoxetine: 17%

Two scenarios were considered: one in which the proportion of patients receiving methylphenidate increased to 75% (with proportionate reductions in the other medication types), and another in which such use increased to 100%.

In addition to alternative analyses as described above, state-specific analyses are presented in Appendix E for the Medicaid population.

Increasing the use of first-line MPH in school-age children with ADHD from approximately half to 75% resulted in a 30% budget reduction over one year as shown in Table 8 on the following page. Doubling the use of methylphenidate as first-line therapy to 100% (Scenario 2) more than doubled these savings. This corresponded to a decrease in total Medicaid payments of approximately $32 million in Scenario 1 and $66 million in Scenario 2 across the region.

Table 8. Estimated economic impact of varying the rate of first-line methylphenidate use in school-aged (6-18 years) children in a Medicaid population (2010 US dollars).

		Scenario 1		Scenario 2	
	Baseline* (~50% MPH)	75% MPH	Net Change vs. Baseline	100% MPH	Net Change vs. Baseline
Number Using as First Line Medication (n)					
Methylphenidate	48,955	71,424	(22,469)	95,232	(46,277)
Atomoxetine	15,968	8,215	7,753	0	15,968
Mixed amphetamine salts	30,310	15,593	14,717	0	30,310
Outcomes & Resource Use					
Positive Treatment Response (n)	35,236	35,236	(0)	35,236	(0)
Positive Treatment Response (%)	37.0%	37.0%	0%	37.0%	0%
Payments per child with ADHD (n=95,232)					
ADHD Medication	$955	$618	($337)	$262	($693)
Medication-related visits					
General Practitioner	$94	$94	$0	$94	$0
Specialist	$45	$45	$0	$45	$0
Other	$34	$34	$0	$34	$0
Total	$1,128	$791	($337)	$435	($693)
Annual payments for all children with ADHD	$107,422,889	$75,366,123	($32,056,766)	$41,399,592	($66,023,297)
			-29.8%		-61.5%
Plan payments for Covered Population < 19 years (n=956,700)					
Payment per member per month - overall (PMPMo)	$9.36	$6.56	($2.79)	$3.61	($5.75)

*Baseline distribution of first-line use taken from Christensen, 2010.

5.6 Methods: School-aged Population (Cost-Effectiveness)

The modeling described previously for the cost-effectiveness analysis of preschool-aged children was also used for school-aged children. Important methodological differences in the two analyses are described below.

Management Options

Analyses of the long-term management of ADHD in school-aged children were based on the four management strategies compared in the Multimodal Treatment Study of Children with ADHD (MTA) Cooperative Study: behavioral intervention, medication only, medication plus behavioral intervention, and "community care", which entailed provision of the results of baseline assessments and a list of community mental health resources (MTA Cooperative Group, 2004).

In this study, a total of 579 children aged 7-10 years were randomly assigned to one of the four groups and followed for up to 24 months (MTA Cooperative Group, 1999). Treatment response was based on the SNAP instrument as previously described. Rates of response for each intervention were 32% with behavioral interventions, 37% for medication only, 48% with combined interventions, and 28% in children under community care.

Population

Cost-effectiveness was evaluated in a hypothetical cohort of 1,000 Medicaid patients diagnosed with ADHD and considered the outcomes and costs associated with each modeled management strategy. Children in the school-age population were aged 6-18 years.

Time Horizon

Based on the follow-up available from the MTA study, outcomes associated with management of school-aged children are considered over *two* years.

Treatment-related Utilization and Payments

Behavioral therapy for school-aged children was based on the MTA study protocol and included weekly parent training (27 group sessions and 8 individual sessions, see Table 7), child-focused therapeutic summer camp, and a school-based intervention. Only the payments associated with parent training were considered, however, as the cost of other components were considered to be outside of the payer perspective taken. Compliance with group sessions was 78% over the course of therapy (MTA Cooperative Group, 1999); payments were adjusted downward accordingly. Individual sessions were assumed to occur with 100% compliance, as this information was not measured in the study (MTA Cooperative Group, 1999). Payments for behavioral/psychosocial therapy in children receiving medication only or community care were estimated using ratios of the costs of these services to total costs from a published economic analysis of the MTA study (Jensen, 2005), as utilization of such services was not reported for these treatment groups in available MTA publications.

Medication therapy was assumed to be methylphenidate 10 mg three times daily. As with the preschool analysis, therapy switching was not modeled due to a lack of available data. However, patients were assumed to be at risk of early treatment withdrawal, based on reported medication use percentages from the MTA study (MTA Cooperative Group, 2004).

5.7 Results: School-aged Population (Cost-Effectiveness)

The cost-effectiveness of three active management strategies were compared to community care in school-aged children with ADHD based on the 24-month findings of the MTA study (MTA Cooperative Group, 2004). The results of these analyses are displayed in Table 9 on the following page. Behavioral interventions alone and medication alone showed relatively similar outcomes with respect to treatment response rates (32% vs. 37%, respectively). The combination of behavioral interventions and medication increased the response rate to nearly 50%. All strategies were superior to community care, which had a 28% response rate; it should be noted that, because community care also made use of mental health resources as available, over two-thirds of children in community care reported medication use at some time during the study.

Over two years, active management increased the costs of care by $1,123, $13, and $1,387 over the estimated cost of $1,347 associated with community care for behavioral interventions, medication only, and the combination of both, respectively. Costs in the medication only and community care groups were very similar due to a relatively high estimated use of medication and behavioral services in the community care group.

For behavioral interventions alone, 25 children needed to be treated to achieve one additional treatment response relative to community care; this is a result of a 4% absolute difference in treatment response between the two. The cost per additional treatment response over those achieved by community care was approximately $28,070.

For the medication-only group, the NNT was 11, indicating that for every 11 patients treated, one additional treatment response would be gained, at a cost of $146 per additional response. The combination of medication and behavioral interventions resulted in the greatest number of children responding to treatment (an NNT of 5), but at a cost of $6,865 per response (due to the relatively high cost of behavioral interventions compared to medication).

We also conducted a separate comparison of combined behavioral and medication therapy vs. medication alone. Medication with behavioral intervention results in an 11% absolute increase in the number of children responding to treatment vs. medication alone, at an incremental cost of approximately $1,375 per child. This is equivalent to needing to treat 9 children to obtain one additional treatment response at a cost of approximately $12,300 per response.

Table 9. Cost-effectiveness of ADHD management strategies in school-aged children (6-18 years) over a 2-year time horizon.

	School-age Comparison Multimodal Treatment Study of Children with ADHD (MTA)			
	Behavioral Interventions	**Medication only**	**Medication + Behavioral**	**Community Care (Reference)**
Clinical Outcomes for 1000 Children with ADHD†				
Positive Treatment Response‡ (n)	320	370	482	280
Response Rate (%)	32%	37%	48%	28%
Relative Risk Reduction (vs. Reference Therapy)	6%	13%	28%	
NNT for 1 Additional Child with Improved Outcome	25	11	5	
Cumulative Cost per Child with ADHD				
ADHD Medication (Immediate Release Methylphenidate)	$152	$439	$416	$302
Behavioral/Psychosocial Therapy	$1,430	$34	$1,430	$158
Other Resource Utilization	$887	$887	$887	$887
Total Direct Medical Costs Over 1 Year(s)	$2,470	$1,360	$2,734	$1,347
Cost-Effectiveness				
Total Cost for Treating 1000 Children	$2,469,830	$1,360,177	$2,733,763	$1,347,021
Net Cost for 1000 Children with ADHD (vs. community care)	$1,122,809	$13,156	$1,386,742	
Net Treatment Response for 1000 Children with ADHD	40	90	202	
Cost/Treatment Response	$28,070	$146	$6,865	

*MTA Cooperative Group, 2004; 24 month outcomes

†A negative net difference indicates that the comparator strategy is better than the reference strategy.

‡Positive treatment response reported as a "near normalization" or "excellent responder" score on the SNAP.

5.8 Conclusions

Based on the estimates in this analysis, increases in the use of methylphenidate as first-line therapy (from ~50% to 75%) in school-aged children undergoing medication management for ADHD would result in a reduction in payments for Medicaid programs in New England by approximately 30%, or $32 million. If *all* such children begin on methylphenidate, these savings may be doubled. It is important to note that, for these analyses, all medications were considered to be equally effective, so no changes in the proportions of children responding to treatment were assumed.

The cost-effectiveness analyses, taken as a whole, indicate there is a positive benefit to active management (medication and/or behavioral therapy) over usual or community-based care. The estimated additional cost of active management among preschool children is approximately $160 - $800 over one year of treatment. In school-aged children, these incremental costs range from $13 - $1,400 over *two* years. In all cases, a relatively small number of patients must be treated to achieve an additional response to treatment.

Pairwise analyses in the preschool population must be viewed with caution as these analyses are internally consistent – that is, each analysis stands on its own – but the relative advantage of treatment over usual care cannot be reliably compared across interventions. The comparisons are based on three separate studies which vary in duration, patient and family/caregiver characteristics, comparator therapy, and, most importantly, definition of clinically-significant response. While the analysis of school-aged children evaluated multiple management options from a single study, the comparator was community-based care, which differed in several respects from the usual care/wait-list definition employed in the preschool studies.

5.9 Comparison of ICER Analysis to Published Cost-Effectiveness Analyses

Several studies examining the economic impact of managing children diagnosed with ADHD have emerged over the past decade. A total of five cost-effectiveness studies were identified from the literature (Cottrell, 2008; Faber, 2008; Foster, 2007; Hong, 2009; Jensen, 2005). Three of these studies considered costs and quality adjusted life years (QALYS) as the main outcomes for medication use (atomoxetine or methylphenidate) in school-age children over periods of 1 year (Cottrell, 2008; Hong, 2009) and 10 years (Faber, 2008). Because we did not attempt to measure QALYs in our analysis, it is difficult to compare summary outcomes from these studies with ours. However, the incremental costs for medication assumed in the short-term in these studies were similar to those in our analyses.

Two economic analyses were based on the MTA study that serves as the basis of our school-aged cost-effectiveness analysis (Foster, 2007; Jensen, 2005). In these studies, effectiveness was defined as a composite measure of treatment success similar to our clinically-significant response measure. Cost-effectiveness estimates in this report were slightly lower than those reported in the literature relative to community care for the behavioral intervention alone (cost/response: $28,070 in the ICER analysis vs. $68,128 in the MTA analysis) and the combined medication/behavioral intervention strategy ($6,865 vs. $15,993, respectively), and very similar for medication alone ($360 vs. $146 respectively). This was likely due to our use of a proxy for Medicaid payment levels, as costs based on private-pay estimates (see Appendix D, Table D5) were very similar to those in the MTA study.

6. Questions and Discussion

Following the public CEPAC meeting on June 1, 2012, this section will be completed to capture the discussion of the Council members regarding the adaptation, specifically around these Questions to Guide Discussion.

Introduction

Each public meeting of CEPAC will involve deliberation and voting on key questions related to the supplementary analysis of the AHRQ review being presented by ICER. Members of CEPAC will discuss issues regarding the application of the available evidence to guide clinical decision-making and payer policies. The key questions are developed by ICER with significant input from members of the CEPAC Advisory Board to ensure that the questions are framed to address the issues that are most important in applying the evidence to practice and medical policy decisions.

About the Questions

The general framework within which CEPAC discusses and votes on the evidence is shown below:

Given a health care "intervention A" for "patients with condition X," we will compare its clinical effectiveness for these patients to that of a "comparator B" by voting on the following question:

Is the evidence on risks and benefits "adequate" to demonstrate that "intervention A" is as good or better for "patients with condition X" than "comparator B"?

Discussion and voting will highlight the following issues:

1. The evidence on risks and benefits to determine the *comparative* clinical effectiveness of management options for specific patient populations. In judging comparative clinical effectiveness, there are two interrelated questions: the relative magnitude of differences in risks and benefits; and the relative confidence that the body of evidence can provide in the accuracy of estimates of risks and benefits. Considering these two issues together is required in order to make a judgment of whether the evidence is "adequate" to demonstrate that one intervention is as good or better than another.
2. Issues related to individual patient preferences and values, provider training, volume, or other factors that should be considered in judging the evidence on clinical effectiveness and value.
3. Weighing the evidence on cost-effectiveness and projected budgetary impact to determine the comparative value of various management options for key patient populations.
4. Comments or recommendations related to broader considerations of public health, equity, disparities, and access.

Reasons for Voting "No"

When over half of the Council votes "no," indicating that they believe the evidence is not adequate to demonstrate that an intervention is as good or better than a comparator, CEPAC members who voted "no" will be asked to choose from a set of reasons to explain the rationale for their vote:

1. Insufficient quantity of evidence (i.e. too few studies)
2. Risk of bias inherent in study designs
3. Uncertainty over validity of surrogate outcome measures
4. Uncertainty over duration of clinical benefit
5. Uncertainty over the rates or magnitude of clinical benefits
6. Uncertainty over the rates or severity of potential harms
7. Inconsistency of results of studies
8. Limited generalizability of the evidence to "real world" patients
9. Limited generalizability of the evidence to "real world" clinicians
10. There is adequate evidence that the intervention is inferior to the comparator

Comparative Value:

When a majority of CEPAC votes that the evidence is adequate to demonstrate that an intervention produces patient outcomes as good as or better than a comparator, the Council will also be asked to vote on whether the intervention represents a "high," "reasonable," or "low" value. The value "perspective" that CEPAC will be asked to assume is that of a state Medicaid program that must make resource decisions within a fixed budget for care. While information about hypothetical budget tradeoffs will be provided, CEPAC will not be given prescribed boundaries or thresholds for budget impact or incremental cost-effectiveness ratios to guide its judgment of high, reasonable, or low value.

For each vote, Council members will be asked to identify which element of the information provided to them on "value" was most influential in their judgment: 1) information on the incremental cost for an additional benefit (or for reduction in risk); or 2) information on the budget impact of different care/payment scenarios. Council members will also be asked to describe briefly the rationale for their rating of comparative value.

Questions for Attention Deficit Hyperactivity Disorder (ADHD)

Definitions:

1. *Pre-schoolers*: Children under six years of age.
2. *Patients with ADHD or DBD*: Patients who received a diagnosis of Attention Deficit Hyperactivity Disorder or Disrupting Behavior Disorder (including Oppositional Defiant Disorder and Conduct Disorder) by the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria.
3. *Medication*: Pharmacological interventions used in the treatment of ADHD or DBD, including: methylphenidate (MPH), dextroamphetamine (DEX), mixed amphetamine salts (MAS), atomoxetine (ATX), and guanfacine extended release (GXR).
4. *Parent behavior training*: Manualized programs designed to help parents manage a child's problem behavior using rewards and non-punitive consequences.
5. *Usual care*: Care without medication or specific psychological/behavioral interventions, unless otherwise advised.
6. *Behavioral/psychosocial interventions*: Any one of a number of interventions aimed to assist the child and family through psychological and social therapies (e.g. psychoeducational, parent counseling, and social skills training).
7. *School-based interventions*: Interventions in which teachers are primary interveners and where the interventions take place in a classroom or school setting.
8. *Long-term outcomes*: Numerical or statistical results of any effectiveness or adverse event attributable to an intervention with a combined follow-up and treatment time equal to or greater than 12 months.

Comparative Clinical Effectiveness and Value: ADHD Treatment for Pre-Schoolers (children < 6 years of age)

Comparative Clinical Effectiveness

Based on the findings of the AHRQ review, and time limitations of the CEPAC meeting, we will ask CEPAC for consent to the following stipulations. If there is dissent, then a formal vote will be taken.

- Due to limitations of the available evidence, the evidence is not adequate to demonstrate that any other medication is as good as or better than methylphenidate (MPH) as a first-line treatment for preschoolers with either ADHD or DBD.
- Due to limitations of the available evidence, the evidence is not adequate to demonstrate that any branded parent behavior training (PBT) program is better than any other in preschoolers with ADHD or DBD.

Voting Questions:

1. Is the evidence on risks and benefits adequate to demonstrate that medication is as good as or better than usual care for treating pre-schoolers with ADHD or DBD?

a. If yes, does the evidence suggest that:
    - Medication is as good as (equivalent to) usual care without medication?
    - Medication is better than usual care without medication?

2. Is the evidence on risks and benefits adequate to demonstrate that parent behavior training is as good as or better than usual care for pre-schoolers with ADHD or DBD?
    a. If yes, does the evidence suggest that:
        - Parent behavior training is as good as (equivalent to) usual care?
        - Parent behavior training is better than usual care?

3. Is the evidence on risks and benefits adequate to demonstrate that medication combined with psychosocial/behavioral interventions (including parent-behavior training) is as good as or better than using medication alone to treat pre-schoolers with ADHD or DBD?
    a. If yes, does the evidence suggest that:
        - Medication combined with psychosocial/behavioral interventions is as good as (equivalent to) treatment with medication alone?
        - Medication combined with psychosocial/behavioral interventions is better than treatment with medication alone?

<u>Comparative Value (TO BE ASKED IF >50% OF CEPAC VOTES IN FAVOR OF ADEQUACY OF EVIDENCE ON CLINICAL EFFECTIVENESS)</u>

1. Based on reimbursement levels provided in this report, would you judge the comparative value of medication compared to usual care to be: 1) high value; 2) reasonable value; or 3) low value?

2. Based on reimbursement levels provided in this report, would you judge the comparative value of PBT compared to usual care to be: 1) high value; 2) reasonable value; or 3) low value?

3. Based on reimbursement levels provided in this report, would you judge the comparative value of medication combined with psychosocial/behavioral interventions (including PBT) compared to medication alone to be: 1) high value; 2) reasonable value; or 3) low value?

Comparative Clinical Effectiveness and Value: Long-Term Effectiveness of Treatments for ADHD in children 6 years and older

Comparative Clinical Effectiveness

Stipulation:

- There is sufficient evidence to demonstrate that medications are better than usual care for treating patients with ADHD over the age of 6.

Voting Questions

1. Is the evidence on risks and benefits adequate to demonstrate that any other medications are as good as or better than methylphenidate (MPH) in treating ADHD patients over the age of 6?
    a. If yes, does the evidence suggest that:
        - Other medication(s) are as good as (equivalent to) MPH beyond 1 year?
        - Other medications are better than MPH beyond 1 year?

2. Is the evidence on risks and benefits adequate to demonstrate that parent behavior training (PBT) is as good as or better than usual care in treating ADHD patients over the age of 6?
    a. If yes, does the evidence suggest that:
        - PBT is as good as (equivalent to) usual care beyond 1 year?
        - PBT is better than usual care beyond 1 year?

3. Is the evidence on risks and benefits adequate to demonstrate that medication combined with behavioral/psychosocial interventions is as good as or better than medication alone?
    a. If yes, does the evidence suggest that:
        - Medication combined with behavioral/psychosocial interventions is as good as (equivalent to) medication alone beyond 1 year?
        - Medication combined with behavioral/psychosocial interventions is better than medication alone beyond 1 year?

Comparative Value (TO BE ASKED IF >50% OF CEPAC VOTES IN FAVOR OF ADEQUACY OF EVIDENCE ON CLINICAL EFFECTIVENESS)

1. Based on reimbursement levels provided in this report, would you judge the long-term comparative value of other medications compared to MPH to be: 1) high value; 2) reasonable value; or 3) low value?

2. Based on reimbursement levels provided in this report, would you judge the long-term comparative value of PBT compared to usual care to be: 1) high value; 2) reasonable value; or 3) low value?

3. Based on reimbursement levels provided in this report, would you judge the long-term comparative value of combined medications and behavioral/psychosocial treatments compared to medication alone to be: 1) high value; 2) reasonable value; or 3) low value?

Comparative Clinical Effectiveness and Value: School-Based Interventions for ADHD

1. Is the evidence on risks and benefits adequate to demonstrate that adding school-based interventions to treatment regimens including medication and/or all types of behavioral/psychosocial interventions is as good as or better than medication and/or behavioral/psychosocial interventions alone?
    a. If yes, does the evidence suggest that:
        - Adding school-based interventions to medication and/or behavioral/psychosocial interventions is as good as (equivalent to) medication and/or behavioral/psychosocial interventions alone beyond 1 year?
        - Adding school-based interventions to medication and/or behavioral/psychosocial interventions is better than medication and/or behavioral/psychosocial interventions alone beyond 1 year?

Comparative Value (TO BE ASKED IF >50% OF CEPAC VOTES IN FAVOR OF ADEQUACY OF EVIDENCE ON CLINICAL EFFECTIVENESS)

1. Based on reimbursement levels provided in this report, would you judge the long-term comparative value of adding school-based interventions to medication and/or all types of behavioral/psychosocial interventions compared to medication and/or behavioral/psychosocial interventions alone to be: 1) high value; 2) reasonable value; or 3) low value?

Broader Considerations of Public Health, Equity, and Access

Are there any considerations related to public health, equity, disparities in access or outcomes for specific patient populations, or other social values that should be considered in medical policies related to the use of medications, parent behavior training, or other psychosocial interventions for pre-schoolers and people 6 years old and over for the treatment of ADHD?

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Appendix A

Overview of Parent Behavior Training Programs for ADHD

The AHRQ review covered four main parent behavior training programs listed below. All four programs are designed to help parents manage behavior through rewards and non-punitive strategies and by fostering a positive and caring parent-child relationship. Note: these are the "branded" parent behavior training programs, and one ADHD expert has mentioned that many mental health providers are trained to offer parent behavior training but do not get certified or accredited by these groups.

Program	Description	Cost	Availability	Insurance Coverage
Triple P – Positive Parenting Program ® http://www.triplep.net/	• Parents meet **individually** with a practitioner for 1-1.5 hrs for 10-12 weeks • Program focuses on teaching parents 17 core child management strategies to promote child development and help manage misbehavior • Parents also do **self-directed** study with "homework" from workbooks that help them set and monitor their own goals • Several of the sessions take place in the home • Accreditation offered to professional practitioners with post-secondary qualifications in health, education, or social services with knowledge of child/ adolescent development and experience working with families; not all providers are licensed mental health practitioners	Costs of the program are determined by the providers Options include: -Flat rate -Coverage by insurance -Costs built into overall budget with services provided free to the community	Accreditation available from Triple P Website claims 20,000 practitioners worldwide **146 providers in New England:** Connecticut: 39 (mostly in the Lower Naugatuck Valley) Maine: 38 (practitioners are spread across the state) Massachusetts: 51 (mostly in Springfield and Boston) New Hampshire: 17 (mostly in Groveton and Gorham) Rhode Island: 0 Vermont: 1	For the ADHD and DBD program, most providers are able to bill private insurance and get reimbursed as if it was a "typical" mental health visit; for those Triple P providers that do not accept insurance, costs are out-of-pocket for parents.

Program	Description	Cost	Availability	Insurance Coverage
The Incredible Years® parenting program (IYPP) http://www.incredibleyears.com/	• **Group** sessions for parents run by two specially trained leaders for 12, 2-2.5 hour weekly sessions for 10-14 participants – components of the Basic parent program are: o Program 1 - Strengthening Children's Social Skills, Emotional Regulation and School Readiness Skills o Program 2 - Using Praise and Incentives to Encourage Cooperative Behavior o Program 3 - Positive Discipline - Rules, Routines and Effective Limit Setting o Program 4 - Positive Discipline - Handling Misbehavior • Emphasizes parenting skills to promote children's social competence and to reduce behavior problems, and it teaches parents how to play with children, help children to learn, give effective praise and incentives, use limit-setting, and handle misbehavior. • Leaders are from many disciplines, including counseling, social work, psychology, psychiatry, nursing, and education and have training in child development, behavior management and group process. • Leaders are trained and accredited from the Incredible Years organization	Costs for group parenting estimated at $500/per parent for a full session	Certification available from Incredible Years organization Training is not required for purchase of program	No evidence of insurance coverage found – some private insurers may cover the cost

Program	Description	Cost	Availability	Insurance Coverage
Parent-Child Interaction Therapy (PCIT) http://pcit.phhp.ufl.edu/	• Based on a clinician's guide developed in 1995 by Hembree-Kigin and McNeil • Parents and child meet **individually** with a practitioner (often behind a one-way mirror giving tips via wireless microphone to the parent) for "special playtime" where parents are taught skills to modify unwanted behavior to be deployed during playtime – known as Relationship Enhancement • Parents also learn "discipline skills" where parents are taught behavior management strategies – known as Child Management • Sessions continue until the parent has mastered the skills and the child is in the normal range on a behavior-rating scale; typically 12-20 weekly sessions (1-2 hr sessions) • Practitioners must have at least a Masters degree in a mental health field	Based on rates set by the practitioner; some practices claim $150+ per session for a total of $1800-3000 per course of treatment	Any Masters level practitioner can get certified in PCIT	Some practitioners aid parents in filing paperwork for reimbursement; some claim that PCIT is often covered under insurance plans as family therapy or as individual child psychotherapy if the practitioner is covered by the insurance company; many practitioners offer sliding scale fees

Program	Description	Cost	Availability	Insurance Coverage
New Forest Parenting Program (NFPP) http://www.innovationssoutheast.nhs.uk/index.php?option=com_k2&view=item&id=9:new-forest-parenting-programme-nfpp&Itemid=159	• Consists of 8, once weekly, **individual,** hour-long in-home sessions delivered by a trained nurse-therapist • Provides training for parents on how to best manage and modify their child's behavior • Integrates cognitive-behavioral parent management training with parenting skills based on the developmental literature related to attention and regulation • Can be used in conjunction with or as an alternative to drug therapy • Developed in the UK, being trialed in the US in NY (through a grant from National Institute of Mental Health) • The only program designed specifically to address ADHD symptoms (of the 4 programs cited in the AHRQ review)	N/A – not yet widely offered in the US	Not yet widely offered in the US	N/A – not yet widely offered in the US

Appendix B

Stimulant Pharmacotherapy – Short acting

Generic (Year of FDA approval)	Brand (Year of FDA approval)
Methylphenidate (1997) – 5 mg Also available as oral solution (2010)	Ritalin (1955) – 5 mg
	Methylin (2003)– 5,10,20 mg Also available as **chewable tablets (2003)*** and oral solution (2002)
Dexmethylphenidate (2007) - 2.5,5,10 mg	Focalin (2001)– 2.5,5,10 mg
Dextroamphetamine (2001) – 5,10 mg Also available as oral solution (2008)	Dexedrine (1976) - 5 mg – no longer available
	Dextrostat (1975) – 5, 10 mg – no longer available
Amphetamine-dextroamphetamine (mixed amphetamine salts) (2002) 1.25,2.5,5,7.5 mg	Adderall (1960) - 5,7.5,10,12.5,15,20,30 mg

* No generic available for the formulation listed.

Stimulant Pharmacotherapy – Sustained-release formulations (intermediate- and long-acting)

Generic (Year of FDA approval)	Brand (Year of FDA approval)
Methylphenidate, extended release Generic (2001) – 20 mg Generic (2008) – 10 mg Generic (2011) – 20,30,40 mg Generic (2012) – 18,27,36,54 mg	Ritalin-SR (1982) – 20 mg only
	Ritalin LA (2002) – 10,20,30,40 mg
	Methylin ER (2000) – 10,20 mg
	Metadate CD (2001)– 20 mg Metadate CD (2003) – 10,30 mg Metadate CD (2006) – 40,50,60 mg
	Metadate ER (1988) – 20 mg Metadate ER (1999)– 10 mg
	Concerta (2000)– 18,27,36,54 mg
	Daytrana (2006) – 10,15,20,30 mg (transdermal patch)*
Dexmethylphenidate XR - no generic available	Focalin XR (2005)– 5,10,20 mg Focalin XR (2009) – 30 mg Focalin XR (2010) – 15,40 mg Focalin XR (2011) – 25,35 mg
Dextroamphetamine, extended release Generic (2002) – 5,10,15 mg Generic (2011) – 2.5,5,7.5,20,30 mg	Dexedrine spansule (1976) – 5,10,15 mg
Amphetamine-dextroamphetamine (mixed amphetamine salts) (2009)– 5,10,15,20,25,30 mg	Adderall XR (2001) – 10,20,30 mg Adderall XR (2002) - 5,15,25 mg
Lisdexamfetamine – no generic available	Vyvanse (2007) – 20,30,40,50,60,70 mg

* No generic available for the formulation listed.

Non-stimulant Pharmacotherapy

Generic (Year of FDA approval)	Brand (Year of FDA approval)
Atomoxetine –no generic available	Strattera (2002) – 10,18,25,40,60 mg Strattera (2005) – 80,100 mg
Guanfacine, extended release – no generic available	Intuniv (2009) – 1,2,3,4 mg
Clonidine, extended release – no generic available	Kapvay (2010) – 0.1 mg

Appendix C

Table 1. Studies of Parent Behavior Training in Children < 6 years of age.

Author, Year Study Design	Number of Patients Mean Age % Male Diagnosis	Interventions	Length of Follow-up	Results	
				Child Behavior	Parent Competence
Bagner, DM 2010 RCT	N=28 Mean Age: 3.2 years Male: 71% Diagnosis: clinically significant externalizing behavior based on CBCL	PCIT vs. WLC	Primary analysis: 4 months Secondary Analysis: 8 months	At Primary Analysis: Significantly fewer disruptive and problematic behaviors in PCIT group ECBI-I p=0.0001 ECBI-P p=0.0001	At Primary Analysis: Significantly less stress, less overreactivity in parenting style in PCIT group PSI-SF p=0.004 PS p=0.029
Forehand, RL 2011 RCT	N=39 Mean Age: 4.5 years Male: 51% Diagnosis: mean ECBI at baseline = 129.6	Group Curriculum (GC) vs. WLC	Primary Analysis: 6 weeks Secondary Analysis: 2 months	At Primary Analysis: Significantly lower scores in GC group ECBI-I p<0.05 ECBI-P p<0.01	At Primary Analysis: Significantly lower levels of overreactivity and improved positive parenting in GC group PS-o p<0.05 PS-p p<0.01
Lakes, KD 2011 Prospective Cohort	N=154 Mean Age: 3.8 years Male: 50% Diagnosis: Positive for problem behavior based on SDQ	CUIDAR COPE program	Primary Analysis: 10 weeks Secondary Analysis: 1 year	Significant improvement on multiple subscales of the SDQ (ranging from p<0.05 to p<0.001)	Significant improvement in parenting behavior (PSA) 3 of 10 subscales, p<0.01
McGrath, PJ 2011 RCT	N=80 Mean Age: 4.9 years Male: 78% Diagnosis: ODD	Strongest Families (telephone-based PBT) vs. UC	120, 240 and 365 days	Although significant treatment effects seen at 120 and 240 days, no significant differences seen at 365 days	

Table 1, Continued.

Author, Year Study Design	Number of Patients Mean Age % Male Diagnosis	Interventions	Length of Follow-up	Results	
				Child Behavior	Parent Competence
Morawska, A 2011 RCT	N=67 Mean Age: 3.6 years Male: 55% Diagnosis: mean ECBI at baseline = 146.4	Brief Parent Discussion Group vs. WLC	6 months	Significant improvement in behavior with Parent Discussion Group ECBI-I p=0.008 ECBI-P p=0.008	Significantly lower levels of overreactivity and verbosity with Parent Discussion Group PS-o p<0.001 PS-v p<0.001
Webster-Stratton, CH 2011 RCT	N=99 Mean Age: 5.3 years Male: 76% Diagnosis: ADHD with or without ODD	IYPP (Parent and Child programs) vs. WLC	8 months	Significant improvement in symptoms with IYPP <u>Mother</u> ECBI-I p≤0.001 ECBI-P p≤0.001 <u>Father</u> ECBI-I p≤0.001 ECBI-P p≤0.001 <u>Teacher</u> CBCL-externalizing p≤0.05	Significant improvement in parenting behavior for mother only (4 of 5 domains of PPI) No significant changes in parenting behavior for father (5 of 5 domains of PPI)

<u>Abbreviations:</u> ADHD: attention deficit hyperactivity disorder; CBCL: Child Behavior Checklist; ECBI-I: Eyberg Child Behavior Index – intensity; ECBI-P: Eyberg Child Behavior Index – problem; IYPP: Incredible Years parenting program; LD: learning disability; N: number; N/A: not available; ODD: oppositional defiant disorder; PBT: parent behavior training; PCIT: Parent-Child Interaction Therapy; PPI: Parenting Practices Inventory; PS: Parenting Scale; PS-o: Parenting Scale – overreactivity; PS-v: Parenting Scale – verbosity; PSA: Parenting Strategy Assessment; PSI-SF: Parenting Stress Index – Short Form; RCT: randomized controlled trial; SDQ: Strengths and Difficulties Questionnaire; UC: usual care; WLC: waitlist control

Table 2. Pharmacotherapy in Children 6 years and older.

Author, Year **Study Design**	**Number of Patients** **Mean Age** **Male %** **Diagnosis**	**Interventions**	**Length of Follow-up**	**Adverse Effects**
Didoni, A 2011 Prospective Controlled Cohort	N=130 Mean Age: 10.9 years Male: 86% Diagnosis: ADHD	Methlyphenidate vs. Atomoxetine	1 year	No statistical differences between two groups; most common: decreased appetite (15.4 %), thinning (10.8%); Cardiovascular effects only reported in atomoxetine group: tachycardia (8 cases); Psychotic symptoms reported only in atomoxetine group: 4 patients (hallucinations, mild, transient and acute psychosis)
Trzepacz, PT 2011 RCT	N=394 Mean Age: 10.4 years Male: 90% Diagnosis: ADHD	Atomoxetine vs. Placebo	18 months	Adverse Effects: For those with frequency >5%, increased appetite occurred more in patients receiving placebo vs. ATX (7.1% vs. 1.4%, p=0.006; gastroenteritis occurred more often in patients receiving ATX vs. placebo (8.2% vs. 2.7%, p=0.046); most frequent ADEs in patients were headache and nasopharyngitis; Height: Patients in the ATX group had a smaller mean increase in height vs. placebo (3.23 vs. 4.22 cm); Weight: Patients in the ATX had a significantly smaller increase in weight vs. placebo (1.86 vs. 4.64 kg, p<0.001)
Zhang, H 2010 Prospective Controlled Cohort	N=175 Mean Age: 7.9 years Male: 85% Diagnosis: ADHD	Methylphenidate vs. No medication	2-4 years	Height: Patients receiving methylphenidate experienced significantly greater height gaps over time compared to control (p<0.001); Weight: No significant difference was found between patients receiving MPH vs. control (p>0.05)

Abbreviations: ADHD: attention deficit hyperactivity disorder; ATX: atomoxetine; MPH: methylphenidate; N: number; RCT: randomized controlled trial

Table 3. Incidence of Cardiovascular and Cerebrovascular Adverse Events in Patients Receiving Stimulant Pharmacotherapy: Retrospective Cohort Data.

Author, Year	Number of Patients Person-Years of Follow-up	Medications Included	Mean Age (Range)	Cardiovascular Outcomes	Cerebrovascular Outcomes
Cooper, WO 2011	N=1,200,438 Years of F/U: 2,579,104	MPH Dex-MPH Dex-AMP MAS ATX Pemoline	Mean Age: 11.1 years (2-24)	Sudden cardiac death: HR 0.88 (0.65-3.56) Acute MI: N/A	Stroke: HR 0.93 (0.29-2.97)
Habel, LA 2011	N=443,198 Years of F/U: 806,182	MPH Dex-AMP MAS ATX Pemoline	Median Age: 42 years (34-49)	Sudden cardiac death: RR 0.82 (0.52-1.29) MI: RR 1.08 (0.86-1.36)	Stroke: RR 0.93 (0.65-1.31)
Olfson, M (b) 2012	N=171,126 Years of F/U: 304,310	All MPH and AMP preparations	Ages 6-12 years: 58.2% Ages 13-21 years: 41.8%	*Only 1 severe CV event recorded – no further analysis conducted Less severe CV event: OR 0.69 (0.42-1.12) CV symptoms: OR 1.18 (0.89-1.59)	
Schelleman, H 2011	N=1,207,085 Years of F/U: NR Median days of F/U ranged from 60-611 (IQR ranged from 30-1371)	MPH AMP, including MAS ATX	Median Age: 9-11 years, across groups (3-17)	Sudden death or ventricular arrhythmia: HR 1.60 (0.19-13.60) MI: inestimable (no reported events)	Stroke: inestimable (no reported events)

* Severe CV events: acute MI, subarachnoid or intracerebral hemorrhage, occlusion or stenosis of cerebral arteries, acute cerebrovascular disease, ischemic heart disease, sudden death or respiratory arrest. Less severe CV event: angina, cardiac dsrhythmias or transient cerebral ischemia. CV symptoms: tachycardia, palpitations, or syncope.

Abbreviations: AMP: amphetamine; ATX: atomoxetine; CV: cardiovascular; Dex-AMP: dextroamphetamine; Dex-MPH: dexmethylphenidate; F/U: follow-up; HR: hazard ratio; IQR: interquartile range; MAS: mixed amphetamine salts; MI: myocardial infarction; MPH: methylphenidate; N: number; N/A: not available; NR: not reported; OR: odds ratio; RR: rate ratio

Table 4. Non-pharmacologic Interventions in Children 6 years and older.

Author, Year Study Design	Number of Patients Mean Age Male % Diagnosis	Interventions	Length of Follow-up	Results	
				Child Behavior	Parent Competence
Iseman, JS 2011 RCT	N=29 Mean Age: 13 years Male: 72% Diagnosis: ADHD with LD	School-based (planning strategy instruction) vs. regular math instruction 65.5% of sample received medications for ADHD	Post-intervention (3 weeks) and 1 year	Post-intervention: Experimental group had significant improvement over control in 3 measures of performance (p<0.05) 1-year: Significantly greater improvement maintained in experimental group in 1 subtest (Math Fluency	N/A
McGrath, PJ 2011 RCT	N=72 Mean Age: 8.9 years Male: 75% Diagnosis: ADHD	Strongest Families (telephone-based PBT) vs. UC	120, 240 and 365 days	Statistically significant treatment effects found at 240 (p=0.03) and 365 (p=0.04) days in patients receiving PBT	
Myers, K 2010 Prospective Cohort	N=116 Mean Age: 8.8 years Male: 73% Diagnosis: ADHD	Collaborative Care Model (care manager, pediatrician and psychiatrist) 90% of the patients received concurrent medication	14 months	Significant improvement in ADHD symptoms as assessed by parents (VADPRS, p<0.05); improvement noted by teachers, although not significant (VADTRS, p: not reported)	

Abbreviations: ADHD: attention deficit hyperactivity disorder; LD: learning disability; N: number; N/A: not available; PBT: parent behavior training; RCT: randomized controlled trial; UC: usual care; VADPRS: Vanderbilt ADHD Rating Scales – Parent; VADTRS: Vanderbilt ADHD Rating Scales - Teacher

Appendix D

ADHD Management Strategies: Private Payer Perspective

Table D1. General model input parameters for all private payer analyses.

Unit Item	Input/ Expenditure	Frequency	Total cost per year
Payment Items			
Medication (AWP)			
MPH 5 mg (generic) - immediate release	$0.48	3 doses per day	$526
MPH 10 mg (generic) - immediate release	$0.77	3 doses per day	$844
Atomoxetine	$7.37	1 dose per day	$2,692
Mixed amphetamine salts	$4.62	1 dose per day	$1,687
Parent Behavior Training			
Triple P (Positive Parenting Program)	$140.72	10 sessions per course	$1,407
School age behavioral/psychosocial therapy			
Individual sessions	$140.72	8 sessions per course	$1,126
Group sessions	$71.78	27 sessions per course	$1,938

AWP: Average Wholesale Price; MPH: methylphenidate

Parent Behavior Training versus Usual Care in Preschool Children

Table D2. One-year cost-effectiveness of parent behavior training versus usual care for preschool-aged children with ADHD.

	Preschool Comparison ADHD at risk for conduct problems*		
	Triple P	**Usual Care (Reference)**	**Net Difference**
Clinical Outcomes for 1000 Children with ADHD†			
Positive Treatment Response‡ (n)	620	230	390
Response Rate (%)	62%	23%	39%
Relative Risk Reduction (vs. Reference Therapy)			51%
NNT for 1 Child with Improved Outcome			3
Cumulative Cost per Child with ADHD			
ADHD Medication (Immediate Release Methylphenidate)	$0	$0	$0
Behavioral/Psychosocial Therapy	$1,407	$0	$1,407
Other Routine Resource Utilization	$739	$739	$0
Total Direct Medical Costs Over 1 Year(s)	$2,147	$739	$1,407
Cost-Effectiveness			
Total Cost for Treating 1000 Children	$2,146,591	$739,391	$1,407,200
Cost/Treatment Response			$3,608

*Bor et al., 2002; 81% of sample reported 5 or more risk factors out of 23 for conduct problems. This study was chosen as the results approximate the mean of all studies (n=3) reporting the same outcome measure - Reliable Change Index (RCI) based on the Eyberg Child Behavior Inventory (ECBI) - Intensity subscale

†A negative net difference indicates that the comparator strategy is better than the reference strategy.

‡Positive treatment response reported as the RCI >1.96.

Triple P=Positive Parenting Program, a form of Parent Behavior Training (PBT); Usual Care refers to children on a "waitlist" for PBT

Medication versus Usual Care in Preschool Children

Table D3. One-year cost-effectiveness of medication only versus usual care for preschool-aged children with ADHD.

	Preschool Comparison ADHD with Developmental Disorders*		
	Medication	**Usual Care (Reference)**	**Net Difference**
Clinical Outcomes for 1000 Children with ADHD†			
Positive Treatment Response‡ (n)	500	71	429
Response Rate (%)	50%	7%	43%
Relative Risk Reduction (vs. Reference Therapy)			46%
NNT for 1 Child with Improved Outcome			2
Cumulative Cost per Child with ADHD			
ADHD Medication (Immediate Release Methylphenidate)	$526	$0	$526
Behavioral/Psychosocial Therapy	$0	$0	$0
Other Routine Resource Utilization	$739	$739	$0
Total Direct Medical Costs Over 1 Year(s)	$1,265	$739	$526
Cost-Effectiveness			
Total Cost for Treating 1000 Children	$1,265,351	$739,391	$525,960
Cost/Treatment Response			$1,226

*Ghuman et al., 2009; study of children with a diagnosis of ADHD *and* pervasive developmental disorder (PDD) or intellectual disability (ID).
†A negative net difference indicates that the comparator strategy is better than the reference strategy.
‡Positive treatment response reported as 25% or greater reduction on the CPRS-R-ADHD subscale *and* CGI-I rating of "much improved" or "very much improved" (CGI-I=Clinical Global Impression-Global Improvement; CPRS-R=Conners' Parent Rating Scale-Revised).

Parent Behavior Training with and without Medication in Preschool Children

Table D4. One-year cost-effectiveness of parent behavior training with medication versus parent behavior training alone for in preschool-aged children with ADHD.

	Preschool Comparison Preschool ADHD Treatment Study (PATS)*		
	Training/ Medication	**Training Only (Reference)**	**Net Difference**
Clinical Outcomes for 1000 Children with ADHD†			
Positive Treatment Response‡ (n)	220	130	90
Response Rate (%)	22%	13%	9%
Relative Risk Reduction (vs. Reference Therapy)			10%
NNT for 1 Child with Improved Outcome			11
Cumulative Cost per Child with ADHD			
ADHD Medication (Immediate Release Methylphenidate)	$526	$0	$526
Behavioral/Psychosocial Therapy	$1,407	$1,407	$0
Other Routine Resource Utilization	$739	$739	$0
Total Direct Medical Costs Over 1 Year(s)	$2,673	$2,147	$526
Cost-Effectiveness			
Total Cost for Treating 1000 Children	$2,672,551	$2,146,591	$525,960
Cost/Treatment Response			$5,844

*Greenhill et al., 2006

†A negative net difference indicates that the comparator strategy is better than the reference strategy.

‡Positive treatment response reported % achieving an "excellent response" on the SNAP composite score (SNAP=Swanson, Nolan, and Pelham).

Table D5. Cost-effectiveness of ADHD management strategies in school-aged children (6-18 years) over a 2-year time horizon.

	School-age Comparison Multimodal Treatment Study of Children with ADHD (MTA)			
	Behavioral Interventions	**Medication only**	**Medication + Behavioral**	**Community Care (Reference)**
Clinical Outcomes for 1000 Children with ADHD†				
Positive Treatment Response‡ (n)	320	370	482	280
Response Rate (%)	32%	37%	48%	28%
Relative Risk Reduction (vs. Reference Therapy)	6%	13%	28%	
NNT for 1 Child with Improved Outcome	25	11	5	
Cumulative Cost per Child with ADHD				
ADHD Medication (Immediate Release Methylphenidate)	$492	$1,416	$1,343	$973
Behavioral/Psychosocial Therapy	$3,064	$73	$3,064	$339
Other Routine Resource Utilization	$1,479	$1,479	$1,479	$1,479
Total Direct Medical Costs Over 1 Year(s)	$5,034	$2,967	$5,886	$2,791
Cost-Effectiveness				
Total Cost for Treating 1000 Children	$5,034,116	$2,967,414	$5,885,512	$2,790,592
Cost/Treatment Response	$2,243,524	$176,822	$3,094,919	
Clinical Outcomes for 1000 Children with ADHD†	40	90	202	
Positive Treatment Response‡ (n)				
Response Rate (%)	$56,088	$1,965	$15,321	

*MTA Cooperative Group, 2004; 24 month outcomes; †A negative net difference indicates that the comparator strategy is better than the reference strategy; ‡Positive treatment response reported as a "near normalization" or "excellent responder" score on the SNAP.

Table D6. Estimated economic impact of varying the rate of first-line methylphenidate use in school-aged (6-18 years) children in a private-pay population (2010 US dollars).

		Scenario 1		Scenario 2	
	Baseline (~50% MPH)	75% MPH	Net Change vs. Baseline	100% MPH	Net Change vs. Baseline
1st Line Medication (n)					
Methylphenidate	76,090	111,014	(34,924)	148,019	(71,929)
Atomoxetine	24,818	12,768	12,050	0	24,818
Mixed amphetamine salts	47,110	24,237	22,873	0	47,110
Outcomes & Resource Use					
Positive Treatment Response (n)	54,767	54,767	0	54,767	0
Positive Treatment Response (%)	37.0%	37.0%	0%	37.0%	0%
Payments per child with ADHD (n=148,019)					
ADHD Medication	$1,422	$1,141	($281)	$844	($578)
Medication-related visits					
GP	$157	$157	$0	$157	$0
Specialist	$75	$75	$0	$75	$0
Other	$57	$57	$0	$57	$0
Total	$1,711	$1,430	($281)	$1,132	($578)
Annual payments for all children with ADHD	$253,225,141	$211,654,901	($41,570,240) -16.4%	$167,608,136	($85,617,005) -33.8%
Plan payments for Covered Population < 19 years (n=2,230,500)					
Payment per member per month - overall (PMPMo)	$9.46	$7.91	($1.55)	$6.26	($3.20)

Appendix E

Estimated State-Wide Budget Impact in a School-Aged Medicaid Population

Connecticut

Table E1. Estimated economic impact of varying the rate of first-line methylphenidate use in school-aged (6-18 years) children in a Medicaid population (2010 US dollars).

		Scenario 1		Scenario 2	
	Baseline (~50% MPH)	75% MPH	Net Change vs. Baseline	100% MPH	Net Change vs. Baseline
1st Line Medication (n)					
Methylphenidate	9,727	14,192	(4,465)	18,923	(9,196)
Atomoxetine	3,173	1,632	1,541	0	3,173
Mixed amphetamine salts	6,023	3,098	2,925	0	6,023
Outcomes & Resource Use					
Positive Treatment Response (n)	7,002	7,001	(0)	7,002	0
Positive Treatment Response (%)	37.0%	37.0%	0%	37.0%	0%
Payments per child with ADHD (n=18,923)					
ADHD Medication	$955	$618	($337)	$262	($693)
Medication-Related Visits					
General Practitioner	$94	$94	$0	$94	$0
Specialist	$45	$45	$0	$45	$0
Other	$34	$34	$0	$34	$0
Total	$1,128	$791	($337)	$435	($693)
Annual Payments for all Children with ADHD	$21,345,345	$14,975,541	($6,369,804)	$8,226,260	($13,119,085)
			-29.8%		-61.5%
Plan payments for Covered Population < 19 years (n=190,100)					
Payment per Member per Month - Overall (PMPMo)	$9.36	$6.56	($2.79)	$3.61	($5.75)

Maine

Table E2. Estimated economic impact of varying the rate of first-line methylphenidate use in school-aged (6-18 years) children in a Medicaid population (2010 US dollars).

		Scenario 1		Scenario 2	
	Baseline (~50% MPH)	75% MPH	Net Change vs. Baseline	100% MPH	Net Change vs. Baseline
1st Line Medication (n)					
Methylphenidate	5,603	8,175	(2,572)	10,900	(5,297)
Atomoxetine	1,828	940	888	0	1,828
Mixed amphetamine salts	3,469	1,785	1,684	0	3,469
Outcomes & Resource Use					
Positive Treatment Response (n)	4,033	4,033	0	4,033	0
Positive Treatment Response (%)	37.0%	37.0%	0%	37.0%	0%
Payments per child with ADHD (n=18,923)					
ADHD Medication	$955	$618	($337)	$262	($693)
Medication-Related Visits					
General Practitioner	$94	$94	$0	$94	$0
Specialist	$45	$45	$0	$45	$0
Other	$34	$34	$0	$34	$0
Total	$1,128	$791	($337)	$435	($693)
Annual Payments for all Children with ADHD	$12,295,188	$8,626,101	($3,669,087)	$4,738,429	($7,556,759)
			-29.8%		-61.5%
Plan payments for Covered Population < 19 years (n=109,500)					
Payment per Member per Month - Overall (PMPMo)	$9.36	$6.56	($2.79)	$3.61	($5.75)

Massachusetts

Table E3. Estimated economic impact of varying the rate of first-line methylphenidate use in school-aged (6-18 years) children in a Medicaid population (2010 US dollars).

		Scenario 1		Scenario 2	
	Baseline (~50% MPH)	75% MPH	Net Change vs. Baseline	100% MPH	Net Change vs. Baseline
1st Line Medication (n)					
Methylphenidate	23,620	34,461	(10,841)	45,949	(22,329)
Atomoxetine	7,704	3,964	3,740	0	7,704
Mixed amphetamine salts	14,624	7,524	7,100	0	14,624
Outcomes & Resource Use					
Positive Treatment Response (n)	17,001	17,001	0	17,001	0
Positive Treatment Response (%)	37.0%	37.0%	0%	37.0%	0%
Payments per child with ADHD (n=18,923)					
ADHD Medication	$955	$618	($337)	$262	($693)
Medication-Related Visits					
General Practitioner	$94	$94	$0	$94	$0
Specialist	$45	$45	$0	$45	$0
Other	$34	$34	$0	$34	$0
Total	$1,128	$791	($337)	$435	($693)
Annual Payments for all Children with ADHD	$51,830,674	$36,363,544	($15,467,130)	$19,974,968	($31,855,706)
			-29.8%		-61.5%
Plan payments for Covered Population < 19 years (n=461,600)					
Payment per Member per Month - Overall (PMPMo)	$9.36	$6.56	($2.79)	$3.61	($5.75)

New Hampshire

Table E4. Estimated economic impact of varying the rate of first-line methylphenidate use in school-aged (6-18 years) children in a Medicaid population (2010 US dollars).

		Scenario 1		Scenario 2	
	Baseline (~50% MPH)	75% MPH	Net Change vs. Baseline	100% MPH	Net Change vs. Baseline
1st Line Medication (n)					
Methylphenidate	2,738	3,994	(1,256)	5,326	(2,588)
Atomoxetine	893	459	434	0	893
Mixed amphetamine salts	1,695	872	823	0	1,695
Outcomes & Resource Use					
Positive Treatment Response (n)	1,971	1,970	(0)	1,971	0
Positive Treatment Response (%)	37.0%	37.0%	0%	37.0%	0%
Payments per child with ADHD (n=18,923)					
ADHD Medication	$955	$618	($337)	$262	($693)
Medication-Related Visits					
General Practitioner	$94	$94	$0	$94	$0
Specialist	$45	$45	$0	$45	$0
Other	$34	$34	$0	$34	$0
Total	$1,128	$791	($337)	$435	($693
Annual Payments for all Children with ADHD	$6,007,238	$4,214,579	($1,792,659)	$2,315,123	($3,692,115)
			-29.8%		-61.5%
Plan payments for Covered Population < 19 years (n=53,500)					
Payment per Member per Month - Overall (PMPMo)	$9.36	$6.56	($2.79)	$3.61	($5.75)

Rhode Island

Table E5. Estimated economic impact of varying the rate of first-line methylphenidate use in school-aged (6-18 years) children in a Medicaid population (2010 US dollars).

		Scenario 1		Scenario 2	
	Baseline (~50% MPH)	75% MPH	Net Change vs. Baseline	100% MPH	Net Change vs. Baseline
1st Line Medication (n)					
Methylphenidate	4,462	6,510	(2,048)	8,680	(4,218)
Atomoxetine	1,455	749	706	0	1,455
Mixed amphetamine salts	2,763	1,421	1,342	0	2,763
Outcomes & Resource Use					
Positive Treatment Response (n)	3,212	3,212	0	3,212	0
Positive Treatment Response (%)	37.0%	37.0%	0%	37.0%	0%
Payments per child with ADHD (n=18,923)					
ADHD Medication	$955	$618	($337)	$262	($693)
Medication-Related Visits					
General Practitioner	$94	$94	$0	$94	$0
Specialist	$45	$45	$0	$45	$0
Other	$34	$34	$0	$34	$0
Total	$1,128	$791	($337)	$435	($693)
Annual Payments for all Children with ADHD	$9,791,236	$6,869,370	($2,921,867)	$3,773,434	($6,017,802)
			-29.8%		-61.5%
Plan payments for Covered Population < 19 years (n=87,200)					
Payment per Member per Month - Overall (PMPMo)	$9.36	$6.56	($2.79)	$3.61	($5.75)

Vermont

Table E6. Estimated economic impact of varying the rate of first-line methylphenidate use in school-aged (6-18 years) children in a Medicaid population (2010 US dollars).

		Scenario 1		Scenario 2	
	Baseline (~50% MPH)	75% MPH	Net Change vs. Baseline	100% MPH	Net Change vs. Baseline
1st Line Medication (n)					
Methylphenidate	2,804	4,091	(1,287)	5,455	(2,651)
Atomoxetine	915	471	444	0	915
Mixed amphetamine salts	1,736	893	843	0	1,736
Outcomes & Resource Use					
Positive Treatment Response (n)	2,018	2,018	0	2,018	0
Positive Treatment Response (%)	37.0%	37.0%	0%	37.0%	0%
Payments per child with ADHD (n=18,923)					
ADHD Medication	$955	$618	($337)	$262	($693)
Medication-Related Visits					
General Practitioner	$94	$94	$0	$94	$0
Specialist	$45	$45	$0	$45	$0
Other	$34	$34	$0	$34	$0
Total	$1,128	$791	($337)	$435	($693)
Annual Payments for all Children with ADHD	$6,153,208	$4,316,989	($1,836,219)	$2,371,378	($3,781,830)
			-29.8%		-61.5%
Plan Payments for Covered Population < 19 years (n=54,800)					
Payment per Member per Month - Overall (PMPMo)	$9.36	$6.56	($2.79)	$3.61	($5.75)