

**Attention Deficit Hyperactivity Disorder: Effectiveness
of Treatment in At-risk Preschoolers; Long-Term
Effectiveness in All Ages; and Variability in
Prevalence, Diagnosis, and Treatment**

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Prepared by:

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see <http://effectivehealthcare.ahrq.gov/reference/purpose.cfm>

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment

Executive Summary

Prepared for the Effective Health Care Program
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services

The full report and this summary are available at www.effectivehealthcare.ahrq.gov.

Background and Clinical Context

Children with ADHD, characterized by inattention, over-activity and impulsivity, are most frequently identified and treated in primary school. Population studies indicate that five percent of children worldwide show impaired levels of inattention and hyperactivity. Boys are classified with ADHD approximately twice as frequently as girls and primary school age children approximately twice as frequently as adolescents. ADHD symptoms exist on a continuum in the general population, and are considered as a ‘disorder’ to a greater or lesser degree depending on methods of identification, including who provides the information (e.g., parent or teacher), diagnostic criteria, and the threshold chosen for defining a ‘case’. The developmentally excessive levels of inattention, overactivity and impulsivity characteristic of ADHD are present from an early age. However, preschoolers with early signs of ADHD may also have cooccurring oppositional non-compliant behaviors, temper tantrums and aggression that overshadow symptoms of inattention and overactivity and confound the diagnosis. These concerns may be given the more general label of a disruptive behavior disorder, which include oppositional defiant disorder and conduct disorder as well as ADHD. If not already identified at an early age, preschool youngsters with Oppositional Defiance Disorder (ODD) frequently meet criteria for ADHD by grade school.

Although first described clinically in 1902,^a there were no treatments developed for children with difficulties with attention, hyperactivity and impulsiveness until the 1950s, when the syndrome was identified as “Minimal Brain Damage” or “Hyperkinetic syndrome” and methylphenidate (Ritalin) developed to target the condition.^b The use of pharmacotherapy has increased through the years along with refinements in understanding and acceptance of the condition as a disorder as reflected by its being included into widely accepted classifications systems, such as the Diagnostic and Statistical Manuals (DSM) and International Classification of Disease (ICD). The changes in labels over time reflect the contextual understanding of the condition as one of both environmental and biological etiology— from ‘defects of moral control’ in the Edwardian

^a See Still, 2006²¹³

^b See Eisenberg, 2007⁴

typology, through minimal brain dysfunction' in the 1960s, to Attention Deficit/ Hyperactivity Disorder (ADHD) with identified subtypes, in the 1980s and 1990s.^c Since effective pharmacological agents have been introduced, diagnosis of ADHD and prescriptions for its treatment has grown exponentially, particularly in North America, where the preferred DSM IV criteria identify greater numbers of children than the closely corresponding ICD 10 diagnosis of Hyperkinetic Disorder used more commonly in Europe.^d In the 1970s, the psychostimulants were classified as controlled substances due to rising concerns about misuse and abuse and data collection regarding their use became mandatory. During the same time period dextroamphetamine and methylphenidate were evaluated as effective treatments for children with the syndrome characterized by inattention and hyperactivity. Controversy continues with ongoing concerns identified about misuse in the community as well as a mismatch between who is identified and who is treated.^e (see Table 13).

The Disease Burden Associated With Attention Deficit Hyperactivity Disorder (ADHD)

Throughout childhood and adolescence, clinically significant ADHD is often associated with concurrent oppositional and aggressive behaviors, and also anxiety, low self-esteem, and learning disabilities. Symptoms generally interfere with academic and behavior functioning at school, and may also disrupt family and peer relationships. While ADHD begins before children enter school, it is most commonly identified and treated in primary school, age 7 to 9 years. The literature examining interventions has largely focused on the primary school age group over the years with the hope that intervening at this stage will diminish the adolescent risks of dropping out of school, initiating substance use, and associated conduct, mood and anxiety disorders, and dangerous driving. Preschoolers with ADHD who come to clinical attention most often have co-occurring non-compliant behaviors, temper and aggression that impairs their relationships with family and care providers and interferes with social and emotional development. Overall, levels of symptoms of overactivity and impulsiveness decrease with age, however the majority of children with ADHD continue to show impairment, especially poor attention, relative to same-age peers throughout adolescence and into adulthood. Estimates of prevalence of ADHD among adults world-wide is 2.5 percent.

Scope and Purpose of the Systematic Review

The purpose of this review is to i) critically examine the effectiveness and adverse events of interventions in preschool children with clinically significant disruptive behavior, and therefore at high risk for ADHD and ii) critically examine the comparative long-term effectiveness and adverse events of interventions for ADHD (pharmacological, psycho-social or behavioral and the combination of pharmacological and psychosocial or behavioral interventions) and iii) summarize what is known about patterns of identification and treatment for the condition. Factors to be examined include geography, sociodemographics, temporal aspects and provider

^c See Eisenberg, 2007⁴ & Mayes, 2007²

^d See Lehey, 2006⁵ & Dopfner⁶

^e See Goldman, 1998¹¹ & Schooner, 2007¹² & Costello, 2003¹⁰ & Angold, 2000⁹

background. This systematic appraisal will also identify gaps in the existing literature that will inform directions for future research. The key questions are as follows:

Key Question 1

Among children less than 6 years of age with Attention Deficit Hyperactivity Disorder or Disruptive Behavior Disorder, what are the effectiveness and adverse event outcomes following treatment?

Key Question 2

Among people 6 years of age or older with Attention Deficit Hyperactivity Disorder, what are the effectiveness and adverse event outcomes following 12 months or more of any combination of followup or treatment, including, but not limited to, 12 months or more of continuous treatment?

Key Question 3

How do; a) underlying prevalence of Attention Deficit Hyperactivity Disorder, and b) rates of diagnosis (clinical identification) and treatment for Attention Deficit Hyperactivity Disorder vary by geography, time period, provider type, and sociodemographic characteristics?

Interventions/medications reported in This Review

- Methylphenidate
- Guanfacine extended release
- Atomoxetine
- Parent behavior training
- Psychosocial interventions
- Behavioral interventions
- School based interventions

Conclusions

Treatment of Preschoolers with Disruptive Behavior Disorders

Very few RCTs offer information about parent behavior training interventions designed specifically for preschoolers with ADHD. On the other hand, twenty-eight randomized controlled trials (RCTs) show that parent behavior training is an efficacious treatment for preschoolers with disruptive behavior disorders; eight of these studies documented improvement specifically in ADHD symptoms. Long term extension (follow up) studies for the RCTs of parent behavior training suggest that the benefits are maintained for several years.^f However, no long term study included untreated comparison groups, and attrition over follow-up periods greater than 12 months was high, from 24 percent at 18 months^g to 54 percent at 3 to 6 years,^h limiting interpretation of the results. Studies do not comment on adverse events related to parent behavior training.

Five studies examining combinations of parent behavior training and school or daycare interventions for preschool children at risk for disruptive behavior disorders, and/or ADHD suggest that adding classroom teacher consultation may be important for children in low socioeconomic status (SES) communities, but not for families with educated parents who live in communities with resource.ⁱ Three of these five studies followed children for 12 months;^j the other two assessed children following completion of the initial kindergarten year and at a 2-year followup.^k Benefits of the kindergarten treatment classroom disappeared at 2 years without reinforcement.^l Direct comparisons of identical interventions offered to families of different SES have not yet been performed.

Fifteen reports representing eleven investigations of psychostimulant medication use in preschoolers, primarily immediate release methylphenidate, suggest that it is efficacious and safe; however, the evidence comes primarily from short-term trials lasting days to weeks with small samples. The Preschool ADHD Treatment Study (PATs) addresses a number of important methodological limitations and clinical concerns, examining the potential additional benefit of optimized dose of immediate release methylphenidate for four weeks following a series of 10 parent behavior training sessions. Careful attention to details regarding adverse events and impact of these on medication adherence offers clear information about long-term (up to 10 months) effectiveness and safety in this age group. Parent and teacher reported ADHD symptoms improved, concurrently with parents noting increased mood problems. The PATs study offers information about both the potential benefits and limitations of stimulant medication use in very

^f See Nixon, 2004⁴⁰ & Hood, 2003⁴¹ & FunderBurk, 1998⁴⁵ & Bywater, 2009⁵⁷ & Williford, 2008⁵⁸ & Jones, 2008⁶⁸ & Shelton, 2000⁶⁹

^g See Bywater, 2009⁵⁷

^h See Hood, 2003⁴¹ & Sanders, 2007⁵²

ⁱ See Williford, 2008⁵⁸ & Shelton, 2000⁶⁹ & Berkley, 2000⁷⁰ & McGoey, 2005⁷¹ & Kern, 2007⁷²

^j See Williford, 2008⁵⁸ & McGoey, 2005⁷¹ & Kern, 2007⁷²

^k See Shelton, 2000⁶⁹ & Berkley, 2000⁷⁰

^l See Shelton, 2000⁶⁹ & Berkley, 2000⁷⁰

young children. Limitations include: that preschool children experience more dose-related adverse events than older children, that stimulants interfere with rates of growth, and, that the presence of three or more comorbid conditions and psychosocial adversity are associated with lessened effectiveness of psychostimulant medication following parent training. Only 54 percent of those enrolled in the study entered the medication titration component following parent training, suggesting that parent preferences play an important role in providing optimum care for young children with ADHD.

Among the intervention studies for preschoolers, adverse events were documented for medication interventions as described above, but not for parent training or school-based interventions. Long-term extension studies are few, and suggest that benefits of parent training for disruptive behavior can be maintained over months and perhaps years. Benefits following combined parent training and classroom programs are present at one year. For a single cohort where symptom improvement appeared due primarily to the treatment kindergarten classroom, benefits seen initially were not maintained at the two-year followup.

Long-term Effectiveness and Safety of Interventions in Children Over the Age of 6 Years

Pharmacologic agents. The body of literature examining long-term effectiveness and safety is most robust among samples of children between 6 and 12 years at recruitment, mostly boys with ADHD, combined type, and for studies examining pharmacotherapeutic interventions for the core symptoms of ADHD. The long-term effectiveness and safety of several psychostimulants (e.g. methylphenidate immediate release^m amphetamine,ⁿ OROS methylphenidate,^o dextroamphetamine,^p mixed amphetamine salts,^q and sequential combinations of psychostimulants,^r the norepinephrine reuptake inhibitor, atomoxetine (ATX),^s and the noradrenergic agonists, clonidine^t guanfacine extended release (GXR)^u have been examined prospectively in children and adolescents over the age of 6 years. All of these agents are efficacious for control of inattention, overactivity and impulsiveness for at least 12 months, and few serious adverse events are noted. Global ratings of impairment also indicate continued benefit. Placebo-controlled discontinuation trials are few; one trial discontinued treatment with amphetamine after 15 months,^v and another examined relapse in children receiving ATX for 12 months.^w These trials suggest that some, but not all individuals continue to benefit from medication. Attrition over time occurs for a variety of reasons, including adverse events and ineffectiveness. Retention of participants on active treatment at 12 months varies across studies and agents, from a high of 98 percent for immediate release MPH,^x 75 percent amphetamine,^y 63

^m See Gadow, 1999⁹³ & Smith, 1998⁹⁹

ⁿ See Gillberg, 1997⁹²

^o See Hoare, 2005⁸⁹

^p See Barbaresi, 2006⁸⁷

^q See McGough, 2005⁹⁹ & Findling, 2005¹⁰³ & Weisler, 2005¹⁰⁴

^r See Law, 1999⁹⁷ & Charach, 2004⁹⁸ & Barbaresi, 2006⁸⁷

^s See Wiernickle, 2003¹⁰² & Nichelson, 2004⁹⁵ & Buitelaar, 2007⁹⁶ & Adler, 2005⁸⁸

^t See Steingard, 1993¹⁰¹

^u See Sallee, 2009⁹¹ & Biederman, 2008⁹⁰

^v See Gillberg, 1997⁹²

^w See Buitelaar, 2007⁹⁶

^x See Law, 1999⁹⁷

percent for OROS MPH,^z 58 percent MAS XR,^{aa} 56 percent ATX,^{bb} and 43 percent GXR.^{cc} In general, those who remain on medications show continued benefit and report few adverse events. Twelve of 18 studies reviewed were funded in all in part by industry, possibly leading to enhanced representations of effectiveness and safety.^{dd}

Psychostimulants continue to provide control of ADHD symptoms and are well tolerated for months to years at a time. Overall, there are few studies available which make direct comparisons of long-term outcomes of psychostimulants. Barbaresi 2006^{ee} compares MPH and dextroamphetamine use in a population-based retrospective cohort, boys and girls followed from birth to late adolescence. The mean duration of treatment for any single agent was 3.5 years +/- 3.1 years. The youngest and oldest children among them showed less benefit and more adverse effects. More boys than girls showed a positive response to dextroamphetamine, while fewer children experienced adverse events with MPH than with dextroamphetamine. Concerns about adverse events lead to discontinuation of medications for 15 to 20 percent of children over the age of 6 years using MAS XR.^{ff} Concerns about exacerbation of tics with stimulants appear to be unfounded,^{gg} although sample size remains small and may result in type II error. Use of psychostimulants slows the rate of growth,^{hh} and increases blood pressure and heart rate to a small degree.ⁱⁱ At a group level, the mean changes are clinically insignificant although on rare occasions, individuals discontinue an agent because of changes in vital signs.^{jj}

Atomoxetine has been evaluated for safety and efficacy for ADHD symptoms over 12 to 18 months among children and up to 3 years in adults.^{kk} Unlike studies of other agents, two studies offer direct comparison with placebo for examination of relapse prevention, offering clear evidence of effectiveness in children and teens.^{ll} However, teacher reported outcomes do not document statistically significant superiority of ATX over placebo, as children randomized to placebo following the clinical trial also maintained benefits to some degree.^{mmm} The study set a high threshold for relapse, (e.g. a return to 90 percent of baseline symptom score),ⁿⁿ and in this context, the vast majority of those on ATX (97.5 percent) as well as those on placebo (88 percent) did not relapse. Discontinuation in children and teens due to ineffectiveness appears to be higher (26 percent) and due to adverse events lower (3 percent) than with other agents,^{oo}

^y See Gillberg, 1997⁹²

^z See Hoare, 2005⁸⁹

^{aa} See Smith, 1998⁹⁹

^{bb} See Buitelaar, 2007⁹⁶

^{cc} See Sallee, 2009⁹¹

^{dd} See Lexchin, 2003¹⁰⁵

^{ee} See Barbaresi, 2006⁸⁷

^{ff} See Smith, 1998⁹⁹ & Hoare, 2005⁸⁹

^{gg} See Law, 1999⁹⁷ & Gadow, 1999⁹³

^{hh} See Faraone, 2007¹¹¹ & Charach, 2004⁹⁸ & Swanson, 2006⁸³ & Zabor, 2006¹¹⁴

ⁱⁱ See Findling, 2005¹⁰³ & Gadow, 1999⁹³ & Weisler, 2005¹⁰⁴ & Hoare, 2005⁸⁹

^{jj} See Findling, 2005¹⁰³

^{kk} See Nicholson, 2004⁹⁵ & Wiernickie, 2003¹⁰² & Buitelaar, 2007⁹⁶ & Adler, 2005⁸⁸

^{ll} See Nicholson, 2004⁹⁵ & Buitelaar, 2007⁹⁶

^{mmm} See Nicholson, 2004⁹⁵

ⁿⁿ See Nicholson, 2004⁹⁵ & Buitelaar, 2007⁹⁶

^{oo} See Nicholson, 2004⁹⁵

although these are not direct comparisons. As with psychostimulants, the group means for blood pressure and heart rate show small but clinically insignificant increases.^{pp} Adler et al.,^{qq} offer the only study of a pharmacologic intervention over an extended time period (3 years) in adults with ADHD. Symptom improvement was maintained for those on ATX; discontinuation due to adverse events was somewhat higher than for children (11 percent).

Long-term studies of Guanfacine extended release demonstrate that this agent is also effective in controlling ADHD symptoms for up to two years. High rates (40 to 60 percent) of somnolence, headache and fatigue occur when it is used as a monotherapy, especially in the initial 6 to 8 months of treatment.^{rr} Tolerance appears to be improved with concurrent administration of psychostimulants.^{ss} Changes in vital signs occur but no clear group trends are noted. Individuals may develop clinically significant hypotension and bradycardia.^{tt} Serious adverse events noted include syncope; and 1 percent of participants developed clinically significant changes on electrocardiogram (ECG), such as asymptomatic bradycardia.

Overall, pharmacologic agents used for controlling symptoms of inattention, overactivity and impulsivity of ADHD, show maintenance of effectiveness and safety for long periods of time. Along with decreased symptoms, overall functioning is improved, although studies do not control for adjunctive non-pharmacological interventions. A byproduct of the placebo controlled relapse prevention studies has been the opportunity to collect long-term comparison data suggesting that some children show maintenance of gains on placebo. The majority of children who participate in the trials of newer agents are boys with ADHD combined type and few comorbid conditions.

Psychosocial and Behavioral interventions, alone and in combination with Medication.

Investigations comparing psychosocial/behavioral interventions, alone and in combination to medication management, identified that both medication and combined medication/behavioral treatment are more effective in treating ADHD plus Oppositional Defiant Disorder (ODD) symptoms than psychosocial or behavioral interventions alone. These results apply to children, primarily boys aged 7 to 9 years of normal intelligence with combined type of ADHD, especially during the first 2 years of treatment. The combination of psychosocial and behavioral treatment with medication may have a slight advantage during the first 14 months especially for children with multiple co-morbidities. However, combined treatment is equivalent to medication alone in controlling ADHD and ODD symptoms for up to 2 years if the child shows an early favorable response to medication.

Evaluation of long term outcomes following interventions for ADHD is complex due to multiple patterns of services used. The best quality data is available through the 8 year followup of the multimodal treatment of children with ADHD study (MTA). The initial RCT compared 14 months of management of psychostimulant medication with three other interventions: psychosocial and behavioral treatment, the combination of medication, psychosocial and

^{pp} See Wiernickie, 2003¹⁰²

^{qq} See Adler, 2005⁸⁸

^{rr} See Sallee, 2009⁹¹ & Biederman, 2008⁹⁰

^{ss} See Sallee, 2009⁹¹

^{tt} See Sallee, 2009⁹¹ & Biederman, 2008⁹⁰

behavior treatment, and standard community care. Three years after initiation, the four intervention groups showed comparable outcomes. The majority of ADHD children who received interventions were maintaining improved functioning, although they did not match the functional levels of the non-ADHD comparison group. A small proportion returned to previous levels of poor functioning over time.

In the MTA trial, there was no clear relationship identified between duration of medication use and outcomes. Cohort studies suggest that increased duration of medication was associated with improved grade retention and academic achievement, and may also lessen onset of substance use disorders as well as oppositional defiant, conduct, anxiety and depressive disorders. These cohort studies provide longer duration of follow up into adulthood, but most rely on participant recall to provide information regarding medication use. No prospective studies have been designed to investigate the question directly.

There are very few studies describing long-term outcomes of treatments for ADHD on academic or school based outcomes. There appear to be long-term academic benefits with medication interventions in some domains (e.g., improved absenteeism and grade retention). Combining psychobehavioral and academic skills interventions with medication offers no additional gains from medication alone, at least for children with ADHD without co-morbid learning disabilities. Interventions directed at academic skills in classroom-based programs result in academic enhancement in a range of areas but sustained intervention is required to provide continued academic growth over time.

The domains of academic functioning and school outcomes under investigation vary widely across studies making it difficult to compare results. In addition, few of the studies controlled for learning disabilities and I.Q. Additional aspects to consider are the challenges inherent in examining the co-interventions offered in school and clinic settings.

Variability in Prevalence, Diagnosis and Treatment

One worldwide pooled prevalence estimate of ADHD among those 18 years of age or younger is 5.29 percent (95 percent CI: 5.01-5.56). More boys than girls have ADHD, and children in the age group 5 to 10 years show the highest prevalence. In addition, some studies suggest children from lower SES demonstrate higher levels of symptoms. Research detailing prevalence in other age groups world-wide is generally lacking, with few studies examining prevalence among preschoolers, adolescents, or adults. Primary sources of variability among studies were diagnostic criteria and informant.

Clinical identification of ADHD and treatment, generally defined as use of psychostimulants, increased throughout the early to mid-1990s, but appears to have slowed in the late 1990s and early 2000s in the United States (U.S.). Disparities among those who are identified and receive medication occur. Studies in the U.S., document that more boys than girls, more Caucasians than Hispanics or African Americans, more children living in affluent communities, and more children living in urban rather than rural centers, receive medication treatment. In addition, more children in the Midwest and South receive psychostimulants relative to the Western U.S. Clinical identification by non-physicians and non-medication interventions for ADHD were not captured in the sources of data used.

Key question 1. Among children less than 6 years of age with Attention Deficit Hyperactivity Disorder or Disruptive Behavior Disorder, what are the effectiveness and adverse event outcomes following treatment?

Key Question	Level of Evidence	Conclusion
a. Parent behavior training	Strong	Parent behavioral interventions are an efficacious treatment option for preschoolers with disruptive behavior disorders, and show benefit for ADHD symptoms. These studies support the long-term effectiveness of parent interventions for preschoolers with disruptive behavior disorders, including ADHD symptoms.
b. Multi-component home and school or daycare based interventions	Moderate; strong to moderate reports but few reports	Where there is no socioeconomic burden, multi-component interventions work as well as a structured parent education program. Where there is socioeconomic burden, the treatment classroom appears to be the primary beneficial intervention. However, the relative benefits of the treatment classroom diminished over two years.
c. Medication	Moderate	Methylphenidate is both efficacious and generally safe for treatment of ADHD symptoms, but there has been no long term followup in preschoolers

Key question 2: Among people 6 years of age or older with Attention Deficit Hyperactivity Disorder, what are the effectiveness and adverse event outcomes following 12 months or more of any combination of follow-up or treatment, including, but not limited to, 12 months or more of continuous treatment?

Key Question	Level of Evidence	Conclusion
a. Medication treatment	Moderate	Psychostimulants continue to provide control of ADHD symptoms and are generally well tolerated for months to years at a time. ATX appears to be both safe and effective for ADHD symptoms over long periods of time. Some individuals maintain benefit after discontinuation of medication as shown in studies of the effect of discontinuation of treatment following 12 months of use. Parents report benefit with GXR in reduced ADHD symptoms and global improvement. Monitoring of cardiac status may be indicated. Adverse events are better tolerated when given in combination with psychostimulants.
b. Combined psychostimulant medication and behavioral treatment	Strong Moderate	The results from 3 cohorts indicate both medication and combined medication and behavioral treatment are effective in treating ADHD plus ODD symptoms in children, primarily boys aged 7-9 years of normal intelligence with combined type of ADHD, especially during the first 2 years of treatment. Combined medication and behavioral treatment improves outcomes more than medication alone for some subgroups of children with ADHD, combined type, (e.g., comorbid ODD and anxiety, low SES).
c. Behavioral/	Weak	One report of moderate quality showed that a

Key Question	Level of Evidence	Conclusion
psychosocial		behavioral/psychosocial intervention was more effective for mothers than fathers, who reported less stress and less negative parenting.
d. Parent Behavior training	Moderate	Post-intervention gains are readily maintained at 1 year follow-up and more recent studies suggest that clinically-significant improvements may continue to be observed with time.
e. Academic interventions	Moderate	One strong study showed that classroom-based programs to enhance academic skills are effective in improving achievement scores in multiple domains, but the benefits are sustained only as long as the intervention is implemented.

Key question 3: How do A) underlying prevalence of Attention Deficit Hyperactivity Disorder, and B) rates of diagnosis (clinical identification) and treatment for Attention Deficit Hyperactivity Disorder vary by geography, time period, provider type, and sociodemographic characteristics?

- Context and cultural overlay influence how ADHD is understood from country to country, and thus how it is treated
- Underlying prevalence does not appear to vary much between nations and regions, once differences in methodologies for ascertainment are taken into account
- Rates of diagnosis vary considerably due to cultural context, time period, access to health care services, and provider type, as well as measurement and classification, among other factors; they also vary among regions within the United States
- Appreciation of the combined neuro-developmental and environmental etiologies and magnitude of impairment due to the condition has increased over the past 4 decades.

Remaining Issues

Since the AHRQ review of long term intervention studies for ADHD, published in 1997, researchers have sought opportunities to discover what has happened to the participants of earlier studies, and begun to tackle the challenges of prospective cohort studies. The primary weaknesses relate to these challenges. For interventions for preschoolers with disruptive behavior disorder, a primary challenge is documenting the comparison with the overlying effect of normal maturation; the extended studies do not have untreated comparison groups. Only recently have investigations of parent behavior training included direct measures of ADHD symptoms. Researchers also should describe what, if any, unintended negative consequences occur when offering families parent behavior training for their preschooler.

A second important finding follows the suggestive outcome that parents of different SES groups appear to benefit from different approaches. An important subtext is how the approach to parent behavior training could be adjusted to suit lower SES families as well as examining the mix of school and home approaches. Untapped is the likelihood that ‘care as usual’ varies in different communities leading to diverse outcomes in the comparison group.

The lack of research in adolescents and adults with ADHD presents a major gap in the literature. Also, few participants are girls, have ADHD inattentive subtype, or come from diverse racial or ethnic groups. No clinical studies have been designed to follow children through adolescence and

into adulthood, tracking the mix of interventions obtained by the subjects and the outcomes. Particularly challenging will be coordinating observations regarding academic interventions and outcomes. No prospective studies examining non-medication interventions have enrolled adolescents or adults identified with ADHD to investigate whether interventions at later stages of development are effective for improved functioning.

An important strength of the research in the past decade is the evidence for effective and safe medications for children, youth, and adults with ADHD. There are several documented pharmacological agents that control symptoms for 1 to 2 years. The choices help to optimize effectiveness and tolerability over this time period. Beyond 2 years, benefit appears to be highly variable. Examination of adverse event profiles in the clinical studies suggests that while treatment emergent cardiovascular concerns remain rare, use of GXR may require greater monitoring than psychostimulants or ATX. On a broader scale, health administrative data suggest that neither cardiac events among those 20 and younger, nor cerebrovascular accidents in adults are more frequent among those using medications for ADHD than for persons in the general population. Further examination in appropriate data sources is warranted however as adult users of psychostimulants or ATX may be at increased risk of transient ischemic attacks.

An important complementary source of health services information are the community based population studies that investigate questions about ADHD identification and treatment using epidemiological surveys or existing databases representing actual practice. The key limitations in this body of literature which interfere with the comparability of results are: the use of different sources for sample recruitment, variability among informants, and variability among the instruments used to measure ADHD across geographic areas. Reliability and validity of case identification can also be a concern in administrative data, although the size and representativeness of the sample populations offer compensatory advantages. A quality assessment of this literature, along with guidelines for how to improve the quality of population-based health services research for ADHD is beyond the scope of the current review.

Internet Citation

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Introduction

History

The story of Attention Deficit Hyperactivity Disorder (ADHD) is complex since the condition is identified clinically in the context of society and culture, with the strong influence of history governing the synthesis of these ideas and development of our models, and which in turn influences how we recognize and most effectively help those who display this configuration of behaviors under defined circumstances. Although Key Question 3 will address issues which influence our understanding of prevalence, at this point we include a brief, necessarily truncated, history, with a somewhat expanded timeline of relevant events in Appendix C.

Although anecdotally and in stories, characters with ADHD-like behaviors are described much earlier, the first clinical description of the syndrome was presented by Sir Frederick Still in 1902.¹ In this series of lectures, subsequently published in *The Lancet*, he describes children, more often boys than girls, who display ‘an abnormal capacity for sustained attention causing school failure, even in the absence of intellectual retardation’. He provides virtually a textbook description of ADHD children: his assessment and interpretations perhaps influenced and obscured slightly with other conditions now categorized separately and, in keeping with the understanding of the times, attributed to “defects of moral control”, he presents his observations of these children under different social conditions and environments and enlarges on the limitations and impairments they experience as a result.

Since, however, discoveries usually occur in a larger social context, it cannot be coincidence that this constellation of behaviors was thrown into sharp relief within a generation of the passing of The Educational Act (1876), which mandated elementary education for all children, and it is in contrast to this structured environment that even today, for many children, their attentional difficulties are defined.²

Observing that the sequelae in some survivors of the Spanish influenza epidemic included agitation, in 1922, Tredgold postulated the source of what we now term ADHD as neurologically based and called it ‘minimal brain damage’, although in fact only a few children displayed this post-influenza reaction; however, this theory set the stage for interpreting ADHD for the next half century as a neurological condition, until subsequent scientific discoveries, classification models and social events nudged theoretical constructs towards genetic, social or evolutionary explanations.^{2,3}

Helping these young patients was another matter; and it was not until Charles Bradley identified *d*, l-amphetamine in 1932 and discovered it worked ‘paradoxically’ for some among the in-patient children under his care, did doctors have an effective treatment strategy. The impact of this development, has been that once an apparently effective pharmacological solution appeared, widespread dependence on it as a model for treatment has persisted, even though 50 years later, in 1980, Rapoport observed that the calming and focusing effects of stimulants were apparent in both normal and ADHD children and that age, rather than susceptibility, was likely the defining feature of the drug effect.⁴

Parallel to pharmacological developments, creation of diagnostic categories, psychometric instruments and definitions were proceeding, both deriving from and shaping our understanding of this heterogeneous disorder.^{5,6}

Prescription data have been available for psychostimulant drugs since 1971 when they were re-categorized as Schedule II controlled substances, thus with mandatory reporting requirements. Prescription rates for methylphenidate have climbed from an estimated 4 million annually in 1991, with 1 million amphetamine prescriptions - until by 1999 they had reached 11 million methylphenidate, with 6 million amphetamine.² Despite its status as a controlled substance there is still cause for concern since methylphenidate appears so widely variable beyond the normal range of medical access points such as internet availability, as well as increased use as a 'study aid' on campuses,^{7,8} and evidence of mismatch between who gets diagnosed and who gets prescribed. Eisenberg⁴ cites the Great Smoky Mountain studies by Angold⁹ and Costello,¹⁰ among others, which find a clearly diagnosed prevalence of ADHD 0.9 percent in the population, but rates of psychostimulant prescription more than double that, with most of those being treated not meeting diagnostic criteria;⁴ however, evidence of this mismatch may be substantially less clear-cut, as reported in studies by Goldman¹¹ and Schachar et al.¹²

We close this synopsis of the history of ADHD with reference to another influential, school related legislation; the 2005 introduction and passage of the Child Medication Safety Act Bill (H.R.1790) which was 'enacted to protect children and parents from being coerced into administering a controlled substance or psychotropic drug in order to attend school, and for other purposes,...'.¹³ The introduction of this Bill may re-introduce a level of control into the story of ADHD, enforcing tighter diagnostic criteria; however, the controversies also point to social issues and conditions for which professional and public education will be necessary components in order to develop a widely disseminated, more effective management strategy for ADHD.

Background and Clinical Context

Children with ADHD, characterized by inattention, over- activity and impulsivity, are most frequently identified and treated in primary school. Population studies identify that 5 percent of children world-wide show impaired levels of inattention and hyperactivity. Boys are classified with ADHD approximately twice as frequently as girls, and younger children approximately twice as frequently as adolescents. ADHD symptoms exist on a continuum in the general population, and are considered as a 'disorder' to a greater or lesser degree depending on methods of identification, including who provides the information (e.g., parent or teacher), diagnostic criteria and the threshold chosen for defining a 'case'.¹⁴

The Disease Burden Associated With Attention Deficit Hyperactivity Disorder (ADHD)

Clinically significant ADHD is often associated with concurrent oppositional and aggressive behaviors, anxiety, low self-esteem, and learning disabilities. Symptoms generally interfere with

academic and behavior functioning at school, and may also disrupt family and peer relationships. ADHD begins before children enter school although it is most commonly identified and treated in primary school, age 7 to 9 years.¹⁵ In the preschool age group ADHD is characterized not only by impairment in attention span, excessive impulsivity and over-activity but also is frequently accompanied by additional disruptive behavior symptoms, including severe temper tantrums, demanding, uncooperative behavior and aggressiveness.¹⁶ While levels of symptoms decrease with age, the majority of children with ADHD continue to show impairment relative to same-age peers throughout adolescence and into adulthood. Estimates of prevalence of ADHD among adults world-wide is 2.5 percent.¹⁷

Pharmaceutical Interventions

Multiple short-term studies document that psychostimulant medications, either methylphenidate (MPH), dextroamphetamine (DEX) or mixed amphetamine salts (MAS), effectively decrease the core symptoms of ADHD and associated impairment.¹⁸ These medications are generally safe and well tolerated. Common side effects include poor appetite, insomnia, headaches, stomachaches and increased blood pressure and heart rate. Prolonged use may result in a decreased rate of growth, generally considered clinically insignificant.¹⁵ Concerns have been raised from post-marketing surveillance suggesting a rare incidence of sudden death, perhaps associated with pre-existing cardiac defects, however the rate does not appear to exceed that of the base rate of sudden death in the population.¹⁵ The 2003 United States National Survey of Child Health (NCHS) estimated 4.4 million children ages 4 to 17 years with a diagnosis of ADD or ADHD in the U.S., of whom 56 percent were currently taking medication.¹⁹

Several extended release preparations of psychostimulants have been developed in recent years aimed at improved adherence and symptom control throughout the day as well as decreased abuse potential.²⁰ Non-stimulants (e.g., alpha adrenergic agents and ATX) have also been developed and found to be helpful in controlling symptoms with few adverse events.²¹ However, in general the benefits of medications wear off when they are discontinued. Since ADHD is a chronic disorder, many children, teens and adults stay on medications for years at a time. Given the possibility of cumulative effects over time, a review of evidence regarding benefits and risks of prolonged medication use for ADHD is indicated.

Non-pharmaceutical Interventions

Since ADHD begins before school age, increasing numbers of preschoolers are being identified and treated, sometimes with medications. However, psychostimulants do not yet have government regulatory approval for use in children less than 6 years of age. Recent reviews of treatments for preschoolers with ADHD emphasize use of parenting interventions prior to medication based on general clinical consensus.²² Indeed, the Preschool ADHD Treatment Study (PATs), funded by the U.S. National Institute for Mental Health (NIMH), included parent behavior training as the first phase for all children recruited into the study prior to randomization for the purpose of evaluating efficacy and safety of psychostimulant medication.²³ While the few studies available suggest stimulant medications are effective for the core symptoms of

inattention, hyperactivity and impulsiveness in very young children, medications also appear to cause more adverse events in preschool children than in older children.²⁴ Beyond the PATS, little information exists documenting effectiveness of either medication or non-medication interventions specifically for ADHD in this age group. Part of the difficulty has been lack of clarity regarding reliability and validity of diagnostic criteria and therefore lack of widespread use of the ADHD diagnosis for children under 6 years.¹⁶ To address this information gap we will examine interventions for preschoolers with disruptive behavior disorders, which include ADHD behaviors. Research has accumulated regarding parent training for preschoolers with disruptive behavior in the past decade, but many of the studies do not recruit based on an ADHD diagnosis, rather based on clinically significant disruptive behavior. However ADHD in preschoolers is commonly identified in the context of comorbid oppositional and aggressive behavior.²⁵ A review of these studies will provide useful information about parenting interventions in preschoolers at very high risk of ADHD, especially those with defiant and aggressive behaviors.

Long-term Outcomes

Both retrospective studies and prospective longitudinal studies over long time periods face challenges in controlling for recall and documentation which may affect outcomes. Outcomes of interest for these studies include: persistence of ADHD, new onset psychiatric and substance use disorders, as well as educational, occupational, and social functioning outcomes. Comparisons of treated versus untreated individuals can be hard to interpret as both known and unknown factors play a role over the developmental spectrum from preschool to young adulthood. The natural history of those with ADHD in comparison to those not meeting the diagnostic criteria for ADHD remains poorly documented as standardized diagnostic criteria and methods of investigation have been in existence a relatively short time. Not knowing the natural history of the disorder complicates interpretation of treatment extension studies. Despite these limitations, it is timely to examine the current literature to see what has been accomplished and to consider directions for future research.

Prevalence

Over the past two decades, rates of identification and treatment for people with ADHD have increased as documented by population-based studies using health administrative databases.²⁶⁻²⁸ In some cases, small-area variation in prescriptions have been linked to specific physicians, suggesting that increases in identification may be linked with changes in practice patterns rather than an increase in the underlying prevalence of the disorder.^{29,30} In fact, the underlying prevalence of the disorder in children appears to have been relatively stable since the 1980s, to the extent that it has been measured using identical methods.³¹ Increases in identification and treatment have occurred primarily among girls and older children consistent with changes in clinical guidelines.^{27,32} Increases in off-label prescription of psychotropic medications for very young children have also been noted, presumably for preschoolers identified with ADHD or disruptive behavior.³³

Scope and Purpose of the Systematic Review

The purpose of this review is to i) critically examine the comparative long-term effectiveness and adverse events of interventions for ADHD (pharmacological, psycho-social or behavioral and the combination of pharmacological and psychosocial or behavioral interventions) and ii) critically examine the effectiveness and adverse events of interventions in preschool children with clinically significant disruptive behavior, and therefore at high risk for ADHD and iii) summarize what is known about patterns of identification and treatment for the condition. Factors to be examined include geography, sociodemographics, temporal aspects and provider background. This systematic appraisal will also identify gaps in the existing literature that will inform directions for future research. The key questions are as follows:

Key Question 1

Among children less than 6 years of age with Attention Deficit Hyperactivity Disorder or Disruptive Behavior Disorder, what are the effectiveness and adverse event outcomes following treatment?

Key Question 2

Among people 6 years of age or older with Attention Deficit Hyperactivity Disorder, what are the effectiveness and adverse event outcomes following 12 months or more of any combination of follow-up or treatment, including, but not limited to, 12 months or more of continuous treatment?

Key Question 3

How do A) underlying prevalence of ADHD, and B) rates of diagnosis (clinical identification) and treatment for ADHD vary by geography, time period, provider type, and socio-demographic characteristics?

Methods

Topic Development

The topic of this report and preliminary key questions (KQs) were developed through a public process involving the public, the Scientific Resource Center for the Effective Health Care program of the Agency for Healthcare Research and Quality (AHRQ) (www.effectivehealthcare.ahrq.gov/aboutUS/contract.cfm), and various stakeholder groups. Study, patient, intervention, eligibility criteria, and outcomes, were refined and agreed upon through discussions between the XXX Evidence-based Practice Center, the Technical Expert Panel (TEP) members, our AHRQ Task Order Officer (TOO), and comments received from the public posting of the key questions and protocol document.

Analytic Framework

Following consultation with key informants, the AHRQ Task Order Officer (TOO), and our investigative team, we developed our key research questions. Figure 1 shows a flow diagram indicating the relationship between research questions in this Comparative Effectiveness Review (CER).

This framework depicts the key questions within the context of the PICOT (population, intervention, comparison, outcomes and treatment). The figure illustrates how geography, age, provider type, and socio-demographic characteristics may influence the diagnosis and the treatment of Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD). Treatment results in outcomes of improvement or decline in behavior, function or quality of life. Other effects are new onset psychiatric disorder, initiation of substance use, gambling, driving infractions, teen parenthood, legal charges, academic attainment, job stability, relationship stability, physical health, and changes in mental health.

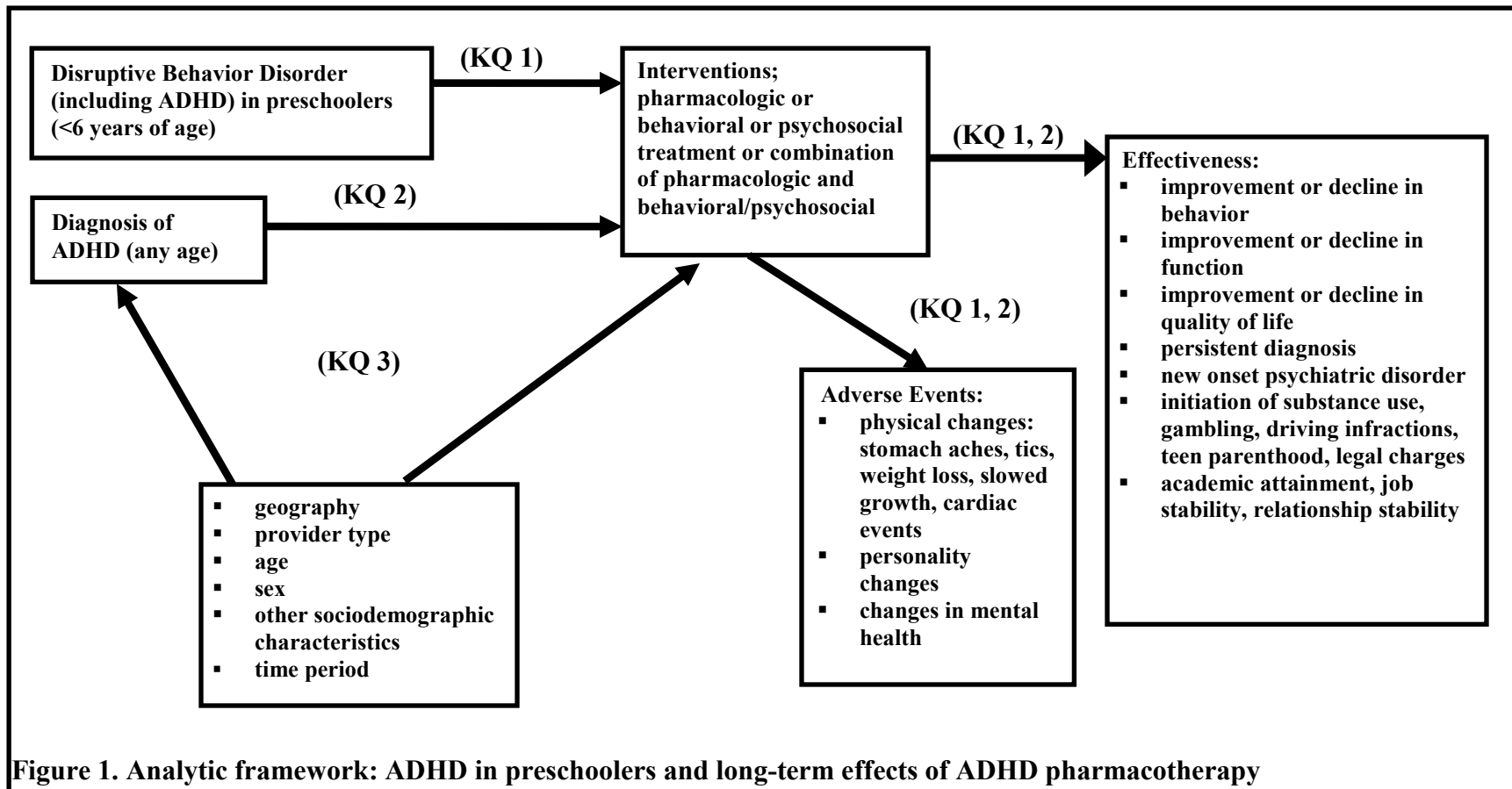


Figure 1. Analytic framework: ADHD in preschoolers and long-term effects of ADHD pharmacotherapy

Table 1. PICOT table for ADHD review

Question	Question 1	Question 2	Question 3
Population	<ul style="list-style-type: none"> • Children <6 years of age AND • Diagnosed with ADHD or at risk for ADHD or diagnosed with Disruptive Behavior Disorder (including ODD and CD by DSM) 	<ul style="list-style-type: none"> • ≥6 years of age (subjects <6 years are described in Question 1) • Diagnosed with ADHD by the DSM or ICD criteria that was in use at the time of the study or of the publication 	<ul style="list-style-type: none"> • No age limit for population • Diagnosed with or treated for ADHD
Intervention	<ul style="list-style-type: none"> • Any pharmaceutical treatment • Any psychosocial or behavioral or parent training treatment or combination treatment • Not including alternative treatments (e.g., diet, massage) 	<ul style="list-style-type: none"> • Any pharmaceutical treatment • Any psychosocial or behavioral or parent training treatment or combination treatment • Not including alternative treatments 	<ul style="list-style-type: none"> • Any pharmaceutical treatment • Not including alternative treatments
Comparator/ Design	<ul style="list-style-type: none"> • Comparative studies (RCT, cohort, case/control) • Any drug or psychosocial or behavioral treatment or combination treatment compared against placebo or any other of the above treatments • Not, case series or case reports 	<ul style="list-style-type: none"> • Comparative studies (RCT, cohort, case/control) • Any drug or psychosocial or behavioral treatment or combination treatment compared against placebo or any other of the above treatments • Not, case series or case reports <p>AND</p> <ul style="list-style-type: none"> • Combination of followup and treatment time is equal to or greater than 12 months 	<ul style="list-style-type: none"> • Descriptive statistics
Outcomes	<ul style="list-style-type: none"> • Numerical or statistical results of any effectiveness or adverse event outcomes 	<ul style="list-style-type: none"> • Numerical or statistical results of any effectiveness or adverse event outcomes 	<ul style="list-style-type: none"> • Prevalence of ADHD diagnosis or treatment, analyzed by geography, time on drug, provider type, socio-demographic characteristics (i.e., age, sex, family status, race/ethnicity, health insurance coverage)

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder, CD = Conduct Disorder, DSM = Diagnostic and Statistical Manual of Mental Disorders, ICD = International Classification of Diseases, ODD = Oppositional Defiant Disorder, RCT = Randomized Controlled Trial

Methodology for Prevalence Question

For the prevalence question, we searched the literature and screened the resulting citations right up to the full text examination using systematic review methodology. The resulting reports were examined for data that could be used to describe the various aspects of the prevalence of ADHD.

Search Strategy

There is no limit to publication date for studies to be included for KQ1. Studies were limited for KQ2 to any publication from 1997 to 2010 inclusive because long-term treatment of ADHD has already been reviewed by AHRQ for earlier dates.¹⁸ For KQ3, publications dated back to 1980 were included. EMBASE begins in 1980 and prevalence analysis will include data from earlier years.

The following databases were searched for KQ1 and KQ2. MEDLINE, Cochrane CENTRAL, EMBASE, PsycInfo, ERIC (Education Resources Information Center). For KQ3, the Cochrane Library and Eric Database were not searched because clinical trials were not the target of this review. Strategies used combinations of controlled vocabulary (medical subject headings) and text words. The complete search strings used can be found in Appendix A. Searches were performed on December 1, 2009.

Reference lists of eligible studies at full text screening were reviewed. Any potentially relevant citations were cross-checked within our citation database and any references not found within the database were retrieved and screened at full text.

At the time of submission of this draft peer review report, an update of the search in all specified databases is being undertaken.

Study Selection

Criteria for inclusion/exclusion of Studies in the Review

Target Population. For KQ1, the population includes children less than 6 years of age with a diagnosis of ADHD or Disruptive Behavior Disorder (including ODD and CD) by Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria.

For KQ2, the population includes subjects of greater or equal to age 6 years who have been treated for ADHD or are a control group of ADHD subjects, diagnosed with ADHD by DSM or ICD criteria.

For KQ3, the population includes subjects of any age who have been diagnosed with ADHD or treated for ADHD. Because much of this data will come from cross-sectional, survey and

medical databases using drug treatments and survey symptom checklists to identify ADHD subjects, subjects do not require a DSM or ICD diagnosis for inclusion.

Sample Size. There are no restrictions for study sample size.

Study Design and Publication Types

Inclusion:

Full-text reports of clinical trials and comparative observational studies were included for KQ1 and KQ2. For KQ3, we also included cross-sectional reports.

Eligible designs include:

- Experimental studies with comparator groups (randomized and quasi-randomized trials)
- Open label extensions following Randomized Controlled Trials (RCTs)
- Observational studies with comparator groups (retrospective and prospective cohort, and case control)
- For KQ3 only, non-comparative cross-sectional studies

Exclusion:

Letters, editorials, commentaries, reviews, meta-analysis, abstracts, proceedings, case reports, case series, qualitative studies, and theses were excluded.

Non-English publications were excluded for this review.

Definition of Terms

ADHD, ODD and CD will be as defined by the version of DSM or ICD current at the time of the study or of the publication.

Further Search Methods

Study authors were contacted via email for missing outcome or design data. Reference lists of included papers were screened for possibly relevant papers that had not already been screened. Grey literature was identified by the AHRQ Scientific Resource Center and included:

- FDA - Medical Reviews and Statistical Reviews
- Health Canada - Drug Monographs
- Authorized Medicines for EU - Scientific Discussions
- ClinicalTrials.gov
- Current Controlled Trials (UK)
- Clinical Study Results (PhRMA)

- WHO Clinical Trials (International)
- CSA Conference Papers Index
- Scopus - limited to conference papers

Standardized forms were developed in DistillerSR (Evidence Partners Inc., Ottawa, Ontario, Canada) and Microsoft Excel for the purposes of this systematic review.

Types of Comparators

We identified and included studies with comparative intervention groups. From a design hierarchy perspective, comparative group designs provide stronger evidence for efficacy and effectiveness than non-comparative designs.

The interventions (either alone or in combination) may be compared to any of the following:

1. Placebo
2. Same pharmacologic agent of different dose or duration
3. Other pharmacologic agent
4. Psychosocial intervention
5. Academic intervention
6. Any combination of pharmacologic , academic or psychosocial intervention

Outcomes

No limits have been placed on the effectiveness or adverse event outcomes included in this report. Numerical or statistical results of any effectiveness or adverse event outcomes are included.

Data Extraction

Relevant fields of information were extracted from individual studies by trained data extractors using standardized forms and a reference guide. Key study elements were reviewed by a second person (study investigator) with respect to study outcomes, seminal population characteristics and characteristics of the intervention. Disagreements were resolved by consensus.

Abstracted data includes study characteristics (e.g., first author, country of research origin, study design, sample size, clinical indications, and study duration or length of followup). Details of the patient population include age, gender, racial composition, socioeconomic status (SES) (income, education), and co-morbidities (psychiatric and medical disorders). Details of the study intervention include type of intervention (pharmacological and non-pharmacological) and the comparators, dosage of intervention, duration of followup (from immediately post treatment to long term), and characteristics of treatment providers. Characteristics of the outcomes include the type of instrument or scale, type of effect measure (endpoint or change score, measure of variance, standard deviation, standard error, etc.), and definition of treatment response.

Assessment of Methodological Quality of Individual Studies

We interpret methodological quality to include primarily elements of risk of bias, (systematic error) related to the design and conduct of the study. We have selected the Effective Public Health Practice Project, Quality Assessment Tool for Quantitative Studies Risk of Bias Tool.³⁴ The tool, which measure internal validity, contains eight sections that include evaluation of the domains of selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity and analyses. A global rating of strong, moderate, or weak for each report results from agreement by two raters on the combination of all of these items. Ratings result from a combination of the quality of the study design, execution, and reporting. A strong paper will have mostly strong ratings in each section with possibly a moderate rating in one or two of the eight sections. A moderate paper will have mostly moderate ratings for the eight domains, or it will have a split between weak, moderate, and strong ratings. A weak paper could have one or two strong domains, but has three or more weak domains in the rating.

Rating the Body of Evidence

We assessed the overall strength of the body of the evidence using the GRADE approach.³⁵ There are several factors that may decrease the overall strength of the evidence:

1. Study limitations (predominately risk of bias criteria)
2. Type of study design (experimental versus observational)
3. Consistency of results (degree to which study results for an outcome are similar between studies; that variability is easily explained)
4. Directness of the evidence (assesses whether interventions can be linked directly to the health outcomes)
5. Precision (degree of certainty surrounding an effect estimate for a specific outcome)

There are factors recommended by the GRADE working group (e.g., burden of therapy, importance of the outcome being evaluated) that were taken into consideration when assigning a GRADE category.

Data Synthesis

Qualitative Synthesis

For each trial, information on population characteristics (including history of treatment(s), age of first diagnosis, etc.), study outcomes (both of benefit and of harm), sample size, settings, funding sources, treatments (type, dose, duration, and provider), methodological limitations, statistical analyses, and any important confounders were summarized in text and summary tables.

Quantitative Synthesis

The decision to pool individual study results was based on clinical judgment with regards to comparability of study populations, treatments, and outcome measures. Aspects considered were, methodological quality (e.g., high-risk of bias vs. low-risk of bias); clinical diversity (e.g., study population gender, disease severity); treatment characteristics (type of intervention); outcome characteristics (e.g., long-term followup vs. short-term followup, different measuring scales, different definitions of dichotomous outcomes). The extent of heterogeneity was explored through subgroup and sensitivity analyses.

Subgroup and Sensitivity Analysis

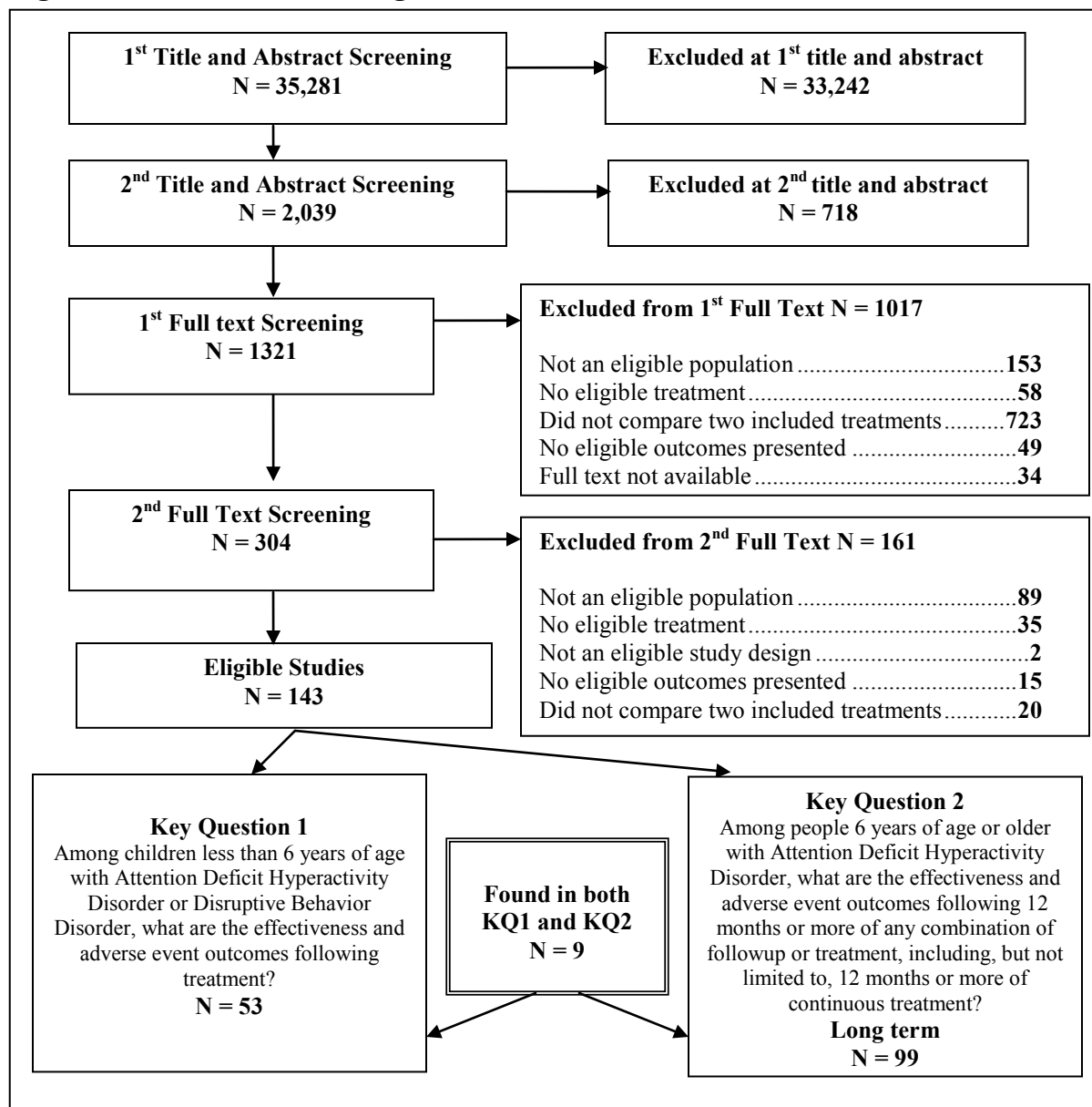
Key patient-specific or intervention-specific factors that may affect the treatment effect were explored. Clinical heterogeneity was assessed by considering any potential differences in participants among the trials (e.g., age, gender, diagnoses, disease severity, definition of response). Methodological heterogeneity was explored by evaluating where studies failed criteria.

To maximize the similarities among studies that could potentially be combined for meta-analyses, we further stratified where possible studies based on: 1) behavior disorder (ADHD, ODD, CD), and 2) age categories (preschool, child, adolescent, adult). There are several patient characteristics that we further explored with sensitivity analyses and these include the following: 1) disease severity (within ADHD only), 2) gender, 3) co-morbidities related to other psychological disorders. Trial specific factors include: 1) duration or dose of intervention, 2) type of treatment provider, and 3) method of defining response.

Results

Figure 2 details the flow of studies and the final subset for review. The search for reports for the treatment questions addressing preschool children and addressing long term treatment or outcomes, yielded 35,281 unique citations. During two levels of title and abstract screening, 33,960 articles were excluded. A total of 1,321 citations proceeded to full text screening. After the final eligibility screening, 143 publications were eligible for data extraction.

Figure 2. Flow of studies through review



A separate search was performed for prevalence reports. The initial yield of papers was 8,481, of which 7,892 were excluded at the title and abstract screening level. Of the remaining 589 papers, an additional 130 papers were excluded at the full text screening level, and 35 papers were

unavailable. The authors addressed this question using data from 48 of the remaining 424 reports.

Key Question 1. Among Children Less Than 6 Years of Age With Attention Deficit Hyperactivity Disorder or Disruptive Behavior Disorder, What are the Effectiveness and Adverse Event Outcomes Following Treatment?

Introduction

The systematic search results for comparative clinical trials of psychosocial, behavioral or pharmacologic interventions for preschoolers with disruptive behavior disorders are organized by type of intervention. The first section describes parent behavior training, with a summary of efficacy trials addressing child disruptive behavior problems and parents' sense of competence. Three of these trials investigated parent behavior training specifically for preschoolers identified with Attention Defecit Hyperactivity Disorder (ADHD) symptoms. The next section summarizes studies investigating long term extensions following the clinical trials. The third and fourth sections report on studies designed to address symptoms of ADHD in preschoolers, as well as other disruptive behavior and school readiness. The third section examines interventions that combine parent behavior training and school or daycare components. The last group of studies examines pharmacological agents, specifically trials of psychostimulants.

Parent Behavior Training Interventions for Preschoolers with Disruptive Behavior Disorders

Three standardized programs of behavior training interventions for parents of preschoolers with disruptive behavior disorders have been developed by separate research groups in the past 25 years. While each program has its own specific features, the Triple P (Positive Parenting of Preschoolers program), Incredible Years Parenting Program (IYPP), and Parent-Child Interaction Therapy (PCIT) share common therapeutic components and are manualized to ensure intervention integrity with dissemination. These programs are designed to help parents manage their child's problem behavior with more effective discipline strategies using rewards and non-punitive consequences. An important aspect of each is to promote a positive and caring relationship between parents and their child. Each program also includes educational components regarding childhood behavior problems and common developmental issues, and may include coaching or consultation to support the parents' efforts.

Thirty-one reports of controlled trials of parenting interventions met criteria for review, of these, 28 met criteria for 'strong' or 'moderate' internal validity and will be the basis of this discussion. Tables 2 and 3 provide information on characteristics of the 31 reports. Most of the studies were randomized controlled trials (RCTs). Most studies examined parent reported child symptom behavior scores, self reported parenting skills and sometimes researcher rated observations of

parent-child interactions. The Eyberg child behavior inventory (ECBI) was the most frequently used child behavior measure, with subscales for frequency and intensity of child disruptive behaviors. Several parenting scales were used, most frequently the parent sense of competence scale (PSOC). Almost all studies compared groups of treatment intervention completers to wait list controls, while one study compared two different interventions,³⁶ and two studies compared variants of an intervention without a treatment control group.^{37,38}

Nine of the trials conducted examined PCIT.³⁹⁻⁴⁷ Two studies evaluated the efficacy of PCIT for preschoolers with symptoms of ADHD.^{42,43} Results from these studies show that PCIT is efficacious in reducing oppositional symptoms and increasing compliance. In addition, both studies reported a reduction in ADHD symptoms post-treatment. Six additional studies evaluated PCIT in oppositional or aggressive preschoolers^{39,41,44-47} and found similar results. At post-intervention, parents who received treatment reported fewer and less intense child externalizing symptoms, in addition to decreased parenting stress and increased internal locus of control.

Of the 28 moderate to strongly rated trials conducted, six studies evaluated the Triple P program or its precursors.^{37,48-53} Four studies examined self-directed variants^{48-50,52}, while the remaining two studies examined enhanced and standard variants of the program.^{51,53} In general, results from these studies show that compared to wait list controls, parents who completed the intervention reported fewer and less intense child behavior problems, less frequent use of dysfunctional discipline strategies, and increased sense of competence in their own parenting skills at post-intervention followup compared with wait list controls. Bor et al.⁵¹ did not find the enhanced intervention, which included adjunctive components addressing partner support and coping skills, to be superior to the standard Triple P intervention on any of their outcome measures.

Five of the trials examined the efficacy of the IYPP compared to wait list control.⁵⁴⁻⁵⁸ Results from these studies showed reductions in problem behaviors and clinically significant gains in families that completed the intervention. An additional study reported a significant decrease in inattention and hyperactivity symptoms even when controlling for post-intervention changes in child deviant behavior.⁵⁵ Another of the 35 trials examined the efficacy of Supportive Expressive Therapy – Parent Child (SET-PC), a psychodynamic psychotherapy, as compared to the IYPP.³⁶ Results show that both interventions were efficacious in reducing externalizing behaviors and increasing parents' psychological function as well as positive interactions between parent and child.

Four of the studies examined the efficacy of the New Forest Parenting Program (NFPP), specifically designed for preschoolers with ADHD.⁵⁹⁻⁶² Results from two studies showed a reduction in ADHD symptoms post-intervention,^{59,62} while reductions in oppositional symptoms were less marked.⁶² One study, in which parent training was delivered by non-specialist nurses as part of routine primary care did not result in any change of ADHD symptoms post-intervention.⁶⁰

Three reports on two RCTs by Pisterman et al.⁶³⁻⁶⁵ reported support for the efficacy of group parent-mediated behavioral intervention to effect non-compliant behavior in preschoolers and to reduce parent stress and improve parenting competence.

A final RCT evaluated a parent training program offered either to individual families in a clinic setting or to groups of parents in a community location. Results showed that parents enrolled in a group and community-based program reported greater improvements of behavior problems at home compared to an individual, clinic-based program and wait list control.⁶⁶ Moreover, the community/group program was found to be much more cost-effective than the individual/clinic program.

In summary, these studies show that parent behavioral interventions are an efficacious treatment option for preschoolers with disruptive behavior disorders. Compared to wait list controls, children show reduced number and intensity of problem behaviors and clinically significant changes post-intervention. In the majority of studies where ADHD symptoms have been measured, these also improve. Moreover, parents report an increased sense of competence and show improved parenting strategies. Self-directed, group, and individual variants of parenting interventions are generally equally effective, though group therapy may be more cost effective when compared to individual therapy.

Table 2. KQ1. Characteristics of parenting interventions

Study	Intervention (PCIT/PPP /IYPP/other)	Length of Intervention primary/ followup	Characteristics of Intervention								
			Mode of delivery			Location of delivery			Adjunctive components		
			Group	Individual	Self-directed	Home	Community	Clinic	intervention with child	Direct health	Parent mental
Matos, 2009 ⁴²	PCIT	3.5m		✓		✓			✓	✓	
Eyberg, 1995 ⁴⁶	PCIT	12wk		✓				✓	✓	✓	
Nixon, 2003 ⁴⁴	PCIT	12wk/6m		✓		✓			✓	✓	
Nixon, 2001 ⁴³	PCIT	12wk/6m		✓		✓			✓	✓	
Shuhmann, 1998 ⁴⁷	PCIT	12wk/4m		✓		✓			✓	✓	
Funderburk, 1998 ⁴⁵	PCIT	12wk/ 12m & 18m		✓				✓	✓	✓	
Hood, 2003 ⁴¹	PCIT	12wk/6y		✓				✓		✓	
Bagner, 2007 ³⁹	PCIT	/4m		✓				✓		✓	
Markie- Dadds, 2006 ⁵⁰	Triple P	17wk/6m			✓	✓					

Abbreviations: AST = Ally Support Training, BKLY = Barkley, CBPT = Community Based Parent Training, CMT = Child Management Training, f/u = followup, HEAR = Helping Encourage Affect Regulation, IYPP = Incredible Years Parenting Program, MCI = multi-component intervention, MPH=Methylphenidate, NFPP = New Forest Parenting Program, PHN = Public Health Nurses, PT = parent training, PCIT = Parent Child Intervention Therapy, PPP = positive parenting of preschoolers, Res Staff = Research Staff, SDBI = self-directed behavioral intervention, SET-PC = Supportive Expressive Therapy – Parent Child, WLC = Waiting List Control

Table 2. (Cont'd) KQ1. Characteristics of parenting interventions

Study	Intervention (PCIT/PPP /IYPP/other)	Length of Intervention primary/ followup	Characteristics of Intervention								
			Mode of delivery			Location of delivery			Adjunctive components		
			Group	Individual	Self-directed	Home	Community	Clinic	intervention with child	Direct health	Parent mental conflict
Markie-Dadds, 2006 ⁴⁸	Triple P	12wk/6m			✓	✓					
Bor, 2002 ⁵¹	Triple-P	15wk/1yr		✓		✓	✓	✓		✓	✓
Sanders, 2007 ⁵²	Triple-P	15wk/3y		✓		✓	✓	✓		✓	✓
Sanders, 1985 ³⁷	Triple-P	7wk/3m		✓		✓	✓				
Dadds, 1992 ⁵³	CMT vs.cmT+AST pre-Triple P	8wk/6m	✓	✓		✓		✓		✓	
Connell, 1997 ⁴⁹	SDBI pre- Triple P	10wk/4m			✓	✓				✓	
Jones, 2007 ⁵⁵	IYPP vs. WLC	12wk/6m followup	✓				✓				
Hutchings, 2007 ⁵⁶	IYPP vs. WLC	12wk	✓				✓		✓		
Lavigne, 2008 ⁵⁴	IYPP	12wk/1yr	✓				✓				
Bywater, 2009 ⁵⁷	IYPP	12wk/12/18m	✓				✓				
Cummings, 2008 ³⁶	SET- PC/IYPP	14wk/1y	✓	✓				✓		✓	
Williford, 2008 ⁵⁸	IYPP	10wk/1y	✓				✓				
Weeks, 1997 ³⁸	NFPP	8wk		✓		✓			✓	✓	
Thompson, 2009 ⁶²	NFPP	8wk/13m		✓		✓			✓	✓	
Sonuga-Barke, 2004 ⁶⁰	NFPP	8wk/5wk		✓		✓			✓		
Sonuga-Barke, 2002 ⁶¹	NFPP	2m, 15w		✓		✓			✓		
Sonuga-Barke, 2001 ⁵⁹	NFPP	2m, 15w		✓		✓			✓		
Cunningham, 1995 ⁶⁶	CBPT	8wk/6m	✓	✓			✓	✓			
Landy, 2006 ⁶⁷	HEAR	15wk	✓	✓			✓				
Pisterman, 1989 ⁶⁴	PT	12wk/3m	✓	✓				✓			
Pisterman, 1992 ⁶³	PT	12wk/3m	✓	✓				✓			
Pisterman, 1992 ⁶⁵	PT	12wk/3m	✓	✓				✓			

Table 3. KQ1. RCTs of parenting interventions

Study	Quality	Sample Characteristics (N; mean age; % male)	Interventions compared	Results	
				Child behavior	Parent competence
Matos, M 2009 ⁴²	Moderate	N = 32; Mean Age: NR Male: NR	PCIT vs WLC	Highly significant reduction in ADHD and oppositional behaviors ECBI-I p <0.000 ECBI-P p <0.000	PPI p <0.000 Increased use of positive parenting practices
Eyberg, SM 1995 ⁴⁶ Primary study related to Shuhmann (1998) ⁴⁷ Hood, (2003) ⁴¹	Moderate	N = 50; Mean Age: 64m Male: 80%	PCIT vs WLC	ECBI-I p <0.01 ECBI-P p <0.00 Disruptive behavior reduced; Post-Tx classroom observations do not differ between referred children and classroom peers	Initial data on short term effect on parenting locus of control PLOC p <0.02
Nixon, RD 2003 ⁴⁴ Related to Nixon 2004 ⁴⁰ see Table 4	Moderate	N = 54 ; Mean Age: 47m Male: 70%	PCIT vs ABB PCIT (6mF/U)	Initially standard PCIT intervention superior but at 6m follow-up the result of the Standard and the Abbreviated programs become similar ST ABB ECBI-I-MR p <0.001 p <0.001 CBCL-E NS NS	Shorter PCIT intervention works as well as standard intervention; Mother report significantly less stress in the abbreviated program; blinded observations of parenting interaction show increased in positive communication ST ABB PSI NS p <0.05 PSOC p <0.05 p <0.05 PLOC p <0.001 p <0.01 P- p <0.01 NS P+ p <0.001 p <0.001

Abbreviations: ABB = Abbreviated PCIT delivery, ADHD = Attention Deficit Hyperactivity Disorder, BKLY = Barkley intervention, CBCL = child behavior checklist, CBPT = community based parenting program, CMT = Child Management Training, DPICS = dyadic parent-child interaction coding scheme, Dx = diagnostic, EBFI = Enhanced Triple P, ECBI-I = Eyberg Child Behavior Inventory - Intensity, ECBI-P = Eyberg Child Behavior Inventory - Problem, ESD = enhanced self directed Triple P, HEAR = Helping Encourage Affect Regulation, IYPP = Incredible Years Parenting Program, m = male, MIT = minimal intervention therapy, MTI = multi-modal treatment intervention, NFPP = New Forest Parenting Program, nPT = supportive non-training parent intervention, NR = not reported, NS = not significant, NT = no treatment, ODD = oppositional defiant disorder, PCIT = Parent-Child Integration Therapy, PCS = Parent counseling and support, PE = group based parent intervention, PLCBO = placebo, PS = parent stress, PSOC = parenting sense of competence, PT = parent training, SD = standard deviation, SET-PC = Supportive expressive therapy-Parent Child, TAU = Treatment as usual, Tx = treatment, WLC = Wait List Control

Table 3. (Cont'd) KQ1. RCTs of parenting interventions

Study	Quality	Sample Characteristics (N; mean age; % male)	Interventions compared	Results	
				Child behavior	Parent competence
Nixon, RD 2001 ⁴³	Strong	N = 34 Mean Age: 47m Male: 82%	PCIT vs WLC	Reduced hyperactivity and improved behavioral flexibility; by 6m, intervention group comparable to normal social validation controls; Tx gains maintained at 6m ECBI-I p <0.01	
Schuhmann, EM 1998 ⁴⁷ Related to Eyberg (1995) ⁴⁶ and Hood, (2003) ⁴¹	Strong	N = 64; Mean Age: 59.5m Male: 81%	PCIT vs WLC	ECBI-I p <0.01 ECBI-P p <0.01 Improved behavior in reported by parents and observed in classroom	Parent report more positive interaction with children; Less parent stress; increased locus of control; maternal perception of child behavior more positive than paternal perception
Funderburk, BW 1998 ⁴⁵	Strong	N = 84; Mean Age: 54m Male: 100%	PCIT vs WLC	Significant improvement in social competence between post-treatment and follow-up (maturational?); Strong generalization of PCIT at 12m; 18m, while still better than pre, classroom shift toward pre-treatment levels.	Home behavior stays within normal limits at 18m, so slide in classroom likely due to classroom demands
Hood, K 2003 ⁴¹	Strong	N = 64; Mean Age: 59.5m Male: 81%	PCIT vs WLC	ECBI-I p <0.01 ECBI-P p <0.01 Improved behavior in reported by parents and observed in classroom	Parent report more positive interaction with children; Less parent stress; increased locus of control; maternal perception of child behavior more positive than paternal perception
Bagner, D 2007 ³⁹	Strong	N = 30; Mean Age: 54m Male: 77%	PCIT vs WLC	Developmentally delayed children showed significantly improved compliance compared to non-treated controls;	Significant improvement in positive communication
Markie-Dadds, C 2006a ⁵⁰	Moderate	N = 63 Mean Age: 42.9m Male: 63%	Triple P vs SD vs WTC	Both SD and EBFI ECBI-I p <0.01 ECBI-P p <0.01 Children showed lower levels of disruptive behavior	Improved at post-treatment but some evidence of relapse effect in parenting at followup. At followup, mothers report decline in perceived self efficacy PSOC-S p <0.001 PSOC-E p <0.05

Table 3. (Cont'd) KQ1. RCTs of parenting interventions

Study	Quality	Sample Characteristics (N; mean age; % male)	Interventions compared	Results	
				Child behavior	Parent competence
Markie-Dadds, C 2006 ⁴⁸	Strong	N = 41 ; Mean Age: 47m Male: 76%	ESD vs SD vs WLC	ECBI-I p <0.001 ECBI-P p <0.001 Children in Enhanced Triple P showed significantly lower levels of disruptive behavior than Standard program, although both interventions demonstrated significant improvement over WLC	PDR-T ESD SD p <0.01 NS Mothers in Enhanced Triple-P report higher levels of perceived parenting efficacy than mothers in standard Triple P condition
Bor, W 2002 ⁵¹	Strong	N = 87 Mean Age: 41m Male: 68%	Triple P vs EBFI vs WLC 1y followup	Behavior improved under both enhanced and standard Triple P interventions ECBI-I p <0.01 ECBI-P p <0.001	No change in negative parenting style, Both enhanced and standard program effected change to an equally significant degree; neither intervention reduced inattentive behavior from post to follow-up PS p <0.001 PSOC p <0.001
Sanders, MR 2007 ⁵²	Strong	N = 139; Mean Age: 85m Male: 68%	Triple P vs EBFI vs SD vs WLC	ECBI-F p <0.01 Enhanced, Standard and Self-directed all showed maintenance of Txd gains; Changes in disruptive behavior maintained or further improved	Sustained improvement at 1 and 3 yr followup; PSOC p <0.05
Sanders, M 1985 ³⁷	Weak	N = 20 Mean Age: 4.1y Male: 60%	CMT vs CMT + Planned Activities Training (pre-Triple P)	Tx reduced non-normal behavior (p = 0.0004) Both strategies effective	Change in parenting (initial p = 0.0003) maintained in all settings at follow-up (p <0.01)
Dadds, M 1992 ⁵³	Moderate	N = 22 Mean Age: 54.8m Male: 68%	CMT vs CMT with ally (pre-Triple P)	Children showed improved behavior under both child management and Child management with Ally	Mothers' perceived support system best predictor of response to treatment conditions
Connell, S 1997 ⁴⁹	Moderate	N = 24 Mean Age: 49.3m Male: 43%	Triple P self directed vs WLC	Self-directed Triple P with telephone contact effectively reduced disruptive behavior ECBI- P p <0.00 ECBI-I p <0.00	PS-T p <0.00 Mothers report greater sense of competence, parenting satisfaction and reduced dysfunctional parenting behaviors

Table 3. (Cont'd) KQ1. RCTs of parenting interventions

Study	Quality	Sample Characteristics (N; mean age; % male)	Interventions compared	Results	
				Child behavior	Parent competence
Jones, K 2007 ⁵⁵ See Hutchings, 2007 ⁵⁶	Strong	N = 79; Mean Age: 46m Male: 68%	IYPP 12w/6m	Using clinical cutoff criteria, 58% of Tx group compared with 33% of WLC had followup scores below the level of clinical concern Conners p <0.013 DPICS-CD p >0.004	Over half of parents in Tx group show clinically significant improvements in parent reported negative behavior
Hutchings, J 2007 ⁵⁶ See Table 4: 2007 ⁵⁵ , Bywater T, 2009 ⁵⁷ , Jones K, 2008 ⁶⁸	Strong	N = 116; Mean Age: 53m Male: 58%	IYPP vs WLC 6m followup	Significant reduction in anti-social and hyperactive behavior and increased self control ECBI-I p <0.001 ECBI-P p <0.001 Conners p <0.001	Improved measures of perceived parenting stress and positive communication
Lavigne, JV 2008 ⁵⁴	Strong	N = 117; Mean Age: 54m Male: 53%	IYPP vs MIT	Significant behavior improvement with intervention ECBI-I p <0.002 ECBI-P p <0.001	Dose effect – little effect of therapist led intervention over bibliotherapy unless parents attended significant proportion of sessions PSI p <0.01 PLOC p <0.02
Bywater, T 2009 ⁵⁷	Strong	N = 116; Mean Age: 53m Male: 58%	IYPP vs WLC 6m followup	Significant reduction in anti-social and hyperactive behavior and increased self control ECBI-I p <0.001 ECBI-P p <0.001 Conners p <0.001	Improved measures of perceived parenting stress and positive communication
Cummings, JG 2008 ³⁶	Strong	N = 54; Mean Age: NR Male: 61.1%	IYPP vs SET-PC	Both interventions show significantly improved cooperation and enthusiasm CBCL-E p <0.004 ECBI-I p <0.070	SET-PC essentially equivalent in outcome to IYPP and IYPP is more cost effective and does not require same intensity of intervention leader training

Table 3. (Cont'd) KQ1. RCTs of parenting interventions

Study	Quality	Sample Characteristics (N; mean age; % male)	Interventions compared	Results	
				Child behavior	Parent competence
Williford, AP 2008 ⁵⁸	Strong	N = 96; Mean Age: 53m Male: 72%	IYPP vs NT 1 yr followup	Intervention decreased child disruptive behavior in the classroom	Positive impact on parenting behavior, but no difference in caregiver report of perceived changes of child behavior between intervention and control groups; teachers in consultation model and parents in intervention model report significantly improved behavior (at least 1SD decrease in at least one measure of disruptive behavior)
Weeks, A 1997 ³⁸	Weak	N = 57; Mean Age: <6yrs Male: 61%	NFPP vs TAU	Most parents felt child improved relative to baseline	
Thompson, MJJ 2009 ⁶²	Strong	N = 41; Mean Age: 52m Male: 100%	NFPP vs TAU	Large effect size (>1) of intervention on ADHD behaviors (p = 0.008); Impact of intervention on ODD less pronounced.	No significant improvement in measures of maternal mental health
Sonuga-Barke, EJ 2004 ⁶⁰	Strong	N = 89; Mean Age: 36m Male: NR	PT vs WLC	Parent training did not significantly improve ADHD symptoms	Maternal well-being decreased in PT and WLC conditions; Change between groups 0.22 (CI,95% -0.23 to 0.67); difference may be due to specialist vs non-specialist health visitors
Sonuga-Barke, EJ 2002 ⁶¹	Strong	N = 83; Mean Age: 36m Male: NR	PT (preNFPP) vs WLC	Intervention related to high levels of improvement in child behavior unless mother also has ADHD	High levels of maternal ADHD limit behavioral improvement in child
Sonuga-Barke, EJ 2001 ⁵⁹	Strong	N = 78; Mean Age: 36m Male: 62.9%	PT (preNFPP) vs PCS vs WLC	Parent training effect size usually found in range associated with stimulant medications; Clinically significant improvement in child behavior under parent training condition; little or no effect with PCS	PT had more effect on measures of parent satisfaction than PCS

Table 3. (Cont'd) KQ1. RCTs of parenting interventions

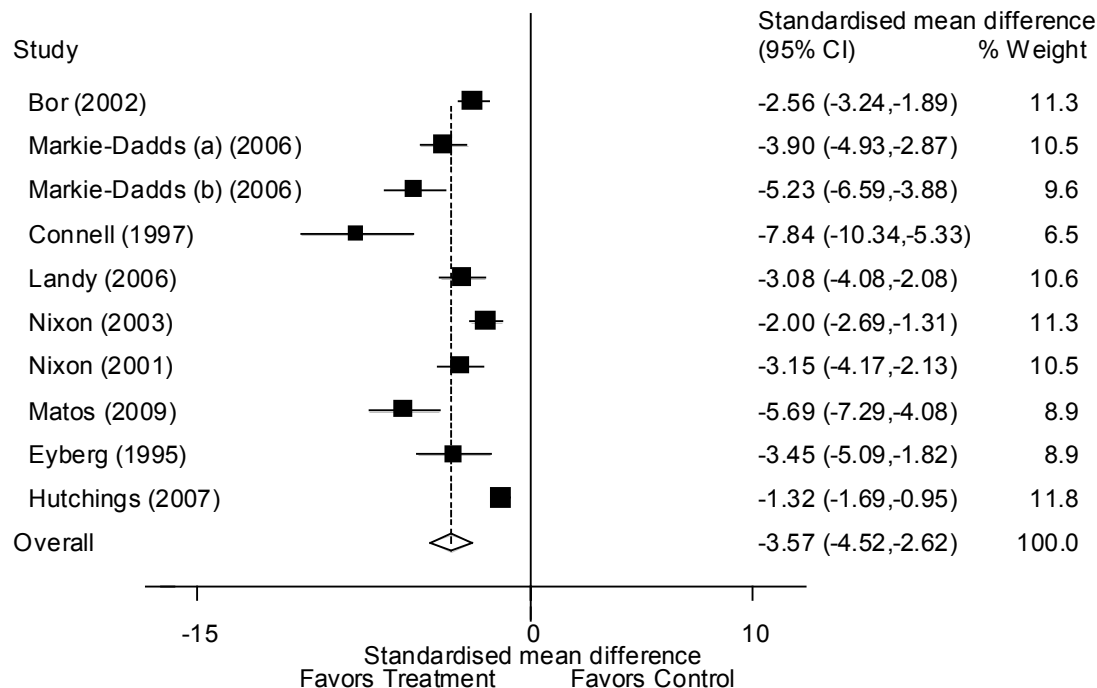
Study	Quality	Sample Characteristics (N; mean age; % male)	Interventions compared	Results	
				Child behavior	Parent competence
Cunningham, CE 1995 ⁶⁶	Strong	N = 150; Mean Age: 54m Male: 50.6%	CBPT	Significant improvements in child behavior CBCL-E p <0.001	Significant group improvement over clinic/individual, post and f/u points; Sense of Competence more improved in clinic/individuals than in group intervention; immigrant, ESL and parents of severely behavior disordered children more likely to enroll in community groups; Community Tx groups more than 6 times more cost effective than clinic and individual groups
Landy, S 2006 ⁶⁷	Weak	N = 35; Mean Age: 53m Male: 80%	HEAR vs WLC	ECBI-I p <0.01 CBCL-A p <0.01	Significant Improvement in parenting knowledge, reported sense of parenting competence and attitude to helping child. Confidence p <0.001
Pisterman, S 1989 {28944}	Strong	N = 50; Mean Age: 49m Male: 81%	Parent training vs WLC	Positive Tx effect on child compliance p <0.001	Positive Tx effect on parental style of interaction and management skills; effects maintained at 3m followup
Pisterman, S 1992 ⁶³	Moderate	N = 57; Mean Age: 47m Male: 91%	Parent training vs WLC	Significantly increased child compliance p <0.01	Parents observed to have increased quality and frequency of positive parenting communication; improved parental compliance-management skills
Pisterman, S 1992 ⁶⁵	Strong	N = 91, Mean Age: 50m Male: 85.9%	Parent training vs WLC	Lack of concordance between measures of observed vs reported child behavior	Group parent training had positive impact on parenting stress and parental sense of competence, independent of actual improvements in observed child and parent behavior

Meta-analysis of Parent Behavior Training for Disruptive Behavior Disorder in Preschoolers

Four meta-analyses were performed in order to document the degree of benefit following parent behavior training for disruptive behavior disorders in preschoolers. For studies with three arms, we combined the two parent behavior training arms into one treatment arm, assuming the mean score difference between the post- and pre- intervention has equal variance for the treatment groups that we combined. These meta-analyses are based on the assumption that the correlation coefficient between the post- and pre- treatment scores is 0.5. Sensitivity analysis was done based on different assumptions on the correlation coefficient (-0.8, -0.5, -0.3, 0.3, 0.5, 0.8). The same results were obtained in the sense of significant overall treatment effect and heterogeneity level.

The first two analyses investigated frequency and intensity of child problem behaviors by including those RCTs that used the parent report Eyberg Child Behavior Inventory (ECBI). Ten studies were included in the first meta-analysis, which measured the mean score difference between treatment and control groups on the ECBI Intensity subscale.^{42-44,46,48-51,56,67} Results show significant reduction in the ECBI Intensity score in the treatment group, compared to the control group, with standardized mean difference = -3.57 (-4.52, -2.62) (Figure 3).

Figure 3. Meta-analysis for mean score difference between treatment and control for child behavior outcome (ECBI intensity score, assume correlation coefficient between post- and pre score is 0.5)



Heterogeneity chi-squared = 97.71 (d.f. = 9) p = 0.000

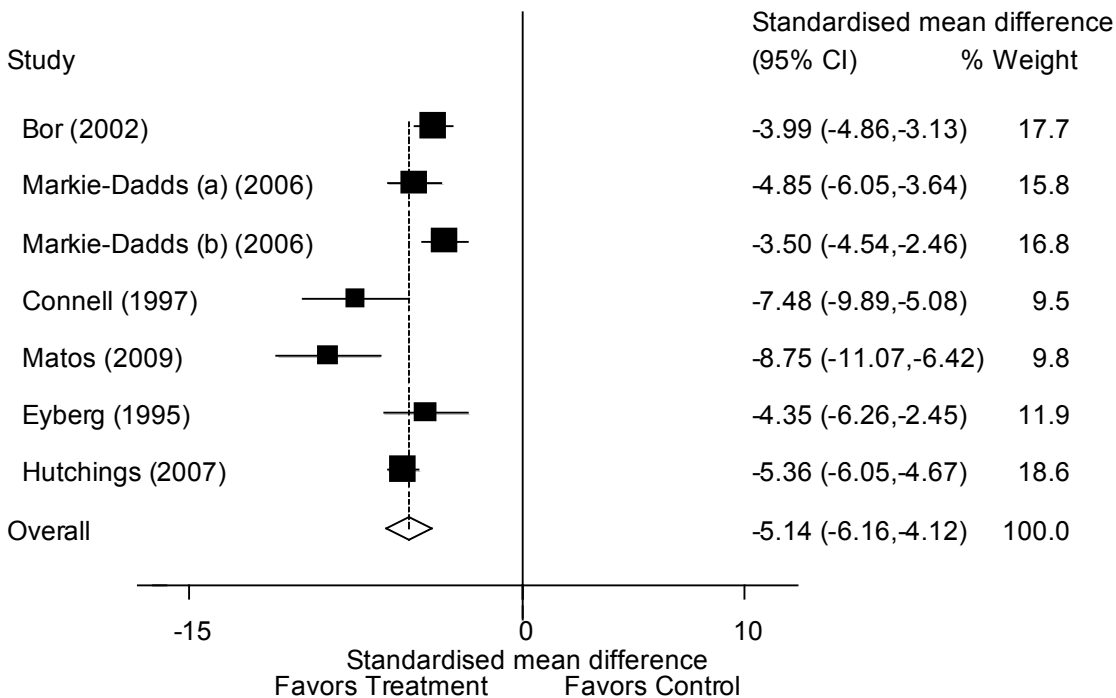
I-squared (variation in SMD attributable to heterogeneity) = 90.8%

Estimate of between-study variance Tau-squared = 1.9576

Test of SMD=0 : z= 7.37 p = 0.000

Seven studies were included in the second meta-analysis examining the mean score difference between treatment and control groups on the ECBI problem subscale.^{42,46,48-51,56} Results show significant reduction in the ECBI problem score in the treatment group compared to the control group, with standardized mean difference = -5.14 (-6.16, -4.12) (Figure 4).

Figure 4. Meta-analysis for mean score difference between treatment and control for child behavior outcome (ECBI problem score, assume correlation coefficient between post- and pre score is 0.5)



Heterogeneity chi-squared = 27.94 (d.f. = 6) $p = 0.000$

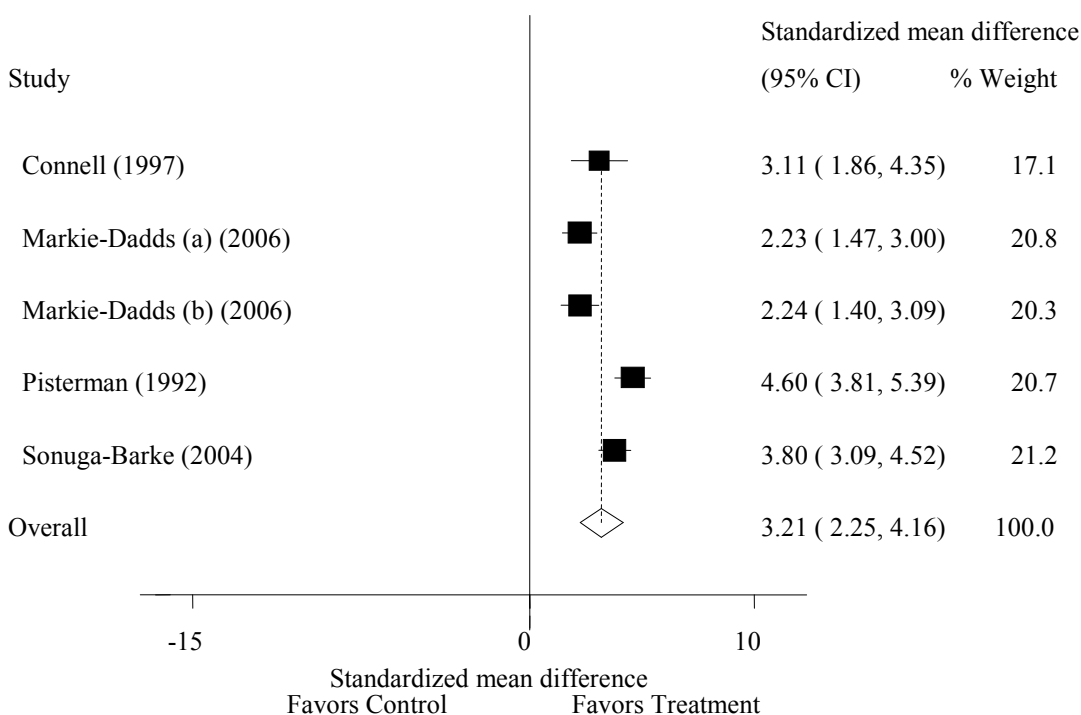
I-squared (variation in SMD attributable to heterogeneity) = 78.5%

Estimate of between-study variance Tau-squared = 1.3213

Test of SMD=0 : $z = 9.92$ $p = 0.000$

The third and fourth meta-analysis investigated parent competency by including those RCTs that used the efficacy subscale and total score on Parent Sense of Competency (PSOC) measure. Five studies were included in the analysis examining the mean score difference between the treatment and control groups on the efficacy subscale of the PSOC scale.^{48-50,60,65} Results show significant increase in the efficacy score in the treatment group compared to the control group, with standardized mean difference 3.21 (2.25, 4.16) (Figure 5).

Figure 5. Meta-analysis for mean score difference between treatment and control for parenting skills outcome (PSOC efficacy score, assume correlation coefficient between post- and pre score is 0.5)



Heterogeneity chi-squared = 25.66 (d.f. = 4) p = 0.000

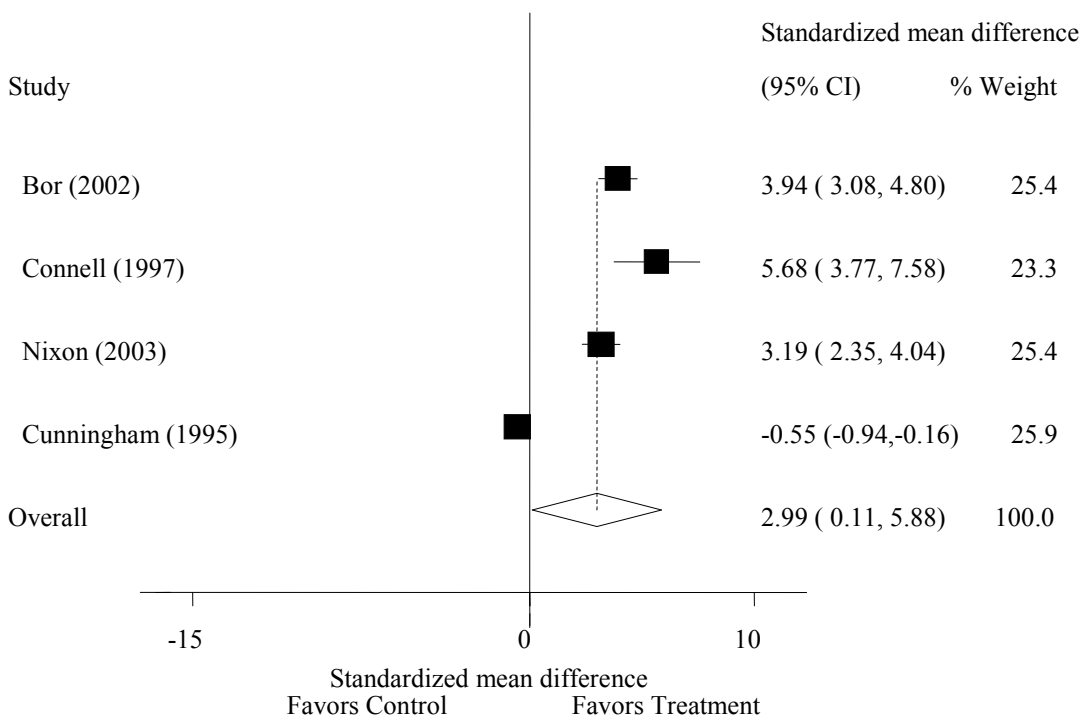
I-squared (variation in SMD attributable to heterogeneity) = 84.4%

Estimate of between-study variance Tau-squared = 0.9894

Test of SMD=0 : z= 6.57 p = 0.000

Four studies were included in the meta-analysis of the total score on the PSOC measure.^{44,49,51,66} Results show significant increase in parent sense of competency in the treatment group compared to the control group, with standardized mean difference 2.99 (0.11, 5.88) (Figure 6).

Figure 6. Meta-analysis for mean score difference between treatment and control for parenting skills outcome (PSOC total score, assume correlation coefficient between post- and pre score is 0.5)



Heterogeneity chi-squared = 154.15 (d.f. = 3) $p = 0.000$
 I-squared (variation in SMD attributable to heterogeneity) = 98.1%
 Estimate of between-study variance Tau-squared = 8.3166

Test of SMD = 0: $z = 2.04$ $p = 0.042$

These meta-analyses confirm the efficacy of parent behavior training interventions for preschool disruptive behavior. However, based on the chi-square test of heterogeneity and I-square statistics which describes the percentage of variation across studies that is due to heterogeneity, there is significant heterogeneity for all four analyses. Sensitivity analyses show that removal of the Connell 1997⁴⁹ Matos 2009⁴² and Hutchings 2007⁵⁶ results on ECBI intensity score and ECBI problem score are within acceptable levels of heterogeneity. These studies were examined to identify potential sources of sample heterogeneity, but none were found. While the meta-analyses show statistical heterogeneity, this does not appear to be clinically meaningful, as all studies demonstrated benefit on the included measures following parent behavior training interventions.

Long-term Extensions of Controlled Trials of Parenting Interventions

This section describes results from the extension studies investigating maintenance of behavior benefits for preschoolers following parent behavior training (see Table 4). Seven cohorts of preschoolers were followed for greater than 12 months after enrolment in a clinical trial examining parent interventions for disruptive behavior disorders. Long-term effects were examined across 9 studies^{40,41,45,51,52,57,58,68,69} and ranged from 1 to 6 years after treatment. Most studies examined parent-report and clinician observation of maintenance of treatment gains; one study examined maintenance of treatment effects in the school environment.⁴⁵ No extension study included untreated comparison groups, and attrition over the followup period ranged from 24 percent at 18 months⁵⁷ to 54 percent at 3 to 6 years,^{41,52} limiting interpretation of the results. In general, these extension studies suggest that post- treatment gains, including improvements in ADHD symptoms, are maintained over time.

In summary, parenting interventions are effective in reducing child disruptive behavior and improving parenting skills, and the benefits are maintained for at least 10 months following completion of the treatment.

Table 4. KQ1. Long-term extensions of clinical trials of parenting interventions

Study	Strength	Attrition from study (dropouts/ randomized)	Program Length of RCT/ followup	Results	
				Child behavior	Parent competence
Hood, 2003 ⁴¹ Related to Eyberg. 1995 and Schumann, 1998 ⁴⁷ see Table 2	Moderate	28;NR;NR	PCIT 12w/6yr	75% of children maintained behavioral improvement and made continuing gains	Long term effects on improved parenting self efficacy
Funderburk, 1998 ⁴⁵ see also Tables 2, Table 3 and Table 5	Strong	84; 4y8m; 100%	PCIT 12w/12m and 18m	Significant improvement in social competence between post-treatment and followup (maturational?); Strong generalization of PCIT at 12m; less so at 18m, with shifts toward pre-treatment levels.	Home behavior stays within normal limits at 18m, so slide in classroom likely due to classroom demands
Nixon, 2004 ⁴⁰ Related to Nixon 2003 ⁴⁴ see Table 3	Moderate	54; 46.75m; 70%	PCIT vs. ABB PCIT 12w/1yr	Tx gains in both standard and abbreviated PCIT are maintained at 1 and 2 year followup	positive changes in parenting style and communication maintained
Shelton, 2000 ⁶⁹ Extension of Barkley, 2000 ⁷⁰ , see Table 3, and Table 5	Moderate	151; 4.8; 68%	BKLY 10m/2yr	Early intervention in class may not produce enduring effects once Tx withdrawn; improvement may be due to maturation effect; Only small proportion of disruptive children may be truly at risk for psychiatric disorder	No benefits to parenting program post 1y

Abbreviations: ABB = Abbreviated PCIT delivery, BKLY = Barkley intervention, CBCL = child behavior checklist, CBPT = community based parenting program, Dx = diagnostic, EBFI = Enhanced Triple P, ECBI-I = Eyberg Child Behavior Inventory - Intensity, ECBI-P = Eyberg Child Behavior Inventory - Problem, ESD = enhanced self directed Triple P, HEAR = Helping Encourage Affect Regulation, IYPP = Incredible Years Parenting Program, MIT = minimal intervention therapy, MTI = multi-modal treatment intervention, NFPP = New Forest Parenting Program, nPT = supportive non-training parent intervention, NT = no treatment, ODD = oppositional defiance disorder, PCIT = Parent-Child Integration Therapy, PCS = Parent counseling and support, PE = group based parent intervention, PLCBO = placebo, PS = parent stress, PSOC = parenting sense of competence, PT = parent training, RCT = randomized controlled trial, SET-PC = Supportive expressive therapy-Parent Child, TAU = Treatment as usual, Triple P = positive parenting of preschoolers, Tx = treatment, WLC = Wait List Control

Table 4. (Cont'd) KQ1. Long-term extensions of clinical trials of parenting interventions

Study	Strength	Attrition from study (dropouts/ randomized)	Program Length of RCT/ followup	Results	
				Child behavior	Parent competence
Bywater, 2009 ⁵⁷ See Hutchings, 2007 ⁵⁶ Table 2 and Jones 2007 ⁵⁵ and Jones 2008 ⁶⁸	Strong	104; 4.5y; 58%	IYPP 12w/ 12m and 18m followup	Significant improvement in child behavior maintained at 18m post Tx	Significant improvement in parenting behaviors; improvement reported in levels of perceived parental stress and depression measures
Jones, 2008 ⁶⁸ See Hutchings, 2007 ⁵⁶	Strong	96; 4.5y; 72%	IYPP 12w/18m	positive effect of IYPP on all aspects of measured child behavior	Significant improvement in +ve parenting behavior;
Williford, 2008 ⁵⁸ Also in Table 2 and Table 3 as RCT and Table 5 as mixed non-pharmacological intervention	Strong	96; 4.5y; 72%	IYPP 10wk/ 1 yr	Intervention decreased child disruptive behavior in the classroom	positive impact on parenting behavior, but no difference in caregiver report of perceived changes of child behavior between intervention and control groups; teachers in consultation model and parents in intervention model report significantly improved behavior (at least 1SD decrease in at least one measure of disruptive behavior)
Sanders, 2007 ⁵² Also included in Table 2 and Table 3	Strong	139; 84.94m; 68%	Triple P vs. EBFI vs. SD 15wk/3yr	ECBI-F p <0.01 Enhanced, Standard and Self-directed all showed maintenance of Txd gains; Changes in disruptive behavior maintained or further improved	Sustained improvement at 1 and 3 yr followup; PSOC p <0.05

Table 4. (Cont'd) KQ1. Long-term extensions of clinical trials of parenting interventions

Study	Strength	Attrition from study (dropouts/ randomized)	Program Length of RCT/ followup	Results	
				Child behavior	Parent competence
Bor, 2002 ⁵¹ Also included in Table 2 and Table 3	Strong	87; 41m; 68%	Triple P vs. EBFI 15wk/ 1y	Behavior improved under both Enhanced and Standard Triple P interventions ECBI-I p <0.01 ECBI-P p <0.001	No change in negative parenting style, Both enhanced and standard program effected change to an equally significant degree; neither intervention reduced inattentive behavior from post to followup PS p <0.001 PSOC p <0.001

Effectiveness of Combinations of Parent Training and School- or Daycare-based Interventions for Preschool Children with Disruptive Behavior Disorder or ADHD

Five articles examining multiple component psychosocial and/or behavioral interventions for disruptive behavior in preschool children met criteria for review.^{58,69-72} This group of studies did not include a focus on pharmacology interventions, but primarily examined combinations of parent behavior training and school- or daycare-based interventions. Of these, one met quality criteria for strong internal validity,⁷² and four met criteria for moderate internal validity.^{58,69-71} See Table 5.

These five studies included a specific focus on effectiveness of interventions for children with ADHD symptoms. Two studies recruited preschoolers using clinical diagnostic assessments, and examined an intensive multicomponent intervention (MCI) comprised of parent behavior training (PT) plus school or daycare consultation for preschool children with ADHD.^{71,72} One of these trials compared MCI with diagnostic assessment and community care treatment as usual⁷¹ and the second compared MCI to diagnostic assessment and a standardized parent education program.⁷² These trials enrolled children from primarily middle class, educated families, with three percent on social assistance. The three remaining studies in this group recruited children using high ADHD and disruptive behavior disorder symptom ratings on screening measures.^{58,69,70} One study⁷⁰ examined a 1 year intervention which included parent training and a specialized treatment classroom, alone and in combination, compared to a no treatment control group for preschoolers with high levels of parent reported ADHD and other disruptive behavior symptoms. These children were drawn from low to middle socioeconomic status (SES), predominately European American families, 39 percent of whom received social assistance. This sample was followed longterm by Shelton et al.,⁶⁹ who evaluated these children 2 years post intervention in comparison to a community control. The final study of children with ADHD symptoms compared teacher consultation and parent training versus services as usual for preschoolers in Head Start programs.⁵⁸ These children were from predominantly low SES African American families whose preschoolers had high levels of ADHD and Oppositional Defiance Disorder (ODD) behaviors on screening measures. Overall, for these studies of combined parent training and teacher or classroom interventions, parent participation in groups for behavior training in all studies in this group was modest even when transportation and babysitting were provided, and sessions occurred at convenient times. In this way the parent training interventions differed from those in the RCTS described earlier where parent training intervention outcomes were measured for children whose parents completed the intervention.

Two studies^{71,72} investigated the effectiveness of a multi-component intervention (MCI) for preschoolers with ADHD who generally came from families from a middle income background. Children who received the MCI did equally well as children whose parents were enrolled in the parent education (PE) program⁷² or who received community treatment as usual.⁷¹ Parents in the MCI group attended a mean of 37 percent of 20 sessions in and 60 percent of families received a home behavior plan, while school plans were developed for 82 percent of children. Parents in the PE group attended 30 percent of 20 sessions, but received no additional services by protocol.⁷² Child behavior, social skills and school readiness improved significantly over 12 months in both groups. In the study where the comparison intervention was community treatment as usual,

approximately 20 percent received stimulant medication at some point during the intervention.⁷¹ These studies suggest that additional resources for home-based behavior plans, or classroom/daycare based behavior plans do not provide increased benefit for preschool children with ADHD, beyond that provided by diagnostic assessment and well-organized parent education programs, or community treatment as usual for children in families of middle income. These studies had few children from low SES background.

In contrast, another study⁷⁰ showed that at the end of a school year-long intervention, classroom interventions demonstrated significant positive impact on teacher-reported disruptive behavior and social skills outcomes, compared to parent training alone and to a no-treatment comparison. In the parent training groups, 68 percent of parents attended less than 5 of 14 sessions. Ten children (six percent of the sample) received medication, half were in the classroom interventions, half not. The classroom program included behavior training to improve classroom compliance, social skills training and self control training, along with an emphasis on early academic skills. Their first grade teachers were provided with information about the child and general suggestions about management, and offered additional consultations over the next three months, but only 10 percent of teachers accepted. Two years later, however, Shelton et al.⁶⁹ found that children who had received the class intervention no longer showed improved behavior relative to those who did not receive a classroom intervention, suggesting that the benefits derived from the classroom intervention were not maintained 2 years later. The study did not examine the 2 year maintenance effects of parent training.

Williford et al.⁵⁸ examined school consultation and parent training compared with services as usual, in preschoolers from low SES, primarily African American families enrolled in Head Start programs. The group receiving combined school and home intervention showed improved child behavior and social skills reported by both teachers and parents; in addition, both teachers and parents showed improved child management skills. The majority of parents (65 percent) did not attend more than 50 percent of the sessions, but those who did reported increased parenting skills.

Summary and Limitations. Very few studies offer information about the benefits of psychosocial/ behavioral interventions for preschoolers with disruptive behavior disorder who are at risk for ADHD. The five studies reviewed examine the question of efficacy or effectiveness of offering parent training groups combined with school or daycare based interventions for ADHD symptoms, oppositional and aggressive symptoms and school readiness. The outcome measures examined and the methods of analysis vary widely from study to study, precluding meta-analysis. Descriptive comparison of these studies suggests that SES is an important determinant of outcome in this age group following identification of disruptive behavior disorder. However, direct comparison within a single study would provide the best information to answer this question.

Table 5: KQ1. Summary of studies comparing non-pharmacological combination treatment modalities for preschoolers with ADHD or with Disruptive Behavior Disorder

Study	Study Design Quality Rating	ADHD or DBD Or both	Study Participants (N; mean age; % males) SES	Interventions compared					Intervention duration (month)	Followup length (month)	Results: Effectiveness	Comments Other details
				PT Behav	Tchr Conslt	classroom	CC/PT EDU	No				
Barkley, 2000 ⁷⁰ Followup Shelton, 2000 ⁶⁹	RCT Moderate	DBD	158; 4.8y; 40% lower SES	✓			✓		BRKLY 10w		Early intervention results in significant improvement in DBD which may not endure once Tx withdrawn CBCL-At p = 0.008 CBCL-A p = 0.002 No improvement in academic skills;	No benefit in parent training program after training phase; only a small proportion of disruptive children may be truly at risk for future psychiatric disorder
Shelton, 2000 ⁶⁹ Followup to Barkley, 2000 ⁷⁰	followup to RCT Moderate	DBD	158; 4.8y; 66.5% Predominantly lower SES	✓			✓		BRKLY 10w	2y	CBCL-T p = 0.001 Despite ongoing signs of risk in DB children, significant improvement with maturity – some so that at followup they had no sign of DB.	Small proportion of DB truly at-risk; subsequent service utilization not affected by early intervention

Abbreviations: BMT = Behavior Management Therapy, BRKLY = Barkley, CBCL-A = Child Behavior Checklist-Aggression, CBCL-At = Child Behavior Checklist-Attention, CBCL-T = Child Behavior Checklist-Thought, DBD = Disruptive Behavior Disorder, H = Home, IYPP = Incredible Years Parenting Program, MCI = Multi-component Intervention, PCIT = Parent Child Interaction Therapy, PT = parent training

Table 5. (Cont'd) KQ1. Summary of studies comparing non-pharmacological combination treatment modalities for preschoolers with ADHD or with Disruptive Behavior Disorder

Study	Study Design Quality Rating	ADHD or DBD Or both	Study Participant s (N; mean age; % males) SES	Interventions compared					Intervention duration (month)	Followup length (month)	Results: Effectiveness	Comments Other details
				PT Behav	Tchr Conslt	classroom	CC/ PT EDU	No				
Williford, 2008 ⁵⁸	Prosp cohort Strong	At risk for ADHD/ ODD	96; 4.5y; 70% Head Start	✓	✓	✓			IYPP 4m	1yr	Intervention decreased child DBD in the classroom	effective BMT prevents escalation of DBD. teachers in consult model & parents in PT model report significantly improved behavior (at least 1SD decrease in at least one measure of DBD)
McGoey, 2005 ⁷¹	RCT strong	Risk ADHD	57; 4.0y; 85.9% Primarily middleclass			✓	✓		IYSS 12w	3m 9m 12m	Minimal stat difference Small positive effects social control school and home; moderate increase in +ve parenting	Child compliance not increased over control group
Kern, 2007 ⁷²	Prosp cohort Strong	Risk ADHD	135, 4y; 78.5% Mixed population SES	✓			✓		12m	1yr	Significant decrease in problem behaviors (ADHD & aggression) in both groups; Stat sig improvement in behavior, social and preacademic skills in both conditions	No difference between modalities may be due to dose effect of MTI intervention, i.e.: only 1/2 Tx group received all 3 parts of MCI

Efficacy and Safety of Psychostimulant Interventions for Preschool Children with ADHD

This section reviews pharmacologic interventions for preschoolers with documented ADHD. Fifteen articles representing 11 studies^{24,73-86} examined efficacy of psychostimulants, primarily immediate release methylphenidate (MPH), prescribed two or three times daily in preschool children with documented ADHD. The largest randomized clinical trial, the Preschool ADHD Treatment Study (PATS),^{24,81-84} was rated as a strong study and is described in detail below. There was one additional strong study⁸⁵ and the remaining nine studies were moderate in internal validity. Except for the PATS, samples were generally small. Study participants were primarily boys from middle SES families, with ADHD combined type, or hyperactive impulsive type. Two studies examined children with ADHD and developmental disabilities or pervasive developmental disorders.^{76,78} Clinical trials generally were of short duration, lasting days to weeks. Almost all of the studies investigated immediate release MPH, in comparison to placebo.^{74-78,80,85,86} One study⁷⁹ compared the most effective and well-tolerated dose of either MPH or mixed amphetamine salts to placebo. All studies noted clinically significant symptomatic improvements on psychostimulant medication. Those studies which compared adverse events of medication or placebo, noted that behaviors attributed to side effects were present in subjects on placebo as well.^{76,77,79} For those children who participated in fixed dose titrations, adverse events were more common and of greater intensity at high than low dose.⁷⁷ Poor appetite, social withdrawal, lack of alertness, stomach ache, irritability, and rebound were noted as increased on stimulants relative to placebo.^{76,79}

One study, compared combinations of medication and parent intervention.⁷³ Heriot et al., randomized 26 preschool children with ADHD to four conditions: a single dose of 0.3 mg/kg 2 times daily (bid) immediate release MPH or placebo in combination with parent behavior training or parent support.⁷³ Only 12 children (61 percent), ages 3 to 5, and their parents completed the study. Comparison of individual pre-post analyses, indicated that children in active treatment conditions showed improvement relative to those in non-active treatments. All children in the combination active MPH plus active parent training condition showed symptomatic improvement in at least one domain whereas only one child showed improvement in one domain in the non-active interventions condition. Some individual children receiving only one active treatment also benefited. This study suggests efficacy for both MPH and for parent behavior training, with the combination addressing a wider range of needs for a greater number of children.

Preschool ADHD Treatment Study. The multisite National Institute of Mental Health (NIMH) funded PATS,^{24,81-84} offers high quality evidence about efficacy, safety, and effectiveness of immediate release MPH, 3 times daily (tid), for preschool children 3 to 5 years of age. The study included several stages, and ensured that parents of ADHD children received 10 weeks of parent training prior to initiation of medication. The sample were 76 percent boys, 63 percent Caucasian, and 76 percent two parent families, of which 97 percent had completed high school. Only 165 children of 303 enrolled (54 percent) actually entered the randomized double blind crossover titration trial following parent training sessions, and the preliminary open label medication safety lead-in phase. However, overall characteristics of the sample remained essentially the same.

Of the 303 participants enrolled, 279 entered physiotherapy, and 261 completed the sessions. Following this, 34 (11 percent of original sample) declined further participation or did not want to use medication, Eighteen families (6 percent) were satisfied with their child's improvement, and another 19 (6 percent) showed significant improvement. Of these, 183 enrolled in the open label safety lead in phase. One hundred sixty five who tolerated the open label safety lead-in phase entered the double blind titration trial. The investigation of methylphenidate efficacy consisted of a randomized five week double blind cross-over titration trial including four different MPH doses (1.25 mg, 2.5 mg, 5.0 mg, 7.5 mg) and placebo, given t.i.d. to identify best dose. Best dose was determined from parent and teacher reports of symptom ratings and side effects during the cross-over titration trial. One hundred fourteen children entered and 77 completed the next phase, a four-week double blind RCT comparing best dose to placebo. And finally 140 entered the 10 month open label maintenance phase. Between each phase families could opt to discontinue the study or move on to another phase. For example 61 families opted to move to the open-label maintenance phase prior to completing the 4 week RCT parallel phase.

Eleven of 183 children (6 percent) enrolled in the open label lead-in phase had moderate to severe adverse events and were not eligible to enter the titration phase. An additional 21 of 183 (11.5 percent) of children did not tolerate the highest dose, 7.5 mg t.i.d., and received a second week at 5.0 mg t.i.d. during the titration trial.⁸⁴ These numbers suggest a substantial proportion, of preschool children experience moderate to severe adverse events with doses of methylphenidate within recommended range of doses. Five additional children did not tolerate the crossover titration or parallel phases, while 12 were placebo responders and 7 were MPH non-responders. Forty children experienced behavioral deterioration during the parallel RCT.

The PATS study offers good evidence for efficacy of MPH in improving core ADHD symptoms using several different measures. Symptom improvement was noted during crossover titration phase for methylphenidate with mean optimal dose 0.7 ± 0.4 mg/kg/day, and with mean optimal total daily dose 14.2 ± 8.1 mg/kg/day compared with placebo.⁸⁴ During the 4 week parallel phase functional outcomes included small positive effect for teacher- but not parent- rated ADHD symptoms and social competence on MPH, no improvement in parental stress, and moderate worsening of parent-rated child mood on MPH; clinicians, on the other hand, rated children as improved with strong effect size,⁸¹ these findings were contrary to expectations. In addition, noted to have more comorbid conditions were less likely to benefit from the MPH intervention. Those 15 (9 percent of 165) who had 3 or 4 comorbid conditions were more likely to have psychosocial adversity and did not respond to MPH.⁸²

It is hard to know what to make of the fact that parent ratings and clinicians ratings do not agree about effectiveness of MPH treatment during the 4 week parallel trial. Parent ratings showed little benefit and some functional worsening for children on best dose MPH compared to those on placebo, while clinician's global impression documented improvement. One explanation could be that the parent and teacher rated symptom measures reported in this phase of the study are designed to be used as screening measures and therefore are not sufficiently sensitive to change over time.

Adverse Events. The PATS study provides the best quality evidence regarding adverse events in preschoolers using MPH.²⁴ In the study, adverse event recordings included spontaneous reports

by parents to physician's general inquiry about child's health as well as parent and teacher reports on research forms. adverse events were recorded whether or not they could be attributed to use of MPH. Moderate severity of adverse event was defined as causing some functional impairment and/or requiring medical attention or intervention (e.g., over-the-counter medication for headache). Severe adverse events prevented functioning in a major area of daily life and /or presented a serious medical threat. A serious adverse event had to meet U.S. Food and Drug Administration (FDA) definition (requiring hospitalization or lead to persistent incapacity).

Physicians also monitored vital signs, height and weight. Tachycardia was defined as resting heart rate >120 beats / minute, twice at the same visit. Hypertension was defined as blood pressure (BP) above 95th percentile for age and gender on two readings at the same visit. If such a reading was noted then the child's BP was measured again within 7 -14 days. If the BP remained elevated then an adverse event for hypertension was noted. Only severe ratings are reported in the article where BP was >20mmHg above limit.

Results show that emotionality/irritability was the most common reason for families to discontinue MPH use in the early stages of medication use. Of the 21 children who discontinued the study because of adverse events, nine discontinued because of emotionality/irritability.²⁴ These observations are concordant with functional outcomes reported above for the parallel phase where parents indicated worsening in child mood in the MPH group.⁸¹ Early termination from medication was also related to symptomatic behaviors such as increased talking, restlessness, and "spaciness" suggesting that poor efficacy may also interfere with adherence. Other adverse events, such as sleep difficulties and appetite loss, were tolerated, and were not associated with termination of MPH trial.²⁴

While emotional adverse events were reported most frequently during double blind titration trial they did not occur more frequently for children while on MPH in any of the dose conditions compared with placebo. By contrast, trouble sleeping, appetite loss, dull/ listless/tired, stomach ache, social withdrawal, and buccal/ lingual movements were reported more frequently by parents while children were on MPH than on placebo.²⁴ Changes in vital signs, BP and pulse occurred in the similar frequencies in both active treatment and placebo groups. Eight children exceeded the norms for BP on a single visit; none exceeded the norms on a second visit. Cardiovascular adverse events therefore were of no clinical significance during the titration trial.²⁴

Overall, the study evaluating safety and tolerability of MPH for preschoolers in the PATS confirms that physiological adverse events are common for young children with ADHD (spontaneously reported by 30 percent of parents) but serious clinically significant adverse events attributable to MPH are rare.²⁴ Eleven percent of children who started medication discontinued treatment due to adverse events.

Growth rates were impacted by use of MPH.⁸³ While the children enrolled were significantly larger than average for their age at baseline, they also showed significant reductions in rate of growth over the period of the study. The children were on average 2.0cm taller and 1.8kg heavier than peers at baseline. For those who remained on MPH, the annual growth rate was 22 percent

less than expected for height (1.4cm/yr) and 55 percent less than expected for weight (1.3kg/yr).⁸³

Adherence. While the main message of the PATS is that MPH is generally safe for young children, a secondary message is that parents remain uncertain about using stimulant medications for preschoolers. Even in this select group of families willing to participate in research, 34 of 261 (13 percent) who completed the 10 session parent training did not want medications, while another 18 (7 percent) were satisfied with the child's improvement; indeed 19 (7 percent) showed significant improvement in ADHD symptoms following parent training. Only 183 of original 303 (60 percent) children entered the open label safety lead-in trial and 140 (46 percent) entered the maintenance phase following the trial. Of these only 95/303 (31 percent) completed the 10 months.²⁴

Table 6: KQ1. Summary of studies reporting interventions with pharmacological agents for preschoolers with ADHD

Study	Study design Quality rating	Sample N Mean age(SD) %Male	Interventions compared				Results		Comments Duration of intervention or followup
			MPH	MAS	PT	Placebo	Effectiveness	Safety	
Wigal T 2006 ²⁴ (PATS)	RCT Strong	N = 183 Age: 4.75y Male: 74%	✓		✓	✓	Significantly increased ADHD behaviors suggest lack of drug efficacy ADHD-B p >0.0001	Serious and severe adverse events LDp HDp P-TS <0.005 <0.0001 Occurrence of adverse events increased between lower and high dose conditions 30% of parents spontaneously report moderate to severe symptoms after baseline.	1 wk open label lead-in, 5wk RCT, 5wk parallel phase, 10m open label maintenance 11% discontinued due to adverse events Preschooler adverse events similar to ADHD symptoms
Swanson J 2006 ⁸³ (PATS)	Extension of RCT Mod	N = 140 Age: 4.4y Male: 74%	✓			✓		Evaluation of growth rates over one year of MPH use ADHD children started out larger and heavier than norms, and while growth slowed on MPH regimen, they still were larger and heavier than norm at end of one year	1 year followup

Abbreviations: ADHD-B=Attention-Deficit-Behavioral; CCT=Clinical Controlled Trial; CGI=Clinical Global Impressions; FI=field independence; F/U=followup; H=Hyperactivity; HD=High Dose; LD=Low dose; MAS=Mixed amphetamine salts; Mod=Moderate; MPH=Methylphenidate; NR=not reported; ODD=oppositional defiance disorder; PATS=Preschoolers with Attention Deficit/Hyperactivity Disorder; PC=Prospective cohort; PR=parent rating; PT=Parent Training; P-TS=Parent-Trouble sleeping; SE=side effects; stat sig=statistically significant; TR=teacher rating; y=year

Table 6. (Cont'd) KQ1. Summary of studies reporting interventions with pharmacological agents for preschoolers with ADHD

Study	Study design Quality rating	Sample N Mean age (SD) %Male	Interventions compared				Results		Comments Duration of intervention or followup
			MPH	MAS	PT	Placebo	Effectiveness	Safety	
Greenhill L 2006 ⁸⁴ (PATS)	RCT Strong	N = 165 Age: 4.75y Male: 74%	✓			✓	ADHD symptoms showed significant decreases on MPH at 2.5 mg, 5 mg, and 7.5 mg three times daily doses but not for 1.25 mg daily, compared with placebo	92% tolerated MPH on open safety lead-in phase. Appetite, sleep, stomach ache, social withdrawal, lethargy. Less common tachycardia, high blood pressure; possible seizure	70 wk protocol Titration trial – significant reductions on symptom scales-, although effect size (0.4-0.8) smaller than for school-age children
Ghuman R 2007 ⁸² (PATS)	RCT Strong	N = 165 Age:4.74y; Male: 74%	✓			✓	High co-morbidity subgroup showed no improvement with increased MPH dose response compared to significant response in Moderate, Low or No co-morbidity groups		5 wks 14 variables examined, # of co-morbid disorders served as moderator of MPH response; Children in High co-morbidity subgroup had more family adversity than compared to No, Low, or Mod co-morbidity
Abikoff H 2007 ⁸¹ (PATS)	RCT Mod	N = 114 Age: 4.39y Male:80%	✓			✓	Secondary outcomes Functional measures: PR and TR SWAN symptom scores did not show improvement on MPH. CGI improved. PR depression worsened. TR social competence improved.		Families participated in 10 Parent Training sessions prior to RCT; Best dose of MPH compared with placebo over 4 weeks

Table 6. (Cont'd) KQ1. Summary of studies reporting interventions with pharmacological agents for preschoolers with ADHD

Study	Study design Quality rating	Sample N Mean age (SD) %Male	Interventions compared				Results		Comments Duration of intervention or followup
			MPH	MAS	PT	Placebo	Effectiveness	Safety	
Handen B 1999 ⁷⁶	RCT Mod	N = 11 Age: 4.0 to 5.11y Male: 82%	✓			✓	Significant improvement on teacher ratings of hyperactivity and inattention as well as activity levels and compliance	Nearly half the children experienced significant adverse events(withdrawal, crying, irritability)	Developmentally delayed children with ADHD respond to MPH, however may be more susceptible to adverse drug side effects
Ghuman J 2009 ⁷⁸	Cross-over Mod	N = 14 Age: 3 to 5y Male: NR	✓			✓	Improved behavior reported by parents and observed in clinic	Buccal-lingual movements significantly increased in Tx group	Response to MPH more subtle and variable than among older and/or typically developing children;
Cohen N 1981 ⁸⁶	CCT Mod	N = 24 Age: 4 to 6y Male: 88%	✓		✓	✓	PR child behavior improved at 1 year but their ratings in clinic were not significantly better	At 1-year followup, unmedicated children showed significant drop in verbal IQ while children on meds did not.	No evidence that any treatment more effective than any other; may be a function of maturation;
Schleifer M 1975 ⁸⁰	RCT Mod	N = 26 Age: 49m Male: NR	✓			✓	H-scores p <0.01 FI p <0.0001 Ref p <0.01		3wks intervention Hyperactivity in this population a heterogenous phenomenon

Table 6. (Cont'd) KQ1. Summary of studies reporting interventions with pharmacological agents for preschoolers with ADHD

Study	Study design Quality rating	Sample N Mean age (SD) %Male	Interventions compared				Results		Comments Duration of intervention or followup
			MPH	MAS	PT	Placebo	Effectiveness	Safety	
Musten L 1997 ⁷⁷	Cross-over Mod	N = 31 Age: 4.0 to 5.9y Male: 83%	✓			✓	Dosage effects not uniformly evident; positive effects on cognitive measures;	Increased adverse events and increased severity with higher doses	MPH improves functioning of preschool children similar to school-age children; no evidence that ODD was contraindication
Firestone P 1998 ⁸⁵	Cross-over Strong	N = 31 Age: 4y10m Male: 87%						Higher dosage of stimulant medication related to intensified frequency and magnitude of adverse events.	Younger children may display different behaviors than school-age while on stimulant medications; behaviors may have been associated with the condition rather than side effects
Heriot S 2007 ⁷³	RCT Mod	N = 16 Age: 4.78y Male: 81%	✓		✓	✓	Most clinically significant results in MPH +PT where 4/4 improved in two or more domains. In PT only and in MPH only, 3 /4 improved in one or more domains. In placebo and parent support 1/ 4 improved in one domain		MPH prescribed at 0.3 mg /kg twice daily

Table 6. (Cont'd) KQ1. Summary of studies reporting interventions with pharmacological agents for preschoolers with ADHD

Study	Study design Quality rating	Sample N Mean age (SD) %Male	Interventions compared				Results		Comments Duration of intervention or followup
			MPH	MAS	PT	Placebo	Effectiveness	Safety	
Barkley R 1984 ⁷⁵	RCT Mod	N = 60 Age: NR Male: 100%	✓			✓	Greater drug effects in task period over play period	#SE p <0.05 Low and high dose both produced greater number of side effects	5wks Only HD Ritalin improved child compliance
Barkley R 1988 ⁷⁴	RCT Mod	N = 27 Age: 46.8m (+/-6.7) Male: 70%	✓			✓	Increased positive parent/child interactions		4wk intervention Interpreted as supporting +ve effects on parent/child interactions
Short E 2004 ⁷⁹	Cohort Mod	N = 28 Age: 5.25y Male: 85%	✓	✓		✓	Improvement in behavior with either MPH or MAS.	Titrated to best dose, there were minimal differences between number or severity of adverse events on active medication or placebo.	4wk intervention Comparing best dose and placebo. Best dose of either MPH twice daily or MAS once daily identified by a preliminary trial

Summary and Limitations

There are few short-term studies, most with small sample size examining psychostimulant use in preschoolers. Of these only one small study⁷³ compares medication directly with parent training and the combination of medication and parent training. The medication dose it examines is low compared with doses suggested by other studies. The sample size was very small perhaps due to attrition (16/26 children completing interventions), precluding the usual statistical analysis for controlled trials examining efficacy. The second trial, the PATS study, offered careful analysis of psychostimulants following 10 sessions parent behavior training, a format consistent with clinical consensus for treatment of ADHD in preschoolers. It confers information about parent preferences, documents the small proportion of children benefiting from a series of parent training groups, and the additional benefits as well as adverse events posed by medication use in preschool children with ADHD. It examines functional as well as symptom outcomes, with information from several informants. The study shows that for children with no or one comorbid condition, MPH is very effective, similar to its effectiveness in samples of older children. As informative as this study is, it deserves replication in other samples, especially in light of the finding that presence of three or more comorbid conditions and psychosocial adversity decreases the effectiveness of psychostimulant medication.

Key Question 2. Among People 6 Years of Age or Older With Attention Deficit Hyperactivity Disorder, What are the Effectiveness and Adverse Event Outcomes Following 12 Months or More of Any Combination of Follow-up or Treatment, Including, but not Limited to, 12 Months or More of Continuous Treatment?

Introduction

Studies examining the long-term effectiveness and safety of pharmacologic interventions are an important focus of the current review. With the advent of new technologies and formulations of psychostimulants and the development of non-stimulant agents for use in ADHD, industry sponsored research has provided several high quality extension studies following participants in clinical trials. As well, researchers have used chart reviews and examinations of clinical database information to learn about the naturalistic patterns and long term outcomes of stimulant use for children with ADHD.

Longterm Effectiveness and Safety of Psychostimulants, Atomoxetine and Guanfacine Extended Release Interventions for ADHD

In all, we found 18 studies representing 16 cohorts, nine in children and one in adults, that offer details about long-term treatment effectiveness and safety of pharmacologic interventions.⁸⁷⁻¹⁰⁴ (Table 7). Six were rated as strong reports⁹²⁻⁹⁷ while nine reports^{87-91,98,102-104} were of moderate internal validity and three⁹⁹⁻¹⁰¹ were assessed as weak by the Quality Assessment tool. Only studies rated as strong and moderate internal validity are discussed in this section.

Of these, one cohort describes psychostimulants without distinguishing between MPH and dextroamphetamine (DEX) agents^{97,98} while other reports describe amphetamine, MPH immediate release, dextroamphetamine, mixed amphetamine salts, and OROS MPH.^{87,89,92-94,97,103,104} Four reports describe cohorts of participants in trials of the norepinephrine reuptake inhibitor Atomoxetine (ATX); one of these is an extension of clinical trials in adults.^{88,95,96,102} Two reports focus on the safety and continued efficacy of the noradrenergic agonist, Guanfacine extended release (GXR).^{90,91} Over all, the pharmacologic agents found to be efficacious and safe in shorter length trials provide continued maintenance of ADHD symptomatic improvement for at least 12 months; few serious adverse events are noted. Global ratings of impairment also indicate continued benefit. Placebo-controlled discontinuation trials are few; one trial discontinued treatment with amphetamine after 15 months,⁹² and another examined relapse in children receiving ATX for 12 months.⁹⁶ These trials suggest that many, but not all individuals continue to benefit from medication.

Most participants are children between 6 and 12 years at recruitment, primarily boys with ADHD, combined type. The more recent trials recruit few children with comorbid conditions except ODD. Attrition over time occurs for a variety of reasons, including adverse events and ineffectiveness. Retention of participants on active treatment at 12 months varies across studies and agents, from a high of 98 percent for immediate release MPH,⁹⁷ 75 percent amphetamine,⁹² 63 percent for OROS MPH,⁸⁹ 58 percent MAS XR,⁹⁴ 56 percent ATX,⁹⁶ and 43 percent GXR.⁹¹ In general, those who remain on medications show continued benefit and report few adverse events. Twelve of 18 studies reviewed were funded in all or in part by industry, possibly leading to enhanced representations of effectiveness and safety.¹⁰⁵

The following sections are organized by agent under investigation.

Psychostimulants

The focus of one study⁸⁷ was a population based birth cohort with details from school records as well as medical records. They identified 379 children with “research identified ADHD”, of which 295 received stimulant treatment; with 66 percent treated with MPH and 30 percent treated with DEX. The children were followed until median age 17.6 years for those who received stimulants, and median age 18.6 for those who did not. The pattern of use was marked by interruptions and changes of stimulant type, with a median of 3 treatment episodes (defined as

initiating or changing dose, or changing agent) per child. Boys were 1.8 times (95 percent CI: 1.1–3.1, $p = 0.025$) more likely to receive stimulants than girls. Median age of onset for start of treatment was 9.8 years, those with ADHD inattentive type (ADHD-I) were slightly older at 12.7 years and children with ADHD combined type (ADHD-C) were 9.2 years of age. Median duration of treatment was 33.8 months, somewhat less for those with ADHD-I (19.1 months) than those with ADHD-C (40.6 months). Nearly three-fourths of treatment episodes with either MPH or DEX resulted in a favorable response; more boys than girls experienced a positive response with DEX (OR 3.4 (1.5-7.54); $p = 0.002$). DSM IV subtype was not differentially associated with favorable response. Eight percent of episodes were associated with a documented side effect; DEX was more likely than methylphenidate to be associated with a side effect (OR 1.8, (1.1–3.0); $p = 0.034$). More side effects were noted for younger children and older adolescents.

One study⁹⁸ followed 91 children who had been participants in a 12 month RCT of MPH and parent groups (see also Law and Schachar⁹⁷). They were seen annually in a naturalistic followup. They noted that patterns of adherence varied considerably, with some children continuing to use medications, some discontinuing and some using intermittently over 5 years. High baseline symptom scores were associated with longer adherence to psychostimulant medication (any type) and greater treatment response. However, children with high levels of symptoms remained symptomatic at year five, despite stimulant treatment. Children receiving medication also showed high levels of clinically significant side effects, compared to children off medication; the most common side effect was loss of appetite.

Gillberg et al.,⁹² examined amphetamine response in 62 children, 6 to 11 years old, with ADHD, 10 percent of whom had pervasive developmental disorder, and 16 percent of whom had mild developmental delay (IQ 51 to 72). The study was initiated with single-blind amphetamine treatment where all children improved in Conners parent and teacher ratings, followed by a 12 month double blind placebo randomized discontinuation trial of amphetamine. The primary outcome measured was time to discontinuation of double blind treatment; 71 percent of those randomized to placebo and 29 percent of those randomized to amphetamine stopped treatment or went on to open treatment, $p < 0.001$. A final single blind discontinuation of amphetamine to placebo at month 15 for those still on amphetamine led to some statistically insignificant deterioration in teacher symptom scores, but not parent scores. Other changes over time included improved IQ for children treated with amphetamine for 9 months or more compared with children treated with placebo for 6 months. Adverse events discussed included poor sleep which occurred less frequently on single blind amphetamine than at baseline, although 33/59 children reported poor appetite following 3 months of single blind amphetamine; abdominal pain and tics occurred at baseline and in both amphetamine and placebo conditions. Tics were also noted for children at baseline and on amphetamine and on placebo. Of greater concern, hallucinations were noted for four children, three on amphetamine and one on placebo; dose reduction or discontinuation remedied the hallucinations quickly. Weight gain on amphetamine was less than expected over 15 months, height was not clearly affected.

Two studies specifically addressed the question of worsening of tics with MPH, examined development of tics while on active treatment and on placebo. One study⁹³ examined tics in 34 children with ADHD and chronic multiple tic disorder, ages between 6 and 12 years. There was

no statistically significant worsening of tics, and maintenance of benefit for ADHD symptoms over 2 years. Similarly, the other study⁹⁷ examined 91 children with ADHD but without baseline tic disorder. Nearly 20 percent of the children on active treatment and 17 percent of those on placebo, developed significant tics (RR 1.17 (95 percent CI 0.31 – 4.40)) while deterioration of tics occurred for 33 percent of those with preexisting tics on both active and placebo interventions (RR 1.0 (0.4 – 1.85)). Both reports concluded by noting that for individual children dose adjustment or discontinuation may be required.

One study⁸⁹ examined OROS methylphenidate in 105 children, who had been stabilized on immediate release (IR) MPH. Following a 3 week open trial of once daily MPH at doses of 18 mg, 36 mg, or 54 mg, 88 percent of families wished to enter the 12 month extension trial and 63 percent completed it. Effectiveness was rated higher among children 10 to 16 years, those taking either 36 mg or 54 mg daily, and for children with ADHD inattentive type. Of the 47 percent of participants who discontinued, 24 percent were for lack of efficacy, and 15 percent for adverse events (insomnia (N = 4); abdominal pain (N = 2); and other (N = 2) Four children (4 percent) experienced serious adverse events. Adverse events reported in ≥ 5 percent were headache (9.5 percent), tics (7.6 percent), and were not dose related.

One study⁹⁴ examined once daily mixed amphetamine salts (MAS XR) in 568 children, 6 to 12 years, 78 percent boys, 92 percent with ADHD, combined type, who had previously participated in one of two randomized placebo controlled trials with no clinically relevant adverse events. The participants started the 24 month extension trial in three subgroups, those who remained on MAS XR, placebo or no active treatment. All started a 12 month extension at 10 mg MAS XR daily for 1 week followed by weekly titration in 10 mg increments as required to maximum of 30 mg daily. Participants had an option to remain in the study an additional 12 months, for a total of a 24 month extension. For those who were on no active treatment or on placebo, the parent report Conners global index scores improved by >30 percent and that improvement was maintained over 24 months. Their scores were similar to those of the group who had remained on active treatment between RCT and extension study. Fifty-eight percent of children remained on MAS XR for at least 12 months and 48 percent for 24 months. The majority of children received 20 mg daily. Adverse events caused 15 percent of children to withdraw. The adverse events most commonly associated with treatment withdrawal were weight loss (N = 27), decreased appetite (N = 22), insomnia (N = 11), depression (N = 7) and emotional lability (N = 4). Serious adverse events were reported in 18 children (3 percent). Adverse events were more frequent with increasing dose, of those reported in the first 6 months at rates of more than 5 percent were loss of appetite (37 percent), headache (27 percent), insomnia (26 percent), abdominal pain (18 percent), nervousness (17 percent), weight loss (17 percent), and emotional lability (14 percent). Mean blood pressure changes increased by 3.5mm Hg, diastolic blood pressure by 3.5mm Hg, and pulse by 3.4 beats per minute.

Two studies, Findling et al.,¹⁰³ and Weisler et al.,¹⁰⁴ examined cardiovascular adverse events of MAS XR in 24 month open label extension studies of clinical trials. In 568 children¹⁰³ ages 6 to 12 and taking 10 to 30 mg MAS XR daily and in adults,¹⁰⁴ taking 20 to 60 mg daily, modest increases in blood pressure and pulse rate were noted, and small changes in QT intervals on ECG, all findings of minimal clinical significance. Four children discontinued due to cardiac events; one for tachycardia, two for intermittent chest pain associated for one child with

premature ventricular contractions, and the other with sinus bradycardia, and one for hypertension.¹⁰³ Seven adults were withdrawn from the study because of cardiovascular adverse events, two because of palpitations and /or tachycardia and five because of hypertension.¹⁰⁴

Summary of Psychostimulant Reports. Psychostimulants continue to provide control of ADHD symptoms and are well tolerated for months to years at a time. Concerns about exacerbation of tics with stimulants appear to be unfounded, although sample size remains small and may result in type II error. Some of the research summarizes information based on short-acting formulations of psychostimulants, requiring multiple doses daily. For instance, Barbaresi et al.,⁸⁷ reports that MPH is better tolerated than DEX. However, direct comparison of once-daily agents, such as OROS MPH and MAS XR is difficult, as Hoare et al.,⁸⁹ included adolescents and those with ADHD inattentive type, whereas the McGough et al.,⁹⁴ study sample had more than 90 percent with ADHD, combined type. Comparison might suggest that OROS MPH is better tolerated than MAS XR, however both studies had 15 percent of participants withdraw because of adverse events. Also, the methods for collecting adverse events may have been more sensitive in McGough et al.,⁹⁴ as they were collected by both spontaneous reports and by investigator inquiry. It is also possible that participants in the Hoare et al.,⁸⁹ study were offered relatively less effective doses, thereby diminishing the likelihood of adverse events.

Overall, there continue to be too few studies available of long term outcomes of psychostimulants to make direct comparisons of effectiveness and tolerability.

Atomoxetine

ATX is a non-stimulant agent, a norepinephrine reuptake inhibitor that is approved for use in treatment of ADHD. Two studies^{95,96} report on a double blind placebo controlled relapse prevention trial following a 12 week open-label titration trial. Six hundred and four children, ages 6 to 15 years, 90 percent boys and 74 percent ADHD combined type, discontinued any previous medications prior to entering the titration trial. ATX was titrated up to 1.2 mg/kg per day in twice daily doses, with further increases to 1.8 mg/kg /day if indicated. Four hundred and sixteen patients whose symptoms decreased by ≥ 25 percent from baseline entered a 9-month randomized relapse prevention trial; 292 were re-randomized into a second double blind 6-month relapse prevention trial. Fewer children relapsed in the active treatment group 21 percent than placebo group 37 percent, $p < 0.001$. There were no significant treatment interactions with diagnostic subtype, treatment history, age or site. Discontinuation due to adverse events occurred in 9 out of 292 or 3 percent in ATX, and 1 of 124 or 0.8 percent in placebo subjects. Adverse events reported by ≥ 5 percent of participants and statistically different between ATX and placebo groups, include gastroenteritis and pharyngitis for ATX and weight gain for placebo. Both weight gain and height gain were slower in the ATX group. There were no clinical meaningful differences in laboratory values, vital signs or cardiac QT intervals. Adverse events were similar to those reported during acute trials, specifically increases in heart rate, and blood pressure.

Relapse rates during the second relapse prevention trial at 12 months also showed that fewer in the ATX group 2.5 percent relapsed than in the placebo group 12. percent, with risk ratio (RR)

for relapse 5.6 (95 percent CI; 1.2 -25.6). Comparison of the relapse prevention trial following the initial 12 week open label trial, demonstrated that ATX decreased relapse. In addition, the rate of relapse on placebo following a full year of active treatment was lower than following 12 weeks of treatment. The rates of adverse events were similar between ATX and placebo conditions.

One study⁸⁸ reported on 385 (72 percent) of 536 adults with ADHD (mean age 42 years, 64 percent men) who entered an open label continuation trial (up to 97 weeks) of ATX following initial 10 week RCTs. They had discontinued ATX following trials, or remained on placebo and therefore were symptomatic at initiation of the open label trial. ADHD symptoms showed improvement of 33 percent on rating scales for total ADHD symptoms during the initial phase of open label extension; similar improvements occurred for total disability scores. Adverse events were similar to those noted in acute trials, primarily the expected noradrenergic effects, and included increased heart rate (mean change 5.1 beats per minute) increased systolic and diastolic blood pressure (mean change <2.0mm Hg) and mean decrease in weight of 1.3kg. Discontinuation due to adverse events was 11 percent. No clinically relevant changes in laboratory measures or QTc intervals on EKG were noted. Adverse events noted ≥ 10 percent were dry mouth 24 percent, headache 21 percent, insomnia 18 percent, erectile dysfunction 16 percent, nausea 15 percent, constipation 14 percent.

One study¹⁰² reported on cardiovascular effects of ATX noted in an open label, 12 month extension trial following clinical trials for 169 children and adolescents. Initial doses varied from 0.5 mg /kg to 2 mg/kg /day in divided doses. For children mean pulse rate and blood pressure increased during the initial few weeks and blood pressure increased over the first few months with increasing dose. Vital signs tended to stabilize at slightly higher levels over time, and subside upon discontinuation of ATX. Mean increases were small and not clinically meaningful. Likewise, no clinically significant changes were noted in ECG.

Summary of Atomoxetine Reports. Atomoxetine appears to be both safe and effective for ADHD symptoms over long periods of time. The research examining its use considers global functional assessments as well as ADHD symptom change. Relative to studies of other agents the research offers direct comparison with placebo for examination of relapse prevention, offering strong evidence of effectiveness and safety in children and teens. Adler et al.,⁸⁸ offer the only study of pharmacologic intervention over an extended time period in adults with ADHD.

Guanfacine Extended Release

Guanfacine is a non-stimulant noradrenergic agonist with selective effects on cortical alpha 2A adrenoreceptors. Similar to clonidine (another alpha 2 adrenoreceptor agonist which has been shown to be effective in improving some but not all domains for children with ADHD), guanfacine immediate release has been shown to be effective in reducing symptoms in ADHD in short term RCTs. Two industry-sponsored studies examine long-term safety and efficacy of extended release formulations (GXR), in open label extension studies of earlier clinical trials.^{90,91} These multisite studies were similar, enrolling children ages 6 to 17 years, approximately 75 percent boys, and 73 percent ADHD combined type. Biederman et al.,⁹⁰ enrolled 240 (70

percent) of participants in previous trials, and administered GXR in 2 -4 mg doses daily; the other study's⁹¹ sample were from 259 children, given 1 to 4 mg GXR daily; 53 of whom received co-administered psycho-stimulants. Results were similar in both studies. Reductions in ADHD symptom scores from baseline of preceding trial, and improvement in parent rated global impressions were maintained throughout the extension studies; 57 percent and 60 percent were very much improved or much improved from baseline.

Eighty two percent (N = 198) of participants withdrew from the Biederman et al., study by 12 months;⁹⁰ of these 52 (22 percent) were for adverse events and 25 (10 percent) for lack of efficacy. Somnolence, weight increase and fatigue were the most common adverse events for discontinuation, with somnolence or sedation but not fatigue, appearing dose-related. Reports of somnolence, sedation and fatigue diminished over time, with 40 percent of participants reported these symptoms at month 1 decreasing to about 10 percent of those remaining in the trial reporting it at month 8 and beyond. Of 11 serious adverse events reported, three were considered possibly or probably related to the study drug: one event of orthostatic hypotension and two events of syncope. Adverse events reported by ≥ 10 percent of participants were somnolence 30 percent, headache 26 percent, fatigue 14 percent, sedation 13 percent, cough 12 percent, abdominal pain 11 percent, upper respiratory infection 10 percent, and pharyngitis 10 percent. Mild reductions in blood pressure and pulse rates were common and returned to baseline on tapering GXR. Three children had abnormal ECGs judged clinically significant, two with bradycardia and one had junctional escape complexes. Overall hypotension was reported in 7 (3 percent) and bradycardia in 5 (2 percent) children. Two were discontinued due to treatment emergent abnormal ECGs, worsening of a sinus arrhythmia and asymptomatic bradycardia of 46 bpm; two discontinued for hypotension and two for orthostatic hypotension; one discontinued for syncope; all resolved on discontinuation. There were no changes in clinical laboratory analyses and no unexpected changes in height or weight noted.

Sallee et al.,⁹¹ report 77 percent (N = 202) of children withdrew from the study prior to 24 months, 82 percent of those in the monotherapy GXR group and 57 percent of those in the group co-administered stimulants, suggesting the combination of GXR and psychostimulants was better tolerated than GXR alone. Overall, 10 percent stopped for lack of efficacy and 12 percent for adverse events. Adverse events reported in ≥ 10 percent of monotherapy group were somnolence 38 percent, headache 25 percent, upper respiratory infection 16 percent, nasopharyngitis 14 percent, fatigue 15 percent, abdominal pain 12 percent, sedation 12 percent. In the GXR plus stimulants group, no somnolence, fatigue, or sedation were noted; headache occurred in 23 percent, upper respiratory infection 25 percent, nasopharyngitis 15 percent and abdominal pain 15 percent, pharyngitis 11 percent, decreased appetite 13 percent and irritability 13 percent. As in Biederman et al.,⁹⁰ reports of somnolence, sedation and fatigue decreased over time, from 35 percent to below 15 percent over 7 months. Patterns in vital signs suggested no clear trends in blood pressure or pulse. Heart rates less than 50 bpm were noted in 15 (6 percent) children and rates ≥ 100 were noted in nine (3 percent). While 28 children had new abnormal ECGs at end point, only two were considered clinically significant. One of these showed atrioventricular block, and was noted to have shown intraventricular delay on baseline ECGs; this child subsequently discontinued treatment. The other clinically significant finding was a child who showed significant but asymptomatic bradycardia in month three, at 45 bpm. This child had baseline pulse rate of 63 bpm and end of study rate of 76 bpm. For the entire sample, weight and

height gains were as expected with only 6 (2.3 percent) children showing weight gain possibly related to the medication.

In summary, industry sponsored trials of GXR show it to be effective and safe for treatment of ADHD. Parents report benefit in reduced ADHD symptoms and global improvement for a substantial number of children and teens with ADHD. High rates of somnolence, headache and fatigue appear to interfere with its use but diminish following several months of treatment. Tolerance appears to be improved with concurrent administration of psychostimulants. Monitoring of cardiac status may be indicated as there are reports of significant bradycardia, junctional escape complexes and intraventricular delay.

Table 7. KQ2. Summary of studies reporting interventions with pharmacological agents

Study	Study Design Quality Rating	Sample N Age(SD) %Male	Interventions compared	Followup duration	Results	
					Effectiveness	Safety
Psychostimulants						
Andriola, M 2000 ¹⁰⁰	Retrospective cohort Weak	N = 500 Age (range): 7y (4-18y) Male: 70%	MPH vs. pemoline	12m	Improvement MPH <pemoline d/c'd re: ineffective MPH 32%, pemoline 10%	d/c'd re: adverse events: pemoline 22% MPH 5%
Barbarese, W 2006 ⁸⁷	Retrospective cohort Moderate	N = 379 Age (SD): 10.4 (+/- 3.6) Male: 78%	MPH, dex, levo+ dex, pemoline; converted to MPH equivalent units	Birth to mean age 17.2y Tx duration 3.5y (+/- 3.1y)	73.1% favorable response to stimulant treatment positive response to stim less likely for very young and for older adolescents positive repsonse to dex boys>girls	AE dex (10.0%) >MPH (6.1%) No increase in AEs with higher doses of MPH or dex; SEs more common for very young and for older adolescents
Charach, A 2004 ⁹⁸ See also Law ⁹⁷	RCT, systematic F/U Moderate	N = 91 Age (SD): 8.4y (+/-1.6) Male: 81%	MPH vs. placebo, then On vs Off stim meds	12m RCT, followed by 4 y systematic F/U	children with high levels of BL symptoms showed most response to stim, remained on them longest, but remained symptomatic at 5 years	Most common AE was loss of appetite across all time points
Findling, R 2005 ¹⁰³ See also McGough J 2005 ⁹⁴	OLE of CT Mod	N = 568 Age (SD): 8.7y (+/-1.8) Male: 78%	10 to 30 mg MAS XR daily	24 m		small increase in BP, not clinically sig. no apparent dose response 34 TE ECG abnormalities, none clinically sig.
Gadow, K 1999 ⁹³	OLE of CT Strong	N = 34 Age (SD): 8.8y (+/-1.9) Male: 91% + tic disorder	MPH	24m	Behavior improved	No sig worsening of tics No sig change wght & hght percentile Increased BP at 24m

Abbreviations: %ile=percentile; ADHD RS IV=Attention Deficit Hyperactivity Disorder Rating Scale version IV; ADHD-I: Attention Deficit Hyperactivity Disorder – Inattentive; AE=adverse events; amph=amphetamine; ATX=Atomoxetine; BL =baseline, BP=blood pressure; CHQ=child health questionnaire; CT=Clinical Trial; CP=Classroom performance; CGI-IS=Clinical Global Impressions-Impairment scale; C p/t=Conners parent total score; d/c'd=discontinued; dex=dextamphetamine; diff=diffERENCE; DR=dose related; ECG= electrocardiogram; freq=frequency; F/U=followup; GAA=Global Assessment of Adequacy; GAS=Global Assessment Satisfaction; GXR=Guanfacine extended release; hght=height; incr=increase; imp=improvement; int=intervention; IR MPH=methylphenidate; levo=levoamphetamine; LT=long-term; MAS XR=mixed amphetamine salts, extended release; MPH=methylphenidate; NC=non-compliance; OLE=Open Label Extension; PPD=pervasive development disorder; RCT=randomized controlled trial; STP=summer treatment program; sev=severity; sig=significant; SAEs= Serious Adverse Events; stim=stimulant; Ss=subjects; Symp Improv=symptom improvement; OROS MPH=once a day methylphenidate; PDD= ; sat=satisfaction; RCR=retrospective chart review; TE_ treatment emergent; Tx=treatment; vs=versus; w/d=withdrawal; wght=weight

Table 7. (Cont'd) KQ2. Summary of studies reporting interventions with pharmacological agents

Study	Study Design Quality Rating	Sample N Age(SD) %Male	Interventions compared	Followup duration	Results	
					Effectiveness	Safety
Gillberg, C 1997 ⁹²	DB relapse prevention trial Strong	N = 62 Age (SD): 9y (+/-1.6) Male: 84% Comorbidities = PDD & low IQ	Amphetamine vs. placebo	12m DB relapse prevention trial following 3 m active Tx, Placebo withdrawal followup 3m	Symptoms improved > 40%; 29% on amph vs. 71% on placebo d/c'd trial Tx withdrawal at month 15, parent report no deterioration, teacher report mild deterioration WISC-R improved Cp/t changes primarily among older children (9 to 11y)	No increase in tic frequency or severity relative to placebo Hallucinations in 4 Ss (3 amph & 1 placebo)
Hoare, P 2006 ⁸⁹	OLE of CT Moderate	N = 89 Age (SD): 6-16y Male: NR	OROS MPH Stable dose levels; 18 vs 36 vs 54mg	12m	Satisfaction 49% to 69% (GAS); Efficacy 49% to 71% (GAA); >effect in pts older, higher dose, & ADHD-I	12% d/c'd re: adverse events 4 SAEs: 2 depression/suicidal 1 delusions 1 severe aggression
Law, S 1999 ⁹⁷ see also Charach ⁹⁸	RCT Strong	N = 91 Age (SD): 8.4y (+/-1.6) Male: 81%	MPH vs. placebo in Ss	12m	2% on MPH vs. 60% on placebo switched to other arm of trial	No sig. change in tic frequency between Ss on MPH or placebo
McGough, J 2005 ⁹⁴ See also Findling ¹⁰³	OLE of CT Strong	N = 568 Age (SD): 8.7y (+/-1.8) Male: 78%	MAS XR vs no Tx or placebo prior to OLE	24 m	Symptom improvement maintained with LT Tx; No Tx or placebo prior showed 30% decrease in Sx 1% d/c'd re in effective	15% d/c'd re: adverse events; Increased adverse events c higher dose 2 SAEs: convulsions

Table 7. (Cont'd) KQ2. Summary of studies reporting interventions with pharmacological agents

Study	Study Design Quality Rating	Sample N Age(SD) %Male	Interventions compared	Followup duration	Results	
					Effectiveness	Safety
Smith, BH 1998 ⁹⁹	Retrospective cohort Weak	N = 16 Children: Age (SD): 10.2y (+/-1.5) Adolesc: Age (SD): 12y (+/-0.8) Male: 100%	MPH+STP vs. STP + placebo	Mode 3y Range 1-4y (time elapsed from childhood to adolescence)	MPH Effect size (children) > MPH effect size (adolesc)	none discussed
Weisler, R 2005 ¹⁰⁴	OLE of CT Moderate	N = 223 Age (SD): 29.8 (±11.5) Male: 59.3%	MAS XR	24m	NR no assessment of ADHD symptoms presented	21% d/c'd re: adverse events 7 adults w/d due to cardiovascular AE - 2 palpitations and /or tachycardia - 5 with hypertension small mean increase in BP, HR, not clin. Sig.
Atomoxetine (ATX)						
Adler, L 2005 ⁸⁸	OLE of CT Moderate	N = 385 Age (SD): 42.44y (+/- 11.2) Male: 56.1%	ATX	14 wk CT, followed by up to 97 wks OLE	Symp improv > 30% maintained over time Impairment improved Disability improved	10.9% d/c'd re: adverse events
Buitelaar, J 2007 ⁹⁶ See also Michelson ⁹⁵	DB relapse prevention Strong	N = 416 Age (SD): 6-15 y Male: 89.6%	ATX vs Placebo	6m relapse prevention trial following 1yr active Tx	Relapse prevention ATX >placebo ATX relapse 2.5 % Placebo relapse 12.2 %	No adverse events observed growth normal in ATX group
Michelson, D 2004 ⁹⁵ See also Buitelaar ⁹⁶	DB relapse prevention trial Strong	N = 416 Age (SD): 10.6y (±2.3) Male: 89.4%	ATX vs. placebo	12 wk OL Tx, followed by 9m DB relapse prevention trial	ATX: 22.3% relapse placebo: 37.9% relapse	Adverse events: Gastroenteritis and pharyngitis ATX >placebo slowed growth with ATX compared to placebo

Table 7. (Cont'd) KQ2. Summary of studies reporting interventions with pharmacological agents

Study	Study Design Quality Rating	Sample N Age(SD) %Male	Interventions compared	Followup duration	Results	
					Effectiveness	Safety
Wernicke, J 2003 ¹⁰²	OLE of CT Moderate	N = 169 Age (SD): 10.7 (+/- 2.2) Male: 73.1%	ATX vs placebo	minimum 1 yr Tx	NR no assessment of ADHD symptoms presented	mean increases to BP, HR were small and not clinically significant no evidence of increase in QT interval with increased dose of ATX, after correcting for HR
Guanfacine (GXR)						
Biederman, J 2008 ⁹⁰	OLE of CT Moderate	N = 240 Age (SD): 10.5y (+/-2.6) Male: 76.7%	GXR	24m	Symp improvement maintained to 12 m; Parent rated impairment 58.6% improved	D/c'd re: adverse event 22%; Headache, fatigue, somnolence & sedation most common, 6 Ss d/c'd due to CV AEs 3 TE abnl ECGs, clinically significant (2 bradycardia, 1 junctional escape complex) 3 SAEs: 2 syncope, 1 orthostatic hypotension
Sallee, F 2009 ⁹¹	OLE of CT Moderate	N = 262 Age (SD): 10y (+/-2.6) Male: 72.6%	GXR vs. GXR + stim	24m	Symp improv maintained to 24m; CHQ improv maintained D/c'd re: ineffective 13% GXR monotherapy 2% GXR + stim	D/c'd re adverse events: 13.6% GXR monotherapy 5.7% GXR + stim co-therapy 28 TE abnl ECGs; 2 clinically significant (1 bradycardia, 1 intraventricular delay) 9 SAEs: 5 syncope
Other						
Steingard, R 1993 ¹⁰¹	RCR Weak	N = 54 Age (SD): 10.0y (±0.5y) Male: 88.9% ADHD + tic N = 24	Clonidine	4y retro	72% ADHD improvement 75% tics improvement positive response to clonidine: ADHD + tic 96% ADHD -tic 53%	Adverse events 41% sedation D/c'd re: Adverse events: ADHD -tic = 7Ss ADHD+tic = 0 Ss

Adverse Events: Cardiovascular Events, Cerebrovascular Events and Rates of Growth

Due to the special interest in reviewing literature about adverse events for persons using medication for ADHD, two areas of inquiry required adjustments in inclusion criteria: articles about potentially life-threatening events and articles about changes in growth rates. Research about life threatening events requires large population-based samples. Therefore, we included population-based cohort studies of people with ADHD only for these. Three studies were identified; two about cardiac safety^{106,107} and one regarding cerebrovascular events.¹⁰⁸ Recent studies examining growth rates for children using medication have often used age and gender adjusted population norms for comparison. (See Tables 8 and 9)

Cardiac Events: Population Based Studies

Two recent studies^{106,107} examine population rates of cardiac events among children and youth, ages 3 to 20, with recent diagnoses of ADHD, and compared those using stimulant medications to those no longer using stimulants. Rates of hospital admission for cardiac reasons are similar to rates in the general population. Rates of emergency department use were 20 percent higher for those with ADHD who use stimulant medication compared to those who do not.¹⁰⁶ Rates were comparable among those using methylphenidate and amphetamines. Use of concurrent bronchodilators, antidepressants or antipsychotics, age 15 to 20 years, and history of cardiac problems were associated with increased use of emergency department (ED).¹⁰⁷

Cerebrovascular Events: Population Based Study

Holick et al.,¹⁰⁸ used a health insurance database to examine adults with ADHD who initiated either psychostimulant medications or ATX and compared rates of cerebrovascular accidents (CVAs) or Transient Ischemic attacks (TIAs). These groups were matched to each other using propensity scores and compared with a contemporaneous general population control, age and sex matched to the treatment groups. The groups were followed for a mean of 1.5 years during which time 44 CVAs and 21 TIAs were confirmed among the three cohorts using medical record data. There was no difference in the rate of incidents between the ATX or stimulant treated groups. However, the combined ADHD medication cohort exhibited a higher hazard ratio (HR) (3.44, 95 percent CI 1.13 – 10.60) for TIAs compared with the general population after adjusting for baseline risk factors. A similar pattern was not observed for CVAs. These results do not support an increased risk of cerebrovascular events for users of ATX over psychostimulants. However users of ADHD medications may be at higher risk of TIAs than the general population.

Table 8. KQ2. Medication and adverse eventss – long term effectiveness and safety

Study	Med	General Adverse Event	Nervous System	Psych/ Behav	Gastrointestinal	Respiratory	Vascular
Quality Rating							
Psychostimulants							
Andriola M 2000 ¹⁰⁰ Weak	MPH vs. PEM		headache MPH=8% PEM=7% Hyperactivity: MPH=4% PEM=2% Sluggishness: MPH=4% PEM=0% Tics: 4% both groups	Insom: MPH=4% PEM=23% Irrit: MPH=18% PEM=12%	Anorexia: MPH=29% PEM=4% GI distress: MPH=3% PEM=0%		
Barbaresi W 2006 ⁸⁷ Moderate	MPH, MPH equiv units	fatigue 14.2%	headache 26.3% somnia 30.4% sed 13.3%		upper abd pain 10.8%	URT inf 10.4% cough 12.1% Pharyn 10.4%	
Charach A 2004 ⁹⁸ Moderate	MPH	clinically significant adverse event were present for 5 years, most commonly loss of appetite					

Abbreviations: +ve = positive; abd pain = abdominal pain; abn = abnormalities; adj = adjusted; ADHD-I: Attention Deficit Hyperactivity Disorder – Inattentive; AMPH = amphetamine; ATX = ATX; Behav = Behavioral; BP = blood pressure; CarddysR = Cardiac dysrhythmia; CHQ = child health questionnaire; Cong = congestion; CVA = cardiovascular accident; DBP = diastolic blood pressure; Decr app = decreased appetite; Diz = dizziness; ECG = electrocardiogram; GAA = Global Assessment of Adequacy; GAS = Global Assessment Satisfaction; GXR = GXR; HazR = hazards ratio; HRT = heart rate; hyper = hypertension; hypo = hypotension; I/B = impulsive behavior; incr app = increased appetite; inf = infection; Int = interval; irrit = irritability; LT = long term; MAS XR = mixed amphetamine salts Extended Release; Mdn = Median; Meds = Medication; MPH = methylphenidate; N/pharyn = nasopharyngitis; NS = not significant; NT = no treatment; palpit = palpitations; PDD = pervasive development disorder; PEM = pemoline; PGA = parent global assessment; pharyn = pharyngitis; Psych = Psychiatric; QTc = QT interval corrected; RCT = randomized controlled trial; SBP = systolic blood pressure; sed = sedation; sig = significant; somnol = somnolence; Ss = subjects ;stim = stimulant; Tachy = tachycardia; TIA = transient ischemic attack; Tx = treatment; URT = upper respiratory tract; WISC-R = Weschler Intelligence Scale for Children - Revised

Table 8. (Cont'd) KQ2. Medication and adverse events – long term effectiveness and safety

Study	Med	General Adverse event	Nervous System	Psych/ Behav	Gastrointestinal	Respiratory	Vascular
Findling R 2005 ¹⁰³ Moderate	MAS XR vs. Adderall XR vs. placebo						Short-term tx: cardio NS ECG NS changes in BP pulse or ECG NS Longterm tx changes in mean BP and pulse NS
Gadow K 1999 ⁹³ Strong	MPH	no evidence adverse drug effects on growth	no change in motor tics or vocal tics during 2 year maintenance therapy				no evidence adverse drug effects on cardiovascular function after 2 years - small changes in SBP (+6mmHG) and DBP (-3mmHg) compared with placebo
Gillberg C 1997 ⁹² Strong	AMPH vs. placebo	weight gain LT expected height not clearly affected insomnia second most common AE	No change in tics,	Hallucinations: 3 in amph, 1 in placebo	Anorexia most common AE		
Hoare P 2006 ⁸⁹ Moderate	OROS MPH	Anorexia 12% insomnia 3.8%	headache 9.5% tics 7.6%	impulsive behavior 3.8% SAEs: depression/ suicidal in 2, delusions in 1, severe aggression in 1	abd pain 3.8%		

Table 8. (Cont'd) KQ2. Medication and adverse events – long term effectiveness and safety

Study Quality Rating	Med	General Adverse event	Nervous System	Psych/ Behav	Gastrointestinal	Respiratory	Vascular
Holick C 2009 ¹⁰⁸ Moderate	MPH MAS XR						TIA's may be more frequent than population rate for both groups TIA's (N = 21) ADHD meds v general population: adj HR 3.44 (95%CI 1.13 to 10.60) CVA (N = 44) ADHD meds v general population: adj HR 0.71 (95%CI 0.34 to 1.47)
Law S 1999 ⁹⁷ Strong	MPH		no difference in tics after 12 months				
Leibson C 2006 ¹⁰⁹ Weak	STIM vs. no stim	ER visits (not stratified by adverse event: Mean ED visits \pm SD: Tx= 0.6 \pm 0.56 noTx= 0.076 \pm 0.78 Mdn ED visits: Tx=0.47 no Tx=0.52					

Table 8. (Cont'd) KQ2. Medication and adverse events – long term effectiveness and safety

Study	Med	General Adverse event	Nervous System	Psych/ Behav	Gastrointestinal	Respiratory	Vascular
McGough J 2005 ⁹⁴ Strong	MAS XR	6 month anorexia 37% >18 months anorexia 3.5%	6 month headache 27% >18 months headache 18% 6 month twitching 5% SAEs: convulsions 2	6 month Abnormal thinking 4.4%, depression 5% Emotional 14% Nervousness 17%	6 month abd pain 18% >18 month abd pain 7%		
Weisler R 2005 ¹⁰⁴ Moderate	MAS XR						small mean increases in DBP, SBP and pulse not clinically significant Adverse event: hyperten 5/223 (2.24%) Tachy/palpit 2/223 (0.90%)
Winterstein A 2009 ¹⁰⁷ Strong	MPH vs. MAS						456 Ss visited ED with cardiac events Current users: 276/456 (60.5%) adj HR 1.01(95%CI 0.80 to 1.28) Past users: 170/456 (37.3%) adj HR 0.95 (95%CI 0.73 to 1.25)
Winterstein A 2007 ¹⁰⁶ Strong	Stim vs. NT						syncope 33.7% carddysR 32.6% palpit 15.7% hyper 14.7%

Table 8. (Cont'd) KQ2. Medication and adverse events – long term effectiveness and safety

Study	Med	General Adverse event	Nervous System	Psych/ Behav	Gastrointestinal	Respiratory	Vascular
Quality Rating							
Guanfacine (GXR)							
Sallee F 2009 ⁹¹	GXR	fatigue 15.0%	headache 24.8% sedation 12.6% somnol 37.9%		abd pain 12.1%	URT inf 16.0% N/pharyn 14.1%	Hypotension 5% No Q, RS interval ≥120ms
Weak	GXR + stim		headache 22.6%	irrit 13.2%	abd pain 15.1% decr app 13.2%	URT inf 24.5% pharyn 11.3%	
Biederman J 2008 ⁹⁰	GXR	fatigue 14.2% lethargy 5.8% pyrexia 8.3%	dizzy 7.1% headache 26.3% sedation 13.3% somnol 30.4% insomnia 5.0%	irrit 5.4%	abd pain 10.8% nausea 5.8% vomiting 8.3% diarrhea 5.0%	URT inf 10.4% cough 12.1% nasal cong 6.3% N/pharyn 7.9% pharyn 10.4%	change from baseline: Systolic BP -0.8 Diastolic BP - 0.4 Pulse Rate -1.9
Atomoxetine (ATX)							
Adler L 2005 ⁸⁸	ATX	dry mouth 24% erectile dysfunction 16%	headache 21 % insomnia 18 %		nausea 15% constipation 14%		Small mean increases in BP and HR QTc no change, not clin. Sig.
Buitelaar J 2007 ⁹⁶	ATX vs. placebo	Overall adverse event in Tx group: 9/292 (3.1%)	headache: Tx 10.1% placebo 8.6%			N/pharyn; Tx 7.6% placebo 8.6%	
Strong							
Michelson, D 2004 ⁹⁵	ATX vs. ATX	weight loss, slowed growth			gastroenteritis >5%	pharyn >5%	no difference in QT intervals between groups
Strong							

Table 8. (Cont'd) KQ2. Medication and adverse events – long term effectiveness and safety

Study	Med	General Adverse event	Nervous System	Psych/ Behav	Gastrointestinal	Respiratory	Vascular
Wernicke J 2003 ¹⁰² Weak	ATX vs. placebo						<p>Mean changes at end-point (pulse – units in beats; SBP and DBP – units in mm Hg)</p> <p>Children: Pulse: tx=+7.8, placebo=+1.5 p <0.001 SBP: tx=+2.8 placebo=+1.2 p = 0.148 DBP: tx=+2.1 placebo=-0.5 p = 0.002</p> <p>Adults: Pulse: tx=+5.3 placebo=-0.3 p <0.001 SBP: tx=+2.9 placebo=0.0 p = 0.002 DBP: tx=+1.8 placebo=+0.5 p = 0.083</p> <p>Palpitations: tx=3.7% placebo=0.8% p =0.037</p>

Adverse Events: Rates of Growth

Studies examining the effects of psychostimulant treatment on growth rates for children with ADHD are listed in Table 9. Of these, six compared the height and weight to population norms by converting to age and sex population norms using z scores.¹¹⁰⁻¹¹⁵ Two studies compare adult or adolescent height to parent or sibling height or community control groups.^{116,117} Two studies compare growth rates to both population norms and community controls.^{83,118} Over all, the studies rated as strong and moderate identify somewhat diminished rates of growth, for both weight and height in children receiving methylphenidate, DEX or mixed amphetamine salts. Several studies note that clinical samples of children with ADHD are taller and heavier than average for sex and age. There appears to be an association with cumulative dose. Studies suggest that catch up weight gain may occur when children take breaks from medication.

Spencer et al.,¹¹⁹ examined growth in 61 children who had received ATX for 5 years. Both weight and height showed diminished rates of growth at the 12 to 15 month time points relative to population norms but returned to baseline z scores over time.

In summary, medications used for ADHD appear to have a small but distinct dose-related impact on rates of growth for children with ADHD. Limitations in the studies include small sample size, and relatively short duration of studies which interfere with clarification regarding final adult height following years of medication use.

Table 9. KQ2 Summary of studies reporting on medication and growth rate

Study	Study Design Quality Rating	Sample N Mean Age(SD), %Male	Intervention compared	Followup duration	Results
Charach A 2006 ¹¹⁰	Systematic followup to RCT Strong	N = 79 Age: 8.3y (+/-1.5) Male: 81%	MPH or other stim	5y	Long-term use of high doses of stim during a period of 1 to 5 years to have measurable effects on the rate of growth in school-age children with ADHD
Faraone S 2007 ¹¹¹	OLL Moderate	N = 127 Age: 6 to 12y Male: NR%	MPH TD	37m	Adverse event: small but sig delays in growth (hgt, wght, and BMI) Wght & BMI dose dependent Stim naïve and heavier/taller children most likely experience growth deficit Effect on growth strongest year 1 and less over time
Kramer J 2000 ¹¹⁷	Multi-sample longitudinal Weak	N = 97 Age: 8.2y Male: 100%	MPH	TX: 36m (at 4-12y) followup NR~22y	Stim pts at final stature similar in avg. hgt/wght to family, community, or non-stim controls Some adverse events with nausea and vomiting + higher doses of MPH associated with adult growth decrements
Leibson C 2006 ¹⁰⁹	Retrospective cohort Weak	N = 313 Age: 7.7y (+/-1.9) Male: 75%	Stim vs. none	TX: 14days-11.8y followup: 10.2y (+/-1.4)	Extended stimulant Tx associated with decreased ED visits and lower costs but higher total medical costs
Pliszka S 2006 ¹¹⁵	Cohort Moderate	MPH N = 113 Age: 8.5y (+/-2.1) Male: 83.2% MAS N = 66 Age: 9.0y (+/-2.3) Male: 77.2%	MPH vs. MAS	TX: 2.6y (min = 1y) followup: 3y	Effect on height MPH = MAS Effect on weight MAS >MPH

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; assoc = associated; ATX LT = Atomoxetine long term; BMI = body mass index; btwn = between; def = deficits; DEX = dexidrine; exp = experience; diffs = differences; f/u = follow-up; Hgt = height; MAS XR = mixed amphetamine salts Extended Release; MPH = methylphenidate; MPH TD = methylphenidate trans-dermal system; NR = not reported; OLL = open label longitudinal; PEM = pemoline; ADHD = Attention Deficit Hyperactivity Disorder; rel = relationship; sig = significant; stim = stimulant; Pts = patients; Tx = treatment; wght = weight;

Table 9. KQ2 (Cont'd): Summary of studies reporting on medication and growth rate

Study	Study Design Quality Rating	Sample N Mean Age(SD), %Male	Intervention compared	Followup duration	Results
Poulton A 2003 ¹¹²	Retrospective review Moderate	N = 51 Age: 7.2y (+/-1.8) Male: 86%	DEX vs. MPH	TX: 6-42m followup: median 23m	Stim associated with decrease in HGT & WGHT trajectory during first 6–30 months of administration, c characteristic growth curve
Spencer T 2006 ¹¹⁹	5 year OLL Moderate	N = 1312 Age: 11.0y (+/-2.5) Male: 76.5%	ATX LT	TX: 5y followup: 5y	ATX Tx to 5 years- little or no long-term effect on growth and final stature for most patients; persistent decreases from expected may occur in some Pts larger than average before Ttx
Spencer T 1996 ¹¹⁶	4y followup to longitudinal study Moderate	N = 233 Age: 6 to 17y Male: 100%	DEX vs. PEM vs. CTL	followup: 4y	Small but sig diffs in hght in ADHD vs. controls, mostly early teens & use of psychotropic meds No evidence of weight deficits in ADHD children vs. Controls no rel btwn malnutrition & short stature; ADHD assoc with temporary deficits in growth in height through mid-teens, but assoc disappears with age effect appears to be mediated by ADHD and not Tx
Sund A 2002 ¹¹³	Retrospective cohort Moderate	N = 91 Age: 3 to 13y Male: 100%	AMPH vs. MPH	TX: 1y to 5y followup: annually to 5y	Extended AMPH or MPH – no impact on growth. Some Pts show wght loss during the 1st year of Tx, more pronounced with AMPH. Among Pts c reduced weight gain, most >mean wght prior to Tx
Swanson J 2006 ⁸³ PATS	Extension of RCT Moderate	N = 140 Age: 4.4y Male: 74%	Stim vs. none	followup: 1 y	annual growth rates were 20.3% less than expected for height
Swanson J 2007 ¹¹⁸ MTA	RCT Strong	N = 370 Age: 7 to 9.9y Male: 80%	Stim vs. none	followup: 3y	medicated group showed growth of 2.0cm and 2.7kg less than the non-medicated group with no evidence of rebound within 3 y
Zachor D 2004 ¹¹⁴	Retrospective chart-review Moderate	N = 81 Age: 8.5y Male: 72%	MPH vs. DEX vs. Adderall	Tx: 3y followup: 3m, 6m, 12m, 24m, 36m	Pre-pubertal children and those with adverse event appetite suppression more subject to slowed growth No long-term impact on height Diff stim meds had similar growth impact.

Medication vs. Combination Medication Plus Psychosocial/Behavioral Interventions

A total of 25 papers which compared medication management against multi-modal treatment (combined medication plus psychosocial/behavioral interventions) were identified (see Table 10). There were two large multi-centre RCTs conducted in North America which had strong internal validity: National Institute of Mental Health's Multimodal Treatment Study of ADHD (MTA) study, with 14-month intervention and 8-year followup, for which 19 papers are included in this review,^{118,120-137} and the second study led by Abikoff, Hechtman and Klein, with 2-year intervention, of which we include 5 papers.¹³⁸⁻¹⁴² There was one small 6-month intervention RCT with 18-month followup in a Chinese population, which had moderate internal validity.¹⁴³ All 3 RCTs involved predominantly male children aged 7 to 9 with Attention Defecit Hyperactivity Disorder-Combined Type (ADHD-C) and have an IQ above 80.

There were 22 papers with strong internal validity as rated by our assessment tool^{118,120-123,123,125-134,136,138-143} and two papers with moderate rating.^{135,137} The following organizes the discussion by focusing on each study in turn, in order of its overall quality.

MTA Study. The MTA study compared medication management, intensive behavioral treatment (parent training, child-focused treatment, and a school-based intervention), combined medication management and intensive behavioral treatment, and usual community care (CC). The mean age of the participants at study entry was 8.5 years. The medication strategy in the MTA study was intensive and involved a systematic effort to fully suppress ADHD symptoms using methylphenidate in divided doses.¹³⁰ Children receiving combined treatment ended maintenance on a lower dose (31.1 ± 11.7 mg/day) than the medication only group (38.1 ± 14.2 mg/day). Two-thirds of the children in the CC group received medication, mainly methylphenidate (mean dose 18.7 mg/day); their visit duration and frequency were shorter than the MTA-medicated subjects (30 min vs. 18 min and 8.8 vs. 2.3 visits/year respectively).¹²⁶

Primary outcomes analyzed included parent- and teacher-rated ADHD and ODD symptoms, comorbid conditions, reading achievement scores, social skills and functional impairment.¹²⁰ Children in the combined treatment and medication groups showed significantly greater improvement in ADHD symptoms than the behavioral treatment and CC groups. Combined treatment was superior to behavioral treatment and/or CC in improving oppositional/ aggressive symptoms, internalizing symptoms, teacher-rated social skills, parent-child relations, and reading achievement. Connors et al.,¹²⁷ utilized a single composite measure of treatment outcome by combining standardized parent and teacher measures (covering internal problems, external problems and social skills), and found combination therapy to be significantly better than all other treatments, with effect sizes ranging from small (0.28) versus medication, moderate (0.58) versus behavioral treatment, to moderately large (0.70) versus CC. Medication management was significantly superior to behavioral treatment and CC with small effect sizes (0.26 and 0.35 respectively). Behavioral treatment and CC were comparable. Swanson et al.,¹²⁹ utilized a categorical outcome based on the average rating by the parent and teacher of ADHD and ODD symptoms on the Swanson, Nolan, and Pelham, version IV (SNAP-IV) scale. The analysis gave MTA medication algorithm a large effect size (0.59), with combined treatment incrementally superior to medication (effect size of 0.26). Across all treatment groups, rates of Conduct

Disorder (CD) and anxiety disorders were reduced, and rates of mood and learning disorders remained the same at 14 months, with no difference between the treatment groups.¹³²

The MTA 24-month outcome¹²² reported persisting superiority for both combined and medication groups, but with reduced effect size for both ADHD and ODD symptoms. The greater deterioration for the combination and medication groups compared to the behavioral and CC groups from the 14- to 24-month time points was related to patients stopping medication in the two former groups and starting medication in the latter two groups.¹²¹ By 3 years, Jensen et al.,¹³³ did not find any significant difference between treatment groups although each treatment group showed substantial improvements from baseline. There was significant reduction in rates of ODD/CD, anxiety and depressive disorders, but no effect of treatment assignment was seen. Medication use declined for medication and combined treatment groups from >90 percent over the first 14 months to 71 percent, increased from 14 percent to 45 percent for behavioral treatment group and remained stable at 62 percent for CC group. By 8 years, Molina et al.,¹³⁶ found that among those followed up (70.1 percent of original cohort), 32.5 percent of those who were medicated at 14-month were medicated in the past year. There were also no significant differences in medication use among the four treatment groups. They found no significant differences in the primary outcomes or additional outcomes including grades earned in school, arrests, psychiatric hospitalizations and other clinically relevant outcomes between treatment groups. Overall, the ADHD symptom trajectory noted in the first 3 years appeared to be a predictor for the outcomes at 8 years.

Additional post-hoc analyses of the study's 14-month results are discussed here. Jensen et al.¹²⁸ reported that children with comorbid ADHD and anxiety disorders responded equally well to all MTA treatments. Children with ADHD-only or ADHD with ODD/CD responded better to medication and combined treatment, while children with multiple comorbid disorders (anxiety and ODD/CD) responded optimally to combined treatment. Wells et al.,¹²³ found that all three MTA treatments decreased self-reported negative parenting more than CC treatment, with no significant effect of treatment on positive parenting. Using more objective measurement by assessing parent-child interactions in a laboratory setting for 89.9 percent of the families in the MTA study, Wells et al.,¹²⁴ found significantly greater improvements in parents' use of proactive parenting strategies in the combined treatment group than the CC group (Cohen's $d=0.49$) and the medication management group (Cohen's $d = 0.38$). Hinshaw et al.,¹²⁵ found that reductions in negative and ineffective parenting practices at home could be related to improved teacher-reported outcomes in the combination group. Arnold et al.,¹³¹ analyzed ethnicity as a moderator and found that combined treatment produced better outcome than medication management (effect size = 0.36) for the pooled minorities, but not for Caucasians. Hoza et al.,¹³⁷ found that all groups remained significantly impaired on peer-assessed outcomes with no significant difference between treatment groups. Despite the use of an objective outcome, the study's validity was affected by the 'drop out' of half of the original cohort.

A series of analyses using the 36-month data were conducted. It was hypothesized that the loss of relative superiority of the combined treatment and medication management groups could be due to selective treatment of the most severe cases, but Swanson et al.,¹¹⁸ did not find evidence for this self-selection hypothesis. Swanson et al.,¹¹⁸ found decreased growth rates when initiating treatment in stimulant-naïve children; this may be present for up to 3 years of treatment and

accumulate to result in a difference of about 2.0cm in height and 2.0kg in weight. Molina et al.,¹³⁴ could not establish a clear benefit of medication treatment on subsequent delinquency and recommended re-evaluation at older ages. When controlled for baseline delinquency, the psychosocial/behavioral treatment group had lower rate of substance use at 24 months, although this effect of original treatment assignment disappeared at 36 months. Between 24-36 months, medication use was a marker for deterioration, and Swanson et al.,¹³⁵ did not find evidence that self-selection accounted for this.

In summary, the MTA study represents the most comprehensive evaluation of the treatment options for ADHD–C in children aged seven to nine years, to date.

Study by Klein/Abikoff et al. Klein et al.,¹⁴² randomized 103 children with ADHD aged 7-9 who were free of conduct and learning disorders, and who responded to short-term methylphenidate to receive methylphenidate alone, methylphenidate plus multimodal psychosocial treatment (parent training, behavior management training, family therapy and child social skills training), or methylphenidate plus attention control treatment (parental support and education) over a 2-year period. They reported that all subjects ‘relapsed’ when they received placebo substitution at the end of 1 year, suggesting that combination therapy did not attenuate symptom relapse following medication discontinuation.¹³⁹ Significant improvement occurred across all treatments and continued over 2 years, and combination therapy was not superior.¹⁴¹ There were no differences among treatment groups for rates of diagnoses of persistent ADHD, ODD, CD or psychosocial functioning at 24 months.¹³⁸ In stimulant-responsive children with ADHD, the authors concluded there is no support for adding ambitious long-term psychosocial intervention to improve ADHD and oppositional defiant disorder symptoms. There was also no difference in the social functioning variables examined between groups which led the authors to conclude that there is no support for clinic-based social skills training as part of a long-term psychosocial intervention to improve social behavior. These conclusions may not apply for young children who do not show an early favorable response to stimulant treatment or who have comorbidities especially conduct problems. Hechtman et al.,¹⁴⁰ examined the impact of treatment on parental practices. Psychosocial treatment did not enhance parenting practices, as rated by parents and children. Significant improvement in mothers' negative parenting occurred across all treatments and was maintained.

Other Studies. The smaller study of So et al.,¹⁴³ involved 90 ethnic Chinese children who were randomized to receive either methylphenidate or methylphenidate with behavioral treatment for 6 months. The mean dose of medication was 13.6-16.8 mg/day. Although the combined treatment group improved significantly more than the medication management group in ADHD symptoms at the end of the six month treatment period, there was no difference at 12 or 18 months. ODD symptoms improved significantly more in the combined group at 12 and 18 months; there was no noticeable improvement in the medication management group in terms of ODD symptoms. There was faster rate of improvement in ADHD and ODD symptoms in the combined group, and all gains made were sustained in both groups over 18 months. However, the study is limited by the relatively small sample size, high drop out rate in the medication-only group and more significant ODD symptoms among those remaining in the trial.

Table 10. KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD

Study	Study design Quality rating	Study participants (N; age; %male)	Interventions compared					Intervention duration (month)	Followup length (month)	Outcome measures	Results†
			Med	Behav	Comb	CC	No med				
Arnold LE 2003 ¹³¹	RCT (MTA) Strong	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		14 m	14 m	Ethnicity effects on attendance, o/c, acceptance & compliance, sensitivity & response ADHD meds; SES & informant explanations of ethnic effects	Caucasian < African American & Latino on some symptoms (Sig), Response to Tx – no sig diff after controlling for SES Ethnic minority families cooperated with and benefited significantly from Comb Tx > Med for minority families
Conners C 2001 ¹²⁷	RCT (MTA study) Strong	N = 579 Age: 7 to 9y Male: 80%	√	√	√	√		14 m	14 m	Analyses of multiple measures of MTA outcomes	Comb Tx vs. Med Tx NS

†Only statistically significant results are reported.

Abbreviations: –ve = negative; acad = academic; ADHD = Attention Deficit Hyperactivity Disorder; agg = Aggression; anx = Anxiety; assoc = associated; BT = Behavioral treatment; CC = Community Care; CD = conduct disorder; COM = categorical outcome measure; char = characteristics; comb = combined Stimulant + Behavioral treatments; Dx = diagnoses; ED = externalizing disorders; EoT = End of Treatment; FU = followup; ID = internalizing disorders; LD = learning disorder; LT = Long Term; maint = maintenance; MD = Mood disorder; Med = Stimulant medication treatment; MedMgt = Medical Management; MMT = multi-modal treatment; MTA = Multimodal Treatment of Children with ADHD; n/a = not applicable; neg = negative; No med = No Stimulant medication treatment; NS = not significant; o/c = outcome; ODD = oppositional defiant disorder; P = Parent; Rx = prescription; SES = socio-economic status; sev = severity; sig = statistically significant; SNAP-IV = Swanson, Nolan, and Pelham - version IV; sst = social skills training; Sympt = symptoms; TAU = Treatment as usual; T = Teacher; tx = treatment; UMT = unimodal treatment

Table 10. (Cont'd) KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD (cont'd)

Study	Study design Quality rating	Study participants (N; age; %male)	Interventions compared					Intervention duration (month)	Followup length (month)	Outcome measures	Results
			Med	Behav	Comb	CC	No med				
Hechtman L 2005 ¹³²	RCT (MTA) Strong	N = 576 Age: 7 to 9y Male: 80%	√	√	√	√		14 m	14 m	Prevalence of other Dx (ODD, CD, anxiety, depression, MD, LD)	Sig decreases at 14m in Dx of ODD, CD, & Anx not LD or MD CC group developed sig >new ODD and retained more baseline ODD than Comb or Med No sig diffs for specific other conditions. Only the Comb sig >CC in reducing disorders and impairment at 14m in Ss with multiple conditions at baseline. Well-titrated and monitored stimulant medication can decrease ODD and possibly prevent future CD
Hinshaw S 2000 ¹²⁵	RCT (MTA study) Strong	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		14 m	14 m	parenting vs. teacher-reported outcomes	Reduced Neg /Ineffective discipline mediated better school social skills Comb Med+behave Tx >CC only for reductions in –ve parenting Comb Tx → less negative/ Ineffective discipline associated with reduced disruptive class behavior

Table 10. (Cont'd) KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD (cont'd)

Study	Study design Quality rating	Study participants (N; age; %male)	Interventions compared					Intervention duration (month)	Followup length (month)	Outcome measures	Results
			Med	Behav	Comb	CC	No med				
Hoza B 2010 ¹³⁷	RCT (MTA) Moderate	N = 285 Age: 7 to 9.9y Male: 80%	√	√	√	√		14 m	14 m	Peer-assessed sociometric procedures Tx comparisons: Med+Comb vs. Behav+CC; Med vs. Comb; Behav vs. CC	limited evidence re peer-assessed outcomes favoring Tx with Meds
Jensen P 2000 ¹²⁸	RCT (MTA) Strong	N = 579 Age: 8.2y Male: 80%	√	√	√	√		14 m	14 m	<ul style="list-style-type: none"> • Tx effects of ID and ED comorbid disorders with ADHD • Outcomes assessed by head-to-head comparison of singly comorbid groups; CD +ANX • examines diff benefits of specific Tx on comorbid groups, and by effect size 	<p>ADHD co-occur with ID vs. ED</p> <p>ADHD + ANX vs. ADHD and ODD/CD but no ANX vs. ADHD +ANX and + ODD/CD may be warrant classification as ADHD subtypes different from “pure” ADHD</p>

Table 10. (Cont'd) KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD (cont'd)

Study	Study design Quality rating	Study participants (N; age; %male)	Interventions compared					Intervention duration (month)	Followup length (month)	Outcome measures	Results
			Med	Behav	Comb	CC	No med				
Jensen P 2001 ¹²⁶	RCT (MTA) Strong	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		14 m	14 m (monthly followup)	LT Tx: MedMgt, Behav, Comb Optimal Tx vs. CC TAU Relative Tx efficacy & drug action Behavioral health impact	Comb and Med>Behav and CC interventions for ADHD symptoms. Comb Tx>single Tx (Med, Behav) and CC for other function domains (social skills, academics, parent-child relations, ODD, anxiety)
Jensen P 2007 ¹³³	RCT (MTA) Strong	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		14 m	24 m	3 yr followup of MTA	earlier advantage of 14m MTA MED algorithm was no longer apparent; regardless of Tx; but all groups improved from baseline
Molina, 2009 ¹³⁶	RCT (MTA) Strong	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		4w titration 13m maint	8 year	ADHD and ODD symptoms, delinquent behavior, global functioning, depression, academic competence, social skills, driving infractions	No difference between treatment groups for all outcomes 3 year symptom trajectory predicted 8 year outcome

Table 10. (Cont'd) KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD (cont'd)

Study	Study design Quality rating	Study participants (N; age; %male)	Interventions compared					Intervention duration (month)	Followup length (month)	Outcome measures	Results
			Med	Behav	Comb	CC	No med				
Molina B 2007 ¹³⁴	RCT (MTA) Strong	N = 487 Age: 8.5 (± 0.8 y) Male: 80%	✓	✓	✓	✓	✓	14 m	36 m	Prevalence of delinquency and substance abuse and prediction based on Tx and self-selected prescribed meds	MTA > rates of delinquency & substance use. Intensive Behavior less 24 m substance use than other MTA Ss By 24 and 36 months, more days of prescribed meds assoc with more serious delinquency but not substance use
MTA Cooperative Group, 1999 ¹²⁰	RCT (MTA) Strong	N = 579 Age: 7 to 9.9y Male: 80%	✓	✓	✓	✓		14 m	14 m	ADHD sympt; Agg/ODD, Internalizing, social skills, parent-child relations, acad achievement	Comb Tx and Med Tx sig increased > Behav or CC Comb vs. Med Tx -> NS
MTA Cooperative Group, 2004 ¹²¹	RCT (MTA) Strong	N = 579 Age: 7 to 9.9y Male: 80%	✓	✓	✓	✓		14 m	24 m	ADHD; ODD; social skills, IQ, acad, growth, negative/ineffective parental discipline	stim associated with maintained effectiveness but continued mild growth suppression Loss of initial benefit greater for Med and Comb than for Behavior and CC
MTA Cooperative Group, 2004 ¹²²	RCT (MTA) Strong	N = 540 Age: 8.4y (± 0.8) Male: 80%	✓	✓	✓	✓		14m	24 m	ADHD and ODD symptoms, acad, social skills, negative/ineffective discipline	Med > Behavior and CC (SIG) for ADHD and ODD symptoms at 24m, but less than 14m Comb > Med and Behavior > CC NS

Table 10. (Cont'd) KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD (cont'd)

Study	Study design Quality rating	Study participants (N; age; %male)	Interventions compared					Intervention duration (month)	Followup length (month)	Outcome measures	Results
			Med	Behav	Comb	CC	No med				
Swanson J 2001 ¹²⁹	RCT (MTA) Strong	N = 576 Age: 7 to 9y Male: 80%	√	√	√	√		14 m	14 m	EoT status - averaged P & T ratings of ADHD and ODD (SNAP-IV) and low symptom-severity as clinical cutoff to form COM	Summary SNAP-IV scores increased precision of measures by 30%. *Group differences in success (Comb = 68%; Med = 56%; Behav = 34%; CC = 25%) confirmed large effect Med andmmT p <0.05 Confirms primary findings and clarify clinical decisions re:mmT & UMT with meds
Swanson J 2007 ¹¹⁸	RCT (MTA) Strong	N = 370 Age: 7 to 9.9y Male: 80%	√				√	36 m	36 m	Physical growth as function of Stim meds	Stimulant-naïve children with ADHD-C larger before Tx but decreased growth rate after Tx; asymptotes within 3y without evidence of growth rebound
Swanson J 2007 ¹³⁵	RCT (MTA) Moderate	N = 579 Age:7 to 9.9y Male:80%	√	√	√	√		14 m	3 6m	Propensity score analyses of 5 subgroups; Char and sev ADHD	All propensity subgroups showed initial advantage of medication gone by 36m assessment
Vitiello B 2001 ¹³⁰	RCT (MTA) Strong	N = 198 Age: 7 to 9y Male: 80%	√					4 w titration 13 m maint	14 m	Optimal drug dosing	Initial titration dose of MPH in the general range did not prevent need for subsequent adjustments
Wells K 2000 ¹²³	RCT (MTA) Strong	N = 579 Age: 8.5y Male: 80%	√	√	√	√		14 m	14 m	Parenting behav, family stress	negative parenting Behav alone, Med alone, and Comb >CC →Sig

Table 10. (Cont'd) KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD (cont'd)

Study	Study design Quality rating	Study participants (N; age; %male)	Interventions compared					Intervention duration (month)	Followup length (month)	Outcome measures	Results
			Med	Behav	Comb	CC	No med				
Wells K 2006 ¹²⁴	RCT (MTA) Strong	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		14 m	24 m	Constructive parenting Child negativity	Parenting; Comb >MedMgt or CC SIG Treatment effects on child behaviors were NS
Abikoff H 2004 ¹³⁸	RCT Strong	N = 103 Age: 7 to 11y Male: 93%	√	√	√			N/a as per design	2 y	Social functioning	young ADHD - no support for SST as part of a long-term psychosocial intervention Significant benefits from MPH stable over 2 years.
Abikoff H 2004 ¹³⁹	RCT Strong	N = 103 Age: 7 to 11y Male: 93%	√	√	√			N/a as per design	2 y	Symptomatic improvement	long-term psychosocial intervention to improve ADHD, ODD symptoms NS benefits of MPH stable over 2 y
Hechtman L 2004 ¹⁴¹	RCT Strong	N = 103 Age: 7 to 11y Male: 93%	√	√	√			N/a as per design	2 y	Rx, Rx+behav, Rx+psychosocial	Sig improvement occurred across all treatments maintained over 2 y
Hechtman L 2004 ¹⁴⁰	RCT Strong	N = 103 Age: 7 to 11y Male: 93%	√	√	√			N/a as per design	2 y	Parenting	Psychosocial led to better knowledge but not better practice; improvement in mothers' negative parenting maintained
Klein R 2004 ¹⁴²	RCT Strong	N = 103 Age: 7 to 11y Male: 93%	√	√	√			N/a as per design	2 y	Augment effects of meds, not replace them	Successful delivery of comprehensive 2yr psychosocial program
So C 2008 ¹⁴³	RCT Strong	N = 86 Age: 7 to 10y Male: 90%	√	√				6 m	12 m	Rx and Rx+BT for Chinese children	added benefits of Beh +Med Chinese ADHD children with Tx by regular medical and paramedical staff

Summary

Overall, the results from these three cohorts indicate both medication and combined medication and behavioral treatment are effective in treating ADHD plus ODD symptoms in children, primarily boys aged 7-9 of normal intelligence with combined type of ADHD, especially during the first 2 years of treatment. Overall, secondary analyses of the MTA study suggests that combined therapy may have a slight advantage over medication management during the first 14 months (effect size 0.26-0.28),^{127,129} especially for children with multiple co-morbidities.¹²⁸ However, if the child is free of conduct and learning problems and shows an early favorable response to stimulant medication, then medication alone is equivalent to combined treatment in controlling ADHD and ODD symptoms for the first 2 years.^{138,139} The MTA study also suggests that these two strategies *are* superior to psychosocial/behavioral treatment alone or community care during the first 2 years,^{120-122,137} although psychosocial/behavioral treatment is equally effective for children with co-morbid anxiety disorder only during the first 14 months.¹²⁸ Combination therapy and medication management are effective in reducing ODD during the first 2 years of treatment,^{138,139} and superior to psychosocial/behavioral treatment and CC.¹²⁰⁻¹²² It appears that psychosocial/behavioral treatment reduces the risk for substance use for 10 months following intervention, but the effect disappears by 22 months.¹³⁴ No treatment strategy is clearly superior in reducing other co-morbid psychiatric disorders at 14 months or 3 years.^{132,133}

Combining medication with behavioral/psychosocial treatment reduces the dose of medication required, and may retain patients in treatment, at least among Chinese families.¹⁴³ In So's study involving Asian children, the mean daily dose of stimulant medication was less than half that used in the MTA study.¹⁴³ From Abikoff's 2004 study, it may be more cost-effective to treat stimulant-responsive children free of learning and conduct problems with medication alone.^{138,139} Treatment with medication, intensive behavioral treatment or combination of the two can reduce negative parenting, but combined treatment may be the most effective in improving positive parenting.^{123-125,140,141}

Behavioral/Psychosocial Treatment Compared with No Treatment

There was one paper identified which investigated a behavioral/psychosocial treatment program for parents of children with ADHD. The efficacy of a 9-week parent stress management training program for reducing parenting stress and improving parenting style was compared to a wait list control group, and they were followed up at one year. The study by Treacy et al.,¹⁴⁴ of moderate internal validity, involved 63 parents from 42 families with at least one child (aged 6-15) diagnosed with DSM-IV ADHD. They were randomized to either the intervention group or control wait list for 9 weeks. The controls received similar intervention thereafter, and all participants were followed up for one year. The intervention was more effective for mothers than fathers, who reported less stress and less negative parenting. These improvements were maintained at one-year followup.

Long-term Academic Achievement and School Outcomes Following Interventions for ADHD

While children with ADHD have impairments in many areas of functioning, a primary common focus of concern is academic achievement. This section describes 12 studies reporting on academic achievement outcomes, broadly defined as improvements in standardized test scores and report card grades, and decreases in absenteeism and grade retention following interventions for ADHD. The majority of studies reporting on academic functioning, included academic measures as one of several secondary outcomes. Academic outcomes following medication intervention were examined in four studies with moderate and strong quality ratings.^{92,145-147} There were five studies looking at academic effects of multimodal interventions in two cohorts; these are reported in publications describing the randomized clinical trials with strong internal validity^{120,141} and in three publications of moderate quality describing extensions of the MTA study, reporting on assessments at different time points up to 8 years of followup.^{122,133,136} Three reports on two cohorts examined academic achievement as the primary outcome following classroom-based interventions. These studies were rated as moderate internal validity.¹⁴⁸⁻¹⁵⁰ Overall results indicate that there are improvements in academic functioning with medication, especially in reading skills. There is no added benefit with combining behavioral or psychosocial components to the medication interventions. In contrast, classroom-based programs to enhance academic skills are effective in improving achievement scores in multiple domains, but the benefits are sustained only as long as the intervention is implemented.

Following are the results of the studies reporting on academic outcomes, organized by the type of intervention.

Medication Interventions

The medication interventions were primarily psychostimulants. Powers et al.,¹⁴⁵ followed a group of 90 ADHD children for the average duration of 9.13 (SD 1.5) years and the average duration of receiving psychostimulants was 5.33 (SD 3.02) years. They found that adolescents, diagnosed with ADHD at childhood, who had received stimulants for at least 1 year compared to those who did not, had higher scores on three measures of academic achievement; word reading, pseudo-word reading and numerical operation. They also showed higher high school grade point average (GPA). However, the medicated group did not reach the level of academic function of their non-ADHD peers. The study provides evidence of modest positive effect of stimulant medication on long-term academic function. In spite of controlling for IQ, the participants were not matched on co-morbidity of learning disability potentially interfering with the conclusions.

Barbarese et al.,¹⁴⁶ also investigated the benefits of long-term stimulant medication use on academic outcomes in a retrospective birth cohort, including 370 ADHD children. The mean duration of treatment for cases that had a history of receiving medication was 2.8 years. The participants were followed till median age of 18.4 years. There was no difference in regard to mental retardation and learning disability between the two groups. Overall, the authors found a positive correlation between cumulative stimulant dose and last documented achievement skills at a median age of 12.8 years. School absenteeism was significantly lower in the treatment

group; any treatment and duration of treatment with stimulants were both negatively associated with the percentage of days absent. Stimulant-treated children were 1.8 times less likely to be held back in a grade. In contrast, one area of academic skills, the average reading score at the time of the last assessment, was similar between the cases that were treated and those not treated.

Other studies reporting on academic outcomes^{92,147} found that children treated with stimulants experienced improvements in measured IQ and less grade retention.

In summary, it seems that extended use of psychostimulant medications may enhance some dimensions of academic functioning. However, the outcomes reported are diverse and suggest that more investigation of this question is required.

Combination Interventions

MTA studies are described comprehensively earlier in this report. Following is the description of MTA results in academic and school performance. At the 14 months endpoint of the RCT, combined treatment was superior to intensive behavioral treatment and CC in improving reading achievement. At the 24 month assessment, nine months following discontinuation of the interventions, the differential between groups was no longer present.^{121,122} At 36 month assessment, the intention to treat analysis of the study¹³³ also showed no significant differences between the treatment groups on reading achievement scores, similar to the other symptomatic and functional outcomes reported. However, all treatment groups showed substantial improvement from baseline in all domains, although the relative effect size for reading achievement was small compared to other areas (reading 0.1-0.2, ADHD symptoms 1.6-1.7, functional impairment 0.9-1 and social skills 0.8-0.9). After 8 years, intention to treat analyses again showed that originally randomized treatment groups did not differ significantly on academic assessments and grades earned at school.¹³⁶ Looking at the trajectory of symptoms, impairment and academic achievement, there was convergence of treatment groups from 36 months to 8 years and maintenance of improved overall functioning relative to the baseline, except for mathematics achievement. Further examination, however, showed a positive association between past year medication use and mathematics achievement scores at 36 months, 6 years and 8 years; in contrast, past year medication use was associated with higher hyperactivity-impulsivity, ODD symptoms and functional impairment. Past year medication use was interpreted by the authors as suggesting continued rather than new onset use, and therefore may represent longer duration of use.

The other study reporting academic outcomes following extended use of combination psychostimulants and multimodal psychosocial intervention was a 24 month RCT also described in the earlier section of this report.¹⁴¹ They included 103 participants, age 7 to 9 years, with ADHD (excluding those with documented learning disabilities or conduct disorders), who received either MPH alone, MPH combined with multimodal psychosocial treatment, which included academic remediation, or MPH combined with an attention control intervention. Significant improvement in academic functioning was observed with all three interventions at 24 months. There was no advantage on any measure of academic performance with the combination treatment over MPH alone.

In summary, the results of studies investigating combined medication and psychosocial/behavioral interventions indicate improvement from baseline in academic outcomes, with no difference in effect between combined interventions and medication alone. Results from the MTA study suggest there may be different outcome trajectories for reading and mathematics achievement.

Classroom-Based Interventions

The study by Evans et al.,¹⁵⁰ is a controlled clinical trial of Challenging Horizon Program and consultation (CHP-C) vs. CC control group over the intervention period of 3 years and a followup after 6 years. CHP-C was an intervention targeting academic skills such as assignment tracking, note taking and organization skills in addition to social skills training, conversation skills and problem solving. The beneficial results of treatment on ADHD symptoms were few during the first year of intervention but emerged later after 2.5 years. However, neither teacher nor parent rating of academic functioning showed any significant academic benefit. Similarly no long-term effect was found in student GPA.

The study by Jitendra et al.,¹⁴⁸ consisted of a 15 month randomized clinical trial of Intensive Data-based Academic Intervention (IDAI) vs. Traditional Data-based Academic Intervention (TDAI). Volpe et al.,¹⁴⁹ reported the results of this study after 1 year followup. The assessments at 3, 12, and 15 months of the intervention indicated both consultation groups demonstrated improvement in reading and mathematics skills on curriculum-based measurement (CBM) and in report card grades, however grades improved more for reading than for mathematics. The followup study at 1 year after discontinuation of interventions revealed that while students in both groups maintained the previous achievements, continued growth in skills was significant only for reading fluency.

While there are few comparative classroom-based intervention studies lasting 12 months or more, information from the ones available is mixed. Some programs are clearly beneficial and lead to improvement in academic skills for children with ADHD, but only as long as they continue to receive them.

Summary

The review of the academic outcomes with long-term followup of treatment interventions revealed benefits with medication interventions in some limited domains. Combining psychosocial and academic skills interventions with medication offers no additional gains over and above that of medication alone, at least for children with ADHD without comorbid learning disabilities. Interventions for academic skills in classroom-based programs result in academic enhancement but the findings support the need for sustained intervention to improve academic functioning over time.

Table 11. KQ2. Summary of studies reporting academic interventions

Study	Study design Quality rating	Sample characteristics N Age (SD) %Male	Interventions compared	Length of treatment & followup	Results
Barbaresi W 2006 ¹⁴⁶	Retrospective Birth Cohort Moderate	N = 370 Age: median 18y Male: 75%	Stim (MPH equivalent)	Tx: 33.8 m followup: approx 15y	Tx with Stim: decreased rates of absenteeism modest positive correlation between stim and last reading score decrease in rate of dx substance abuse
Biederman J 2009 ¹⁴⁷	Case-control Strong	N = 140 Age: 6 to 17y Male: 100%	Stim vs. Cntl	Tx: 6y (4.7) followup: 10y	Less grade repetition in those treated with stimulants
Evans S 2007 ¹⁵⁰	CCR Moderate	N = 79 Age: 10 to 14y Male: 77%	CHP-C vs. Cntl	TX: 3 acad y followup: every 6m over 3 y	Cumulative long-term benefits for the Tx Teacher & parent reports show no cumulative acad benefits but within-year analyses suggest trend towards benefit in student GPA
Gillberg C 1997 ⁹²	RCT Strong	N = 62 Age: 9y (+/-1.6) Male: 84%	AMPH vs. placebo	Tx: 15 m followup: 18 m	IQ score (WISC-R) improved
Hetchman L 2004 ¹⁴¹	RCT Strong	N = 103 Age: 7 to 9y Male: NR	MPH vs. MPH +MPT vs. MPH+ACT	Tx: 2y followup: to 24m	No advantage on any measure of acad perf or emotional status for the COMB vs. MPH vs. MPH + ACT Significant improvement occurred across all Txs & was maintained over 2 years
Jensen P 2007 ¹³³	RCT (MTA) Strong	N = 485 Age: 7 to 9y Male: 80%	Med Mgt vs. Beh vs. Comb vs. CC	Tx: 14m followup: 36m	Improvement in reading with all intervention, no significant difference between groups

Abbreviations: Acad = academic; ACT = attention control treatment; ADHD = Attention Deficit Hyperactivity Disorder; AMPH = amphetamine; Beh = behavioral intervention; CC = Community Care; CCR = controlled clinical trial; CHP-C = Challenging Horizons Program-training and consultation model; Cntl = control; Comb = combination; dx = diagnosis; F/U = followup; GPA = grade point average; o/c = outcomes; MedMgmt = Medical Management; MPH = methylphenidate; MPT = multimodal psychosocial treatment; MTA = multimodal treatment study; OLE = open label extension; perf = performance; pts = patients; RCT = randomized control trial; SD = standard deviation; Ss = subjects; Stim = stimulant; TDAI = Treatment data based academic intervention; Tx = treatment; WISC-R = Weschler Intelligence Scale for Children - Revised

Table 11. (Cont'd) KQ2. Summary of studies reporting academic interventions

Study	Study design Quality rating	Sample characteristics N, Age, %Male,	Interventions compared	Length of treatment & followup	Results
Jitendra A 2007 ¹⁴⁸	RCT Moderate	N = 167 Age: 104.3m (+/- 14.7) Male: 76%	TDAI	Tx: 2 acad y followup: 15m	Significant positive growth for 9 of 10 dependent variables
Molina B 2009 ¹³⁶	RCT (MTA) Strong	Tx: N = 436 Co: N = 170 Age: 7 to 9.9y Male: NR	Med Mgt vs. Beh vs. Comb vs. CC	TX: 14m followup: 24m, 36m, 6y, 8y	Tx not differ significantly on repeated measures or newly analyzed variables Medication use decreased by 62% after the 14-month controlled trial, but did not change results *ADHD symptom trajectory in the first 3 years predicted 55% of the outcomes MTA Ss worse than the local normative comparison group on 91% of the variables tested
MTA Cooperative Group 2004 ¹²²	OLE of RCT (MTA) Strong	N = 540 Age: 8.4y (+/-0.8) Male: 80%	MedMgt vs. Beh vs. Comb vs. CC	Tx: 14m followup: 10m	MedMgt > Beh and CC; Comb = Medmgt; Beh = CC
MTA Cooperative Group, 1999 ¹²⁰	RCT Strong	N = 579 Age: 8.5y (+/-0.8) Male: 80%	MedMgt vs. Beh vs. Comb vs. (CC)	followup: 14 m	Comb and MedMgt > Beh and CC Comb > MedMgt, Beh and CC for oppositional, aggressive, and internalizing symptoms, social skills, reading achievement and parent-child relations
Powers R 2008 ¹⁴⁵	Prospective longitudinal Moderate	N = 90 Age: 9.11y (+/- 1.22) Male: 88%	ADHD + Stim vs. Cntrl vs. vs. non-ADHD	Tx 30.4m (range 1-76 m) followup: 24m, 36m	Acad outcomes: Stim Ss > Cntrl (p < 0.05). nonADHD > Cntrl Stim pts c ADHD may benefit from long-term adolescent academic performance
Volpe R 2009 ¹⁴⁹	OLE RCT Moderate	N = 167 Age: 104.3m (+/- 14.7) Male: 76%	TDAI	Tx 15m over 3 acad y followup: 1y	Significant positive growth in 2 of 16 variables

Very Longterm Studies Examining Stimulant-Treated and Patients Who Did Not Receive Stimulant Medication Treatment

The studies reviewed in this section examine outcomes which were five or more years after initiation of the intervention. All the studies identified compared those who had been treated with stimulant medication against those who did not. The 6-8 year outcome of the MTA study which compared medication, behavioral and multimodal interventions has been discussed in an earlier section.

There were 14 papers identified. One study was rated with strong internal validity,¹⁵¹ nine studies had moderate internal validity^{98,147,152-158} and four were weak,^{109,159-161} according to the quality assessment tool used. Twelve papers^{98,109,147,151-159} reported on prospective followup studies of one or more cohorts of ADHD youth while two were retrospective studies.^{160,161} As these papers reported on a variety of outcomes, they are summarized according to the outcomes studied. Only studies meeting criteria for at least moderate internal validity are discussed below.

Psychiatric Disorders

Biederman et al.,¹⁴⁷ conducted a case-control, 10-year prospective followup study involving 140 white male children with ADHD, aged 6 to 17 years at baseline, which controlled for parental psychopathology. Out of the 112 participants assessed, 82 (73 percent) had lifetime treatment with stimulant medication, starting at mean age of 8.8 years (SD: 3.5; range: 3–21 years) for a mean duration of 6 years (SD: 4.7). Those who were treated with stimulants were significantly less likely to subsequently develop ODD (HR 0.21), CD (0.21), depressive (HR 0.22) and anxiety (0.15) disorders and were less likely to repeat a grade. There was no significant difference for Bipolar Disorder between groups.

Substance Use Disorders

Katsuic et al.,¹⁵² identified 379 research-identified ADHD children from a birth cohort (74.9 percent boys) and followed them up for a mean duration of 17.2 years; 295 received stimulant medication (alone or in combination, median average daily dose of 21.4 MPH-equivalent units, median duration 33.8 months, median age at treatment 9.8 years) and 84 did not. They found stimulant treatment to be associated with reduced risk for later substance abuse among boys, but not among the girls. Mannuzza et al.¹⁵⁷ followed up 176 MPH-treated Caucasian male children aged 6 to 12 with DSM-II hyperkinetic reaction but without conduct disorder, into adulthood (mean age= 25.3; retention rate 85 percent) and found the early-treated (age 6-7) subjects to have lower lifetime rates of substance use disorders. Age at stimulant treatment initiation was significantly and positively related to the later development of antisocial personality disorder, but was unrelated to mood and anxiety disorders. The study by Biederman et al.,¹⁴⁷ which was described at the beginning of this section, also examined substance use disorders as an outcome. The analysis of 56 medicated and 19 non-medicated boys who were above the age of 15 (53.6

percent of original cohort of ADHD children) at the 4-year followup revealed those who were medicated to be at lower risk for substance use disorders (adjusted OR = 0.15 [0.04-0.6])^{155,159} However, when they reassessed 112 young men (80 percent) after 10 years (mean age at followup = 22 years), they found no associations between stimulant treatment (including age and duration of treatment) and alcohol, drug, or nicotine use disorders.¹⁵⁵ The report by Wilens et al.,¹⁵⁸ on the 5-year outcomes of the same cohort of girls as previously studied by Biederman et al.,¹⁶² assessed 114 (mean age at followup 16.2 years, 94.7 percent white, 67.1 percent treated with stimulants) of the original 140 English-speaking females aged 6-18 with ADHD. They found stimulant treatment to reduce the risk of development of any substance use disorder and cigarette smoking, even after controlling for conduct disorder. Huss et al.¹⁵⁶ performed a multi-site retrospective study on a non-randomized cohort of 215 ADHD children. One hundred and six received treatment with short-acting methylphenidate (mean duration of treatment 2 years 3 months +/- 1 year 1 month) while 109 did not. The medicated group was significantly delayed in their age of onset of regular smoking, by a time period of approximately 2 years. Monuteaux et al.¹⁵¹ followed up 99 subjects (70 percent male, 80 percent white, mean age 13 years) with ADHD involved in an initial year-long placebo-controlled RCT of bupropion treatment (mean dose 3.2 +/- 1.0 mg/kg at week 52) for up to 6.5 years (mean period 12 months). Twenty-nine study subjects received concurrent stimulant treatment (mean maximum dose 1.0 +/- 0.4 mg/kg). They found Bupropion not to be effective in the prevention of smoking, but stimulant treatment was associated with statistically significant lower risk of smoking initiation (HR = 0.2, p = 0.03) as well as continued smoking (HR=0.3, p = 0.02).

Other Functional Outcomes

In their 30-year prospective longitudinal study, Satterfield et al.,¹⁵⁴ followed 179 Caucasian patients diagnosed as 'hyperactive' at age 6-12 whom they reported would have met DSM-IV TR criteria for ADHD (78 percent had parent-reported conduct problems) and studied their official arrest records later in adulthood. There was no statically significant difference in the criminality rates studied between those who had received drug treatment only (N = 103) or those who had received combined treatment (the behavioral component included parent training, individual or group therapy for the child, family therapy and educational therapy). Even the 'most-treated' subgroup who received 2-3 years of combined treatment did not differ in the offending rate from those who received medication management only.

Treatment-adherent vs. Treatment-non-adherent Groups

Charach et al.,⁹⁸ followed up 79 out of 91 participants (mean age 8.40 ± 1.62 years, 81 percent males with no co-morbid anxiety or mood disorder) of a 12-month randomized controlled trial comparing methylphenidate and parent groups. Those who were adherent to medication showed better teacher-reported outcomes at years two and five, however by year five, only 16 treatment-adherent and 14 non-treatment adherent patients remained. Medication did not lose its efficacy after five years, but those who were adherent experienced fewer adverse symptoms. The study sample size was small and adherents tended to have more severe baseline ADHD symptoms.

Summary

The outcomes and time frames varied across studies. Except for Biederman¹⁵⁵ and the Wilens¹⁵⁸ group which studied an exclusively female cohort, all others studied an exclusively or predominantly male sample. Stimulant medication might protect against psychiatric disorders (ODD, CD, depression, anxiety disorder) in the long term (at 10 years). Better quality papers suggest that stimulant medication reduces substance use disorders in late adolescence or adulthood^{152,157,158} while one paper reported no benefit.¹⁵⁵ Two studies suggested stimulant medication may protect against nicotine use^{151,158} Treatment with stimulant medication, especially at an earlier age, may delay onset of smoking and reduce substance use disorder.^{153,156,157}

There appears to be little effect of childhood intervention on criminality over an extremely long period of 30 years.¹⁵⁴

Table 12. KQ2. Summary of controlled studies reporting very long-term (>3 years) outcomes of ADHD treatment

Study	Study design Quality rating	Study participants N mean age (SD) % males	Interventions compared					Intervention Duration	followup (y)	Outcome Measures	Results†
			Med	Behav	Comb	CC	No med				
Biederman J 2008 ¹⁵⁵	Cohort prospective Moderate	N = 140 Age: 6 to >18y Male: 100%	√				√	1y	10y	Adverse event	Deterioration
Biederman J 2009 ¹⁴⁷	Case-control Moderate	N = 140 Age: 6 to 17y Male: 100%	√				√	Mean 6y (4.7)	10y	Psychiatric disorders	Med <No med
Biederman J 1999 ¹⁵⁹	Prospective cohort analytic (2 groups) Weak	N = 75 Age: 17.2 ± 2.1y Male: 100%	√				√	4.4 ± 2.7	4	Substance use	Medicated <un-medicated
Charach A 2004 ⁹⁸	Uncontrolled extension of clinical trial Moderate	N = 79 Age: 6 to 18y Male: 81%	√	√				1yr	4y	Adverse event	Stim improve ADHD symptoms for up to 5 years, but adverse events persist.
Daviss W 2008 ¹⁶¹	Retrospective Weak	N = 75 Age: 6 to 18y Male: 57.4%	√					N/a per design	>5y	Depression	Pharmacotherapy may reduce risk of later depression

†Only statistically significant results are reported.

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; Behav = Behavioral treatment; Comb = Stimulant + Behavioral treatments; CC = Community treatment; CD = Conduct Disorder; ED = Emergency Department; f/u = followup; Med = Stimulant medication treatment; MMT = multimodal treatment; No med = No Stimulant medication treatment; RCT = randomized control trial; SD = standard deviation; Stim = stimulants; Tx = treatment; w/o = without

Table 12. (Cont'd) KQ2. Summary of controlled studies reporting very long-term (>3 years) outcomes of ADHD treatment

Study	Study design Quality rating	Study participants (N; mean age; % males)	Interventions compared					Intervention Duration	followup (y)	Outcome Measures	Results†
			Med	Behav	Comb	CC	No med				
Goksoyr P 2008 ¹⁶⁰	Retrospective Weak	N = 104 Age: 6 to 18y Male: 69.6%	√				√	N/a per design	>5y	Substance abuse; criminality	Tx contributes to increased social and psychological functioning
Huss M 2008 ¹⁵⁶	Cohort retrospective Moderate	N = 215 Age: 6 to 18y Male: 90%	√				√	N/a per design	12y	Nicotine use	No effect of medication but can onset of regular smoking
Lambert N 2005 ¹⁵³	Prospective longitudinal Moderate	N = 492 Age: <6 to >18y Male: 78%	√				√	followup 28y	To age 26y	Substance abuse	Deterioration
Leibson C 2006 ¹⁰⁹	Prospective cohort analytic Weak	N = 313 Age: 7.7±1.9y Male: 75%	√				√	14 days to 11.8 years	7-13	ED visits, medical cost	No difference, but ED visits reduced with increased medication duration
Katusic S 2005 ¹⁵²	Cohort Moderate	N = 379 Age: 18.2 y Male: 75%	√				√	Any Tx during childhood	17.2y	Substance abuse	Substance Abuse: Med <no med
Mannuzza S 2008 ¹⁵⁷	Cohort prospective Moderate	N = 176 Age: <6 to >18y Male; 100%	√				√	1yr	12y	Substance abuse Risky behavior	Early initiation of Rx not increase risk and may benefit Early treatment (6-7) <late treatment

Table 12. (Cont'd) KQ2. Summary of controlled studies reporting very long-term (>3 years) outcomes of ADHD treatment

Study	Study design Quality rating	Study participants (N; mean age; % males)	Interventions compared					Intervention Duration	followu p (y)	Outcome Measures	Results†
			Med	Behav	Comb	CC	No med				
Monuteaux M 2007 ¹⁵¹	Controlled followup to RCT Strong	N = 99 Age: <6 to 18y Male: 70%	√				√	1y	to age 18y	Adverse event & Substance use	No change Medicated <non- medicated
Satterfield J 2007 ¹⁵⁴	Cohort retrospective Moderate	N = 279 Age: 6 to >18y Male: 100%	√		√			3y	30y	Criminality	no change adhd w/o CD; 3y ofmmT not protective of ADHD+CD
Wilens T 2008 ¹⁵⁸	Cohort prospective Moderate	N = 114 Age: 10 to 24y Male: 0%	√				√	1yr	5y	Smoking and substance use disorders	Med reduces risk & delays onset of smoking

Key Question 3. How do A) Underlying Prevalence of Attention Deficit Hyperactivity Disorder, and B) Rates of Diagnosis (Clinical Identification) and Treatment for Attention Deficit Hyperactivity Disorder Vary by Geography, Time Period, Provider Type, and Sociodemographic Characteristics?

Underlying Prevalence

As will be evident from Tables 13 & 14, within the ranges of prevalence reported worldwide, from different regions, and even from different studies in the same region, there are nearly as many estimates as published studies.¹⁴

In this preamble to Key Question 3, we draw upon some relevant literature from a range of academic specialties to briefly describe factors which may influence prevalence estimates by shaping detection in the larger population.

Definition of ADHD

One of the key challenges, of many, which obscures definition of ADHD cases and therefore contributes to the difficulty of defining its prevalence, is the difficulty identifying children and adults in who display the representative behaviors in the middle range of possibility. The nature of the condition is defined in its relationship to context – with other people, families, classrooms, and play yards. Patients at either end of spectrum, those having the true condition and those clearly do not, are quite readily identified; however, there is a large population in the centre for whom the picture is less clear. Rather, the condition is a matter of degree with no startlingly clear boundaries and therefore a continuous variable rather than a categorical one; however, the use of diagnostic criteria to help in its identification also imposes a categorical paradigm, when in truth the picture is much more nuanced.¹⁶³

Criteria for International Comparison

The history of the identification and inclusion of ADHD and related disorders in disease classifications is also instructive in this regard. Since introduction of Hyperkinesia Syndrome of Childhood in DSM-II (1968) and ICD-9 (1977) and ADHD to the DSM-III (1980), sub-categories have burgeoned; which highlights two additional issues which affect prevalence estimates as well as diagnosis of individuals, the evolution of criteria and how these influence who is diagnosed with the condition over time, and how these criteria are interpreted and operationalised in real life situations rather than within the rigorous setting of research.¹⁶⁴ Different prevalence rates have even been derived for the same population when the results from questionnaires based on the diagnostic criteria of DSM-III-R and DSM-IV are analysed.¹⁶⁵

ADHD only recently has been recognised as persisting among the adult population,^{166,167} although it is not yet differentiated from classification with childhood disorder. The work on estimating prevalence of ADHD in adult populations is further obscured since, as a result of lack of diagnosis in childhood, retrospective self report measures are often accepted as a best available proxy for diagnosis of ADHD.^{168,169}

Lower rates of prevalence are generally cited in Europe and there may be more than one explanation or factor contributing to this discrepancy. The DSM criteria, the use of which is favoured in the U.S., are generally cited as being more inclusive so that higher rates are consistently cited in regions and studies which diagnose or reimburse utilising these; in Europe, however, the ICD codes are used preferentially and these are generally agreed to require more stringent interpretation of criteria resulting in much lower reported rates of ADHD.^{5,6,170} Other classification options have also been put forward for consideration, such as the ICF¹⁷¹ which introduces considerations of function and impairment into the picture of ADHD, composite international diagnostic interview (CIDI),¹⁴ another instrument from the World Health Organisation which was used as part of their global mental health survey, the Development and Well-being Assessment (DAWBA) used by the UK for a national statistics study of child psychiatric morbidity¹⁷² and the ADHD Rating Scale,¹⁷³ among many others.

The rigorous application of DSM criteria under research conditions may also result in rates lower than normally cited for a specific region^{10,174} and more apparently in line with those coded by ICD, which seems to indicate factors at work other than those defined by DSM criteria when generalised to the day to day practicalities of diagnosis in the community.

Instruments

A vast array of standardised, and not so standardised, tests have been used to assess ADHD children in research and in clinic, even though these tests may be applied to situations for which they were not designed and the resultant data interpreted in a manner not consistent with their psychometric properties. Even when assessment instruments are validated and applied in a standardised manner, the sheer variety of tests makes comparisons difficult between populations. As well, the manner in which results derived from application of these instruments are collected, interpreted and applied may be the source of further imprecision, as Boyle et al¹⁷⁵ point out in their study of the influence of setting cut-off points and thresholds upon diagnosis and prevalence. They find estimation population prevalence fraught with further difficulty since the logistics of finding trained personnel to make rigorous identifications is impracticable on a global scale but they do not see evidence that checklists and questionnaires completed by nonprofessional observers are an appropriate enough substitute for assessment by mental health professionals. Further blurring of the picture may also occur when subsequent iterations of a standardised test with adjusted cut-off points are issued, since this may make comparison difficult unless researchers are aware of the change, and may result in statistically significant change in the identification of positives, even if they are not clinically significant.¹⁷⁶ To date, there has been limited monitoring reported in the literature of fidelity of application even with the most widely used instruments.

Cultural and Ethnic Observations

Cultural expectations and child-rearing practices may also influence understanding and interpretation of prevalence rates. Harkness observes that expectations regarding normal development in infants vary from country to country, as well as beliefs about sleep hygiene, optimal socialization for infants, and different classroom cultures and expectations as to desirability of whether to teach and promote attention and focus, as in the Netherlands - or to 'stimulate', which is valued in the U.S.^{163,177} Ethnicity may influence interpretation of behaviors, as well; Gidwani et al¹⁷⁸ find differences in perception and interpretation of hyperactivity in U.S. subpopulations, Stevens¹⁷⁹ in regional rates of identification and service provision,¹⁸⁰ while Mattox and Harder¹⁸¹ report similar findings in their review of ADHD in diverse populations, from the perspective of social work.

Point of View

Characteristics of service provider type as well as system of remuneration have been linked to likelihood of diagnosis and treatment.^{2,182,183} In a 1999 survey of Canadian physicians drawn from family physicians, developmental and general paediatricians, and child psychiatrists, the top four explanations selected for increased methylphenidate use were "increasing public awareness of ADHD and its treatments", "pressure from parents and teachers to use medications to treat ADHD", "acceptance of medication as a treatment for ADHD", and "few resources for other interventions".¹⁸⁴

There may be a temporal increase associated between introduction of ADHD into the disorder classifications and studies by Eisenberg⁴ and others early pharmaceutical work which accepted parental and teacher assessments in lieu of clinical diagnosis of a medical professional.

Teachers may exert significant influence in who gets diagnosed since they may be the first to introduce the idea of ADHD to a family as a potential "diagnosis" for their child.¹⁸⁵⁻¹⁸⁹ Until recently, parents in the U.S. could be coerced into putting a child onto medication as a precondition of school attendance, however, introduction of The Child Medication Safety Act of 2005 made this illegal.¹³ Nevertheless, the more subtle influence of halo¹⁹⁰ and rater¹⁹¹ effects may still be found to influence diagnosis, treatment, and thus expressed prevalence rates. Similarly, the concept of 'a good student' is culture-bound, which makes attribution of behaviors and their interpretation as beyond an accepted norm of a particular classroom a very real possibility.¹⁹²

The discrepancy between the reports of parent and teacher informants may also introduce a confounding effect, as noted by Costello et al¹⁹³ in the U. S., while Rowland et al¹⁹⁴ further demonstrate that weight given the observation of a particular informant influence classification into subtype. Discrepancies between parent and teacher assessments have also been identified in Japan.¹⁹⁵

Dependence on self report may be optimal for a certain group of children however, dependence on retrospective report from adults for events or their own behavior as children is as

methodologically fraught as are issues of children in their late teenage years continuing stimulant medications for diagnosed ADHD, at which age some studies find that ADHD teenagers report lower than expected rates of treatment may be self diagnosing resolution of their condition, rightly or wrongly, and responding to a myriad of influences including social pressures to be like everyone else, as well as potential barriers of funding, location and access to service.^{196,197} At the same time, among a slightly older group, several studies have found tremendous societal pressures on university and college campuses to use stimulant medications as “study aids”¹⁹⁸ and that motivated students could quite convincingly feign ADHD symptoms,^{199,200} presumably well enough to acquire prescriptions from harried physicians - which highlights a significant issue in accepting the fact of stimulant prescription as proxy for diagnosis of ADHD when trying to estimate population prevalence.^{10,174} Analysis of prescription in trends in administrative databases, however, can provide insights into service access and provision gaps.²⁶

Parental understanding of effective parenting strategies may influence interpretation of normal child behavior,²⁰¹ much of which will resolve with maturity;^{202,203} and physicians do report prescription of stimulant medications based on pressure from parents or teachers.¹⁸⁴

At the level of the child, many influences can affect presentation of behaviors which mimic ADHD but which are not, since human beings, and children, in particular, have a limited repertoire of response to stress. Researchers have observed family stressors in the forms of poverty,²⁰⁴ trauma,²⁰⁵ insurance status,²⁰⁶⁻²⁰⁹ disordered sleep,²¹⁰ and food insecurity²¹¹ all of which contribute to apparent rates of behavior problems in children of the affected households. In contrast, one study showed that transfer payments appeared to improve outcomes for children in poor households²¹² presumably by reducing some of the familial stresses.

Given the many pitfalls to accurate detection, diagnosis and treatment, when endeavouring to develop prevalence estimates there may still be no adequate substitute for closely investigated histories and tightly defined diagnostic criteria.

Table 13. Timeline of identification of ADHD and development of treatment –derived from Eisenberg⁴ and Mayes²

Year	Nosology/Diagnosis	Country	Environment
1876		U.K.	<i>The Educational Act</i> passed, mandating elementary education for all children, and thus, a structured environment against which childhood ADHD is often identified
1902	Sir G.F. Still ²¹³ describes distinctive constellation of behaviours in children who cannot focus and fail school despite intelligence. He describes their behaviour under various conditions, occurring more often among boys than girls, frequently apparent by early school years, generally showing little relationship to child training and home environment, and commonly sharing a poor prognosis	U.K.	
1922	Tredgold observes agitated behaviours among Spanish Influenza Epidemic(1919) survivors and hypothesises relationship to <i>encephalitic lethargica</i> , referring to the condition as “minimal brain damage”	U.K.	
1932		U.S.	Bradley identifies <i>d</i> , l-amphetamine and observes its “paradoxical” calming and focusing effect on children who were psychiatric inpatients
1952	DSM-1 released; no mention of hyperkinetic syndrome	U.S.	
1950s	“minimal brain damage” “hyperkinetic syndrome”	U.S. U.K.	Research studies on children using antipsychotic drugs such as chlorpromazine (i.e.: Largactil, Thorazine)
1955		Switzerland	Geigy develops methylphenidate (“Ritalin”)

Abbreviations: ADD = Attention-Deficit Disorder; ADHD = Attention-Deficit Hyperactivity Disorder; DSM = Diagnostic and Statistical manual; NIMH = National Institutes of Mental Health; ICD = International Classification of Disease; F =subsection of ICD codes; MPH = Methylphenidate; NSCH = National Survey of Child Health

Table 13. (cont'd) Timeline of identification of ADHD and development of treatment –derived from Eisenberg⁴ and Mayes²

Year	Nosology/Diagnosis	Country	Environment
1957		U.S. Switzerland	Dextroamphetamine included in pharmacotherapy as only effective treatment ADHD, although no evidence about efficacy available since no clinical trials performed Geigy releases “Ritalin” to market; and states their experience with is too limited to make a valid statement as to its usefulness
1958		U.S.	NIMH Pharmacological branch sponsor first ever conference on use of psychoactive drugs in treatment of children
1961		U.S.	“Ritalin” approved for use in children
Mid60s	Questions about link between brain ‘damage’ and hyperactivity; new phrase coined “Minimal Brain Dysfunction” hedging between old terminology and new discoveries		
1965	ICD-8 309 –Behaviour disorders in childhood	W.H.O.	
1967	Inclusion of hyperkinesis as syndrome in World Health Organisational Seminar on Diagnosis and Classification in Child Psychiatry	W.H.O.	
1968	DSM-II released, includes “hyperkinetic syndrome of childhood”	U.S.	NIMH requests longer term studies (i.e. >8weeks) on effects of stimulant drugs on children
End60s	Estimated 150,000 to 200,000 children treated with stimulants (0.002% of child population at that time)	U.S.	
1970	Rutter’s Isle of Wight study; first well designed epidemiological ascertainment of prevalence of ADHD which found 2 cases among 2199 children between ages 10 and 11 (i.e.; 0.9%)	U.K.	

Table 13. (cont'd) Timeline of identification of ADHD and development of treatment –derived from Eisenberg⁴ and Mayes²

Year	Nosology/Diagnosis	Country	Environment
1971		U.S.	<p>Congressional hearing which changed classification of stimulant drugs to controlled substances and making data collection mandatory</p> <p>Wenders book released which notes familial nature of ADHD, pointing way to genetic studies</p> <p>Eisenberg and Connors receive NIMH grants to study methylphenidate</p>
1975		U.S.	<p>Popular Feingold diet published</p> <p>characterisation in the media of medication for hyperactive children as ‘chemical straitjacket’, as reflection of the social period</p>
1977	ICD-9 314 Hyperkinetic syndrome of childhood	W.H.O.	
unclear	<p>ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification)</p> <p>314.00 Attention deficit disorder of childhood w/o hyperactivity</p> <p>314.01 Attention deficit disorder of childhood with hyperactivity</p> <p>314.1 Hyperkinesis of childhood with developmental delay</p> <p>314.2 Hyperkinetic conduct disorder of childhood</p> <p>314.8 Other specified manifestations of hyperkinetic syndrome of childhood</p> <p>314.9 Unspecified hyperkinetic syndrome of childhood</p>	U.S.	

Table 13. (cont'd) Timeline of identification of ADHD and development of treatment –derived from Eisenberg⁴ and Mayes²

Year	Nosology/Diagnosis	Country	Environment
1978		U.S.	Therapeutic response to drugs taken as confirmation of Dx Rapoport observes that both normal children and ADHD children respond to stimulant medications with greater focus; age may be the operative factor in its effectiveness, not 'disorder'
1980	DSM-III released; includes “Attention Deficit/Hyperactivity (ADHD) Disorder “	U.S.	
1987	MPH use(“defined daily doses”) = ~60 million	U.S.	
1991	MPH prescriptions = 4 million Amphetamine prescriptions = 1.3million	U.S.	
1992	ICD-10 F90-F98 Behavioural and emotional disorders with onset usually occurring in childhood and adolescence F90 Hyperkinetic disorders F90.0 Disturbance of activity and attention F90.1 Hyperkinetic conduct disorder F90.8 Other hyperkinetic disorders F90.9 Hyperkinetic disorder, unspecified F91 Conduct disorders F91.0 Conduct disorder confined to the family context F91.1 Unsocialised conduct disorder F91.2 Socialised conduct disorder F91.3 Oppositional defiant disorder F91.8 Other conduct disorders	W.H.O	
1994	DSM-IV released with amplified ADHD subtypes	U.S.	
1999	MPH use (“defined daily doses”) = ~360million MPH prescriptions 11 million/amphetamine 6 million	U.S.	

Table 13. (cont'd) Timeline of identification of ADHD and development of treatment –derived from Eisenberg⁴ and Mayes²

Year	Nosology/Diagnosis	Country	Environment
2000	ICD-10-CA F900 Attention-deficit hyperactivity disorder, pred inattentive F901 Attention-deficit hyperactivity disorder, pred hyperactive F902 Attention-deficit hyperactivity disorder, combination type F908 Attention-deficit hyperactivity disorder, other type F909 Attention-deficit hyperactivity disorder, unspecified type F910 Conduct disorder confined to family context F911 Conduct disorder, childhood-onset type F912 Conduct disorder, adolescent-onset type F913 Oppositional defiant disorder F918 Other conduct disorders F919 Conduct disorder, unspecified	Canada	
2000/3	Great Smoky Mountain studies ^{9,10} report unequivocal prevalence of 0.9% among children between 9 and 16 (2.2% age 9 declining to 0.3% at age 16) but rate of stimulant treatment more than twice rate of unequivocal diagnosis, and majority of children treated did not meet ADHD criteria. Serious mismatch between need and provision. Others ^{12,214} do not find the potential for mismatch so clear cut.	U.S.	
2003	NSCH ¹⁹ survey of children between 4-17: Diagnosed (see below): 4.4 million Medication for ADHD: 2.5 million (56%) Estimated prevalence based on parent report of response to the NSCH survey question “Has a doctor or health professional ever told you that [child name] hasADD or ADHD?” Prevalence reports average 7.8% with variability from 5.0% in Colorado to 11.1% in Alabama	U.S.	Lexchin ¹⁰⁵ among others identifies company sponsored studies more than four times likely to have outcomes that favour sponsor than neutrally sponsored research
2005		U.S.	Child Medication Safety Act Bill (H.R.1790) to protect children and parents from being coerced into administering a controlled substance or psychotropic drug in order to attend school, and for other purposes, as amended.

Table 14. KQ3. A sample of summary prevalence information by region and subgroup

Region / Country	Prevalence	Sex (percentage boys / girls)	Population and Age (%age of diagnosed, if available)	SES (%age of lifetime parent reported Dx)	Rural / Urban	Ethnicity /Race	Diagnostic / screening instrument
Globally							
Fayyad et al. ²¹⁵	3.4%		Adults aged 18-44	Greater prevalence among adults educated to less than university level			WMH ESEMeD
Simon et al. ¹⁷	2.5%		Adults (proportion of population with ADHD appears to decrease with age)				DSM-IV
Polanczyk et al. ¹⁴	5.29%						Variability results primarily from methodological differences
Europe							
Belgium ²¹⁵	4.1%						WMH ESEMeD
France ²¹⁵	7.3%		Adults aged 18-44				WMH ESEMeD
Germany ^{6,216}	4.8%	7.8 % boys 1.8% girls	Preschool 1.5 Primary 5.3 Secondary 7.1 Possible decline in prevalence with age	Preschool 6.4 Primary 5.0 Secondary 3.2 Boys of low SES greatest risk of Dx			FBB-HKS/ADHS

Abbreviations: CBCL = Child Behaviour Check List; CSI – Child Symptom Inventory; DAH = Da escala de; transtorno de déficit de atenção e hiperatividade; DAWBA = P or T – Development and Well-Being Assessment Parent or Teacher Report; DISC = Diagnostic Interview Schedule for Children; DISC = *Diagnostic Inventory* for Screening Children; Dx = Diagnosis; ESEMeD = European Study of the Epidemiology of Mental Disorders; FBB-HKS/ADHS = Fremdbeurteilungsbogen für Hyperkinetische Störungen/ Aufmerksamkeitsdefizit- /Hyperaktivitätsstörungen; HMOs = Health Maintenance Organizations; K-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia; LEBANON = Lebanese Evaluation of the Burden of Ailments and Needs of the Nation; MINI-Plus = Mini-International Neuropsychiatric Interview-Plus; NCSR = National Comorbidity Survey Replication; NHANES = National Health and Nutrition Examination Survey; NSMH = National Survey of Mental Health; O/Pt = Out –patient; OR = Odds Ratio; P-CHIPS = Child Interview for Psychiatric Syndrome – Parent version; SDI = Survey Diagnostic Instrument; SDQ = *Strengths and Difficulties Questionnaire*; SES = Socio-economic Status; SNAP-IV = Swanson, Nolan and Pelham (SNAP) Questionnaire – 4th revision; UAE =United Arab Emirates; VADPRS = Vanderbilt ADHD Diagnostic Parent Rating Scale; VARTRS = Vanderbilt ADHD Diagnostic Teacher Rating Scale; WMH = World Mental Health

Table 14. (cont'd) KQ3. A sample of summary prevalence information by region and subgroup

Region / Country	Prevalence	Sex (percentage boys / girls)	Population and Age (%age of diagnosed, if available)	SES (%age of lifetime parent reported Dx)	Rural / Urban	Ethnicity /Race	Diagnostic / screening instrument
Germany ²¹⁵	3.1%		Adults aged 18-44				WMH ESEMeD
Italy ²¹⁵	2.8%		Adults aged 18-44				WMH ESEMeD
Netherlands ²¹⁵	5.0%						WMH ESEMeD
Spain ²¹⁵	1.2%		Adults aged 18-44				WMH ESEMeD
Russia ²¹⁷	6.25%	8.9% boys 3.6% girls	Ages 12 - 17				SNAP-IV; SDQ; teacher report
Sweden ²¹⁸	4.0%	Not specified	Children ages 6 to 7		Children born in southern rural Sweden in 1986-1987		Parent and teacher interview using rating scale and parent interview
North American							
Canada ²¹⁹	5.8%	50% boys	Children between 4 and 16 years				SDI, with parents, teachers and subject informants
Quebec, Canada ²²⁰	8.9% teachers 5.0% parents 3.3% subjects	unspecified	Children between 6 and 14 years				Interview
U.S. ²¹⁵	5.2%		Adults aged 18-44				WMH NCSR
U.S. ²²¹	4.4%	Men>Women OR=1.6 (p <0.05)	Adults between 18-44			Low prevalence amongst Hispanics and non-Hispanic blacks	Adult ADHD Clinical Diagnosis Scale for screening Clinical reappraisal with DSM-IV interview

Table 14. (cont'd) KQ3. A sample of summary prevalence information by region and subgroup

Region / Country	Prevalence	Sex (percentage boys / girls)	Population and Age (%age of diagnosed, if available)	SES (%age of lifetime parent reported Dx)	Rural / Urban	Ethnicity /Race	Diagnostic / screening instrument
U.S. ²²²	8.7%	51% boys 49% girls Significantly more boys than girls meet DSM-IV criteria (p <0.001)	Children aged 8 to 14	Wealthiest more likely than poor children to receive medication Poor children more likely to meet criteria for ADHD yet less likely to receive consistent pharmacotherapy			DSM-IV NHANES used DISC caregiver module for diagnosis 48% of children received prior diagnosis
Houston TX, U.S. ²²³	2.1%	Lower in girls	11 – 17 years	Drawn from HMOs			DISC-IV (parent report)
Utah Prisons, U.S. ²²⁴	25.5%	men	16-69 years	Incarcerated			DSM-III-R 10% diagnosable as both ADHD and major depression
NHIS Bloom, U.S. ²²⁵ Region Northeast Midwest South West	7.0% 6.4% 7.4% 9.0% 4.9%	10.0% boys 4.0% girls	All children 3-17 years	Health insurance Private 6.3% Medicaid/public 9.5% Other 12.4% Uninsured 5.9% Current Health Status Excellent/ Very Good 6.4% Good 10.4% Fair or Poor 16.6%	MSA of Residence Large 6.8% Small 7.8% Non 7.4% Poverty status* Poor=8.7% Nearpoor=9.2% Not Poor =6.5%		Estimates based on question, “Has a doctor or health professional ever told you that (child’s name) had Attention Deficit Hyperactivity Disorder (ADHD) or Attention Deficit Disorder (ADD)?”

Table 14. (cont'd) KQ3. A sample of summary prevalence information by region and subgroup

Region / Country	Prevalence	Sex (percentage boys / girls)	Population and Age (%age of diagnosed, if available)	SES (%age of lifetime parent reported Dx)	Rural / Urban	Ethnicity /Race	Diagnostic / screening instrument
Puerto Rico ²²⁶	7.5%	10.3% boys 4.7% girls	Highest prevalence in 6-8 age group				DISC-IV
Mexico ^{215,227}	1.9% ²¹⁵ 5.37% ²²⁷		18-44 years ²¹⁵ Adults ²²⁷				WMH; M-NCS ²¹⁵ M.I.N.I.-Plus ²²⁷
South America							
Columbia ²¹⁵	1.9%		Adults				NSMH
Venezuela ^{228,228}	10.03%	7.62%boys 2.41%girls	Ages 4 - 12	More ADHD Dx in lower than in medium and high SES			DISC-IV-P (parent report)
Salvador, Brazil ²²⁹	6.7%	No differences noted by sex	Ages 6 - 17				DAH
Buenos Aires, Argentina ²³⁰	9.0%	No differences noted by sex	Ages 6 - 12	Paed O/Pt in private hospitals			ADHD Rating Scale –IV
Middle East							
Lebanon ²¹⁵	1.8%		Adults aged 18-44				WMH LEBANON
Mashhad, Iran ²³¹	12.3%		Kindergarten age				
Shiraz, Iran ²³²	10.1%	13.6% boys 6.5% girls	Ages 7 - 12				CSI-4
Yemen ²³³	1.3%	2.1% boys 0.5% girls					DAWBA-P; DAWBA-T

Table 14. (cont'd) KQ3. A sample of summary prevalence information by region and subgroup

Region / Country	Prevalence	Sex (percentage boys / girls)	Population and Age (%age of diagnosed, if available)	SES (%age of lifetime parent reported Dx)	Rural / Urban	Ethnicity /Race	Diagnostic / screening instrument
Algeria, Bahrain, Egypt, Gaza, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Sudan, Syria, Tunisia, United Arab Emirates (UAE), and Yemen. ²³⁴	0.5 -0.9 % community vs 5.1-14.9 % school						structured interview in community vs rating scales in school system various instruments
Africa							
Nigeria ²³⁵	8.7%		Ages 6 - 12				VADPRS; VARTRS
Asia							
Mumbai, India ²³⁶	12.2%	19.03% boys 5.8% girls	Ages 4 - 6				Connors +SADS+ DSM-IV based interview
Karachi Pakistan ²³⁷	17.0%		Primarily among children aged 5-10 years				P-CHIPS
Taiwan, China ²³⁸	7.5%		7.5 % 7th grade 6.1 % 8th grade 3.3 % 9th grade	Greater likelihood of diagnosis in boys than girls			Chinese K-SADS-E + CBCL
Hong Kong, China ²³⁹	3.9%		Mean age = 13.8 years				DSM - IV

Table 14. (cont'd) KQ3. A sample of summary prevalence information by region and subgroup

Region / Country	Prevalence	Sex (percentage boys / girls)	Population and Age (%age of diagnosed, if available)	SES (%age of lifetime parent reported Dx)	Rural / Urban	Ethnicity /Race	Diagnostic / screening instrument
Australia ²⁴⁰	Symptoms= 7.5% Functional impairment = 6.8%		Children age 6 to 17	Not specified			Interview and rating scale Informant=parents
Australia ²⁴¹	2.4%parent & teacher 9.9% parent 8.8% teacher		Children age 5 to 11	47.4% boys			Limited agreement between parent and teacher information
New Zealand ²⁴²	3.9% (parent report) 2.8% (subject report)	Not specified	Ages 13 to 15		Cohort of children born in 1977 in Christchurch urban region		Assessed by interview of parent and of subject using DSM-III-R criteria

According to a recent comprehensive systematic review and meta-regression analysis that encompassed studies from all areas of the world, the worldwide pooled prevalence estimate of ADHD among those 18 years of age or younger is 5.29 percent (95 percent CI: 5.01-5.56).¹⁴ Though a significant amount of variability was noted in the comparison of prevalence estimates across world regions, results seemed to indicate that once methodological differences of studies were controlled for, geographic location explained very little of the variability.¹⁴ In fact, after this step, significant differences were only detected between studies carried out in North America and Africa and the Middle East.¹⁴ The requirement of impairment for the diagnosis, diagnostic criteria, and source of information, then, were the main sources of variability in the pooled prevalence estimate of ADHD.¹⁴ For that reason, a standardized methodological approach has been proposed in order to improve the state of epidemiological research in this domain.^{14,243}

Consideration of Geography, Time Period, Provider Type and/or Socio-demographic Factors in Recent Studies of Prevalence

Of the abovementioned factors, recent studies in this area address mostly issues of geography and socio-demographic factors such as age, gender, and in some cases, SES and ethnicity/race in the ascertainment of ADHD prevalence. The bulk of the literature consists of studies of children with ADHD conducted either in North America or Western Europe; with clear gaps in knowledge on the subject of the prevalence of ADHD among adolescents and adults, and in ethnically distinct regions where it has been scarcely researched. As pointed out below, however, some progress has been made on the geographical front.

Children and Youth. Examining recent national surveys, the National Health Interview Survey, 2007 estimated that nearly 4.5 million children in the U.S. between the ages of 3-17 years (7 percent) had ADHD, with a larger proportion of boys (10 percent) than girls (4 percent).²²⁵ In Germany, the KiGGS study (The German Health Interview and Examination Survey for Children and Adolescents, a representative cross-sectional health study of N = 17461 individuals aged 3-17 years) reported an overall lifetime prevalence of ADHD diagnosis of 4.8 percent (95 percent CI: 4.4-5.3), with a significant gender difference: 7.8 percent for boys, 1.8 percent for girls.²¹⁶ Significant effects of age and SES were also detected – the prevalence of a parent-reported lifetime diagnosis was 1.5 percent for those of pre-school age, 5.3 percent (primary school) and 7.1 percent (secondary school) and was 6.4 percent, 5.0 percent and 3.2 percent for low, medium and high SES, respectively.²¹⁶ Logistic regression results highlighted boys of low SES as having the greatest risk of diagnosed with ADHD.²¹⁶ Another report from Germany (the BELLA mental health module of the KiGGS) generally supported these trends, with the exception of a different age effect: they found a decline in prevalence with increasing age (their sample was comprised of 7-17 year olds).⁶ The latter study used different methods to measure ADHD; namely, the German ADHD rating scale (FBB-HKS/ADHS), which is consistent with other DSM-IV scales and assesses functional impairment.⁶

The effects of gender and age (that is, a greater prevalence in boys and a negative association between age and prevalence of ADHD) emerge in studies, though not all studies. In a Puerto Rican community sample of children aged 4-17 years, the 12-month prevalence using the DISC-IV was 7.5 percent (95 percent CI: 6.1-9.3).²²⁶ The estimate for males was 10.3 percent (95

percent CI: 8.0-13.1) vs. 4.7 percent (95 percent CI: 3.1-7.2) for females, with the highest prevalence documented in the 6-8 years age group.²²⁶ In a randomly selected sample from school registers in Venezuela (N = 1535 children aged 4-12 years), the total prevalence estimate (DISC-IV-P) was 10.03 percent (95 percent CI: 7.9-13.03), with a greater prevalence in males (7.62 percent vs. 2.41 percent in females).²²⁸ In addition, a larger proportion of ADHD cases were classified as lower SES than medium or high SES.²²⁸ In contrast, in a sample of 300 children (aged 6-12 years) from outpatient paediatric clinics at private hospitals in Buenos Aires, Argentina, 9 percent (95 percent CI: 6.0-12.8) had positive scores on the DuPaul Scale (consistent with DSM-III-R ADHD) and no gender differences were found.²³⁰ Similarly, in a study of N = 774 school children aged 6-17 years conducted in Salvador, Brazil using a teacher ADHD scale (designed to evaluate ADHD behavioral symptoms in a school setting), 6.7 percent were judged highly likely to have the disorder and no trend with respect to gender was observed.²²⁹

From other settings for ADHD research; a study of preschoolers in Mumbai (N = 1250 aged 4-6 years) whose Conner's index questionnaire (completed by teachers and parents) scores were positive for ADHD (>15) (and who were then interviewed using the SADS and diagnosed by a psychiatrist using a direct interview based on DSM-IV criteria) reported that in total, 12.2 percent were diagnosed, with a significant difference between boys and girls (19.03 vs. 5.8 percent, respectively).²³⁶ Having adopted a similar methodological strategy, 12.3 percent (95 percent CI: 10.3-14.2) were given a diagnosis in a randomly selected sample of kindergarten-aged children (N = 1083) in Mashhad, Iran.²³¹ Another study conducted in nearby Shiraz, in a random sample of 2000 school-aged (7-12 years) children, employing a DSM-IV referenced rating scale of ADHD symptoms (the CSI-4) completed by parents, found that ~10.1 percent obtained screening cut-off scores for (probable) ADHD, with 13.6 percent in boys vs. 6.5 percent in girls.²³² A gender difference (prevalence ratio of 2:1 across the subtypes of ADHD except hyperactivity/impulsive type which had a ratio of 3.2:1) was also revealed in a study of primary school children aged 6-12 years in Nigeria (N = 1112), assessed by means of rating scales based on DSM-IV ADHD criteria - the Vanderbilt ADHD Teacher Rating Scale (VARTRS) and Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS), with an overall estimated prevalence of 8.7 percent.²³⁵

Other relevant, exploratory studies include the following. Among 7-10 year-olds in Yemen (N = 1210, sampled from school registers), the prevalence of various DSM-IV psychiatric disorders (determined in 2 phases, using the SDQ as a screener and both the parent and teacher information included in the Development and Well-Being Assessment (DAWBA) to generate diagnoses in screen positive children) was examined, including ADHD, reported to be among the least common disorders at 1.3 percent (95 percent CI: 0.1-2.5), with a significantly higher prevalence among boys (2.1 (0.1, 4.3) versus 0.5 (0.1, 1.1) for girls).²³³ A cross-sectional study of patterns of mental health morbidity in children attending the psychiatry clinic of a tertiary care hospital in Karachi, Pakistan (N = 200, up to age 14 years included) stated a prevalence estimate of 17 percent; occurring most frequently in those between the ages of 5-10 years.²³⁷ This estimate was ascertained using the P-CHIPS (Child Interview for Psychiatric Syndrome), a structured interview for parents based on DSM-IV criteria.²³⁷ From a high school-based panel study carried out in Taiwan between 1995-97 of N = 1070 students, aged 13-15 years, the weighted 3-month prevalence estimates of DSM-IV ADHD were: 7.5 percent (95 percent CI:

5.1-10.0), 6.1 percent (95 percent CI: 4.6-7.5) and 3.3 percent (95 percent CI: 2.2-4.4) among 7th-graders, 8th-graders and 9th-graders, respectively; with higher odds of the diagnoses in boys than in girls.²³⁸ Cases were identified using the Chinese K-SADS-E along with the teacher report form of the CBCL.²³⁸

Finally, a recent review of all epidemiological studies on ADHD carried out in Arab countries from 1966-2008 (in various samples) reported that the estimate of ADHD symptoms using rating scales in a school setting ranged from 5.1-14.9 percent, whereas estimates of an ADHD diagnosis using structured interviews in children and adolescents ranged from 0.5 percent in school to 0.9 percent in the community.²³⁴ It was noted, however, that the limited number of studies conducted in the designated countries and their employment of different methodologies rendered the task of comparing the results difficult.²³⁴

Some of the recent findings of studies conducted in adolescent samples seem to agree with the gender and age effect(s) proposed in studies of school-aged children. For instance, in a sample of 4175 Houston youths aged 11-17 years from households enrolled in large health maintenance organizations, the DISC-IV prevalence of ADHD (any type) was 2.1 percent (95 percent CI: 1.59-2.54), with lower odds of ADHD noted in females.²²³ However, a study of the prevalence of ADHD symptoms assessed by teacher reports (using the SNAP-IV, SDQ scales) in 536 adolescents (12-17 years) in the European North of Russia found that 8.9 percent of boys and 3.6 percent of girls had positive ratings on the 6 items in either of the ADHD sub-types²¹⁷ and the estimate of DSM-IV ADHD in 541 Hong Kong Chinese adolescents (mean age: 13.8 years, SD: 1.2) from 28 randomly selected high schools was 3.9 percent (95 percent CI: 2.3-5.5).²³⁹

Adults. Estimates of the prevalence of DSM-IV adult (18-44 years) ADHD in the World Health Organization's (WHO's) World Mental Health Survey Initiative (comprising of Belgium, Colombia, France, Germany, Italy, Lebanon, Mexico, The Netherlands, Spain and the USA, N = 11422) were: 3.4 percent (total sample), with a significantly higher estimate in France (7.3 percent) and lower in Colombia, Lebanon, Mexico and Spain: 1.9 percent, 1.8 percent, 1.9 percent, 1.2 percent, respectively.²¹⁵ In terms of socio-demographic correlates; adult ADHD was significantly more prevalent in men and among those with a level of education less than university, though limitations such as imputation and the use of self-report without confirmation were pointed out.²¹⁵ Recently, a meta-regression - perhaps the first of its kind to address these issues, cited a pooled prevalence of adult DSM-IV ADHD of 2.5 percent (95 percent CI: 2.1-3.1), while reporting that the proportion of individuals with ADHD seems to decrease with age.¹⁷ The question of appropriate diagnostic criteria for use with adults was, however, highlighted as a potentially problematic factor in producing epidemiological estimates in this age group.¹⁷ Furthermore, many of the same problems (i.e. methodological and diagnostic differences) that plague ADHD research in children and youths appear also to be relevant in adult studies.¹⁷

Brief Summary

- Most studies illustrate a gender difference in the prevalence of ADHD (boys > girls).

- Age and SES are other socio-demographic factors that have been studied - the age-group ≈5-10 years seem to experience the highest prevalence, along with, as suggested by some, those of lower SES.
- ADHD research detailing prevalence in adults is lacking.
- Key limitations: different sample types (e.g. school, community, clinical) are used, along with different informants/instruments to measure ADHD across geographic areas.

How do Rates of Diagnosis (Clinical Identification) and Treatment of ADHD Vary by Geography, Time Period, Provider Type and/or Socio-demographic Characteristics?

Much variation remains in the literature concerning the factors of interest on the receipt of a diagnosis and the use of psychotropic medication by individuals with ADHD, with some of the characteristics more commonly investigated than others. Though these factors have not been fully investigated, they appear to play a role in determining these outcomes and therefore warrant attention in future studies.²⁴⁴ At present, a review of relevant, timely findings is given below, organised by geographic region.

United States. According to a study of regional and national databases in the U.S., there was a 2.5-fold increase in the prevalence of MPH treatment for youths aged 5-18 years with ADHD during the period 1990-95.²⁸ The justification given seems to relate to an increased duration of medication use, as well as more girls and adolescents receiving treatment and improved public attitudes regarding pharmacotherapy.²⁸ Another study, also using a national data source (the NAMCS: National Ambulatory Medical Care Survey), confirmed the trend of an increase in the prevalence of both diagnosis of ADHD and prescription of stimulant medication for its treatment during the same time period and age group.²⁷ Analysis of a more recent wave of data (1995-2000) from the same source demonstrated that an ADHD diagnosis and/or stimulant prescription was less likely to be recorded during visits by Hispanic-American youths compared to visits by Caucasian youths (aged 3-18 years) however no differences were found between ethnic groups in terms of likelihood of being given a prescription once a diagnosis was given.²⁴⁵ An additional point was that prescriptions were given more frequently to children with ADHD in the south and west areas of the U.S. vs. the northeast.²⁴⁵

Another nationally representative survey (the Medical Expenditure Panel Survey, MEPS) was used to detect whether the use of stimulant medication by those less than 19 years of age in the U.S. continued to rise during the years 1997-2002.²⁴⁶ No significant change between the prevalence of stimulant use in 1997 [2.7 percent (95 percent CI: 2.3-3.1)] and 2002 [2.9 percent (95 percent CI: 2.5-3.3)] was found.²⁴⁶ Overall, use was greatest among 6-12 year olds [4.8 percent (95 percent CI: 3.9-5.6) in 2002] – an estimate that has remained stable since 1998 [4.8 percent, 95 percent CI: 3.7-5.9].²⁴⁶ In turn, during roughly the same time frame and using the same survey, it was found that Hispanic-American as well as African-American children between the ages of 3-18 years were less likely to receive a diagnosis of ADHD (via parent report) compared to Caucasian children.²⁴⁷ Furthermore, once given a diagnosis by a physician, African American children were found to be less likely to ever receive stimulant medication, compared to Caucasian children.²⁴⁷ Children in the 7-12 years age group were most likely to be

diagnosed with ADHD and children with ADHD between the ages of 7-18 years were more likely to receive at least one stimulant prescription relative to children in the 3-6 years age category.²⁴⁷ Finally, using the MEPS data covering the years 2000-02, Caucasian children between the ages of 5-17 years were found to be approximately twice as likely to use stimulants as either Hispanic or African-American children.²⁴⁸ Modeling results indicated that differences in individual/family characteristics (i.e., health insurance status, access to care) accounted for about 25 percent of the discrepancy between Caucasians and Hispanics in stimulant use, though the same characteristics cannot account for any differences between Caucasian and African-American children, with respect to stimulant use.²⁴⁸

A recent review has suggested that being male, belonging to a family with a high education level and having a non-Hispanic ethnic background are factors that are most consistently associated with receiving a diagnosis of ADHD.²⁴⁴ Additionally, the use of stimulants by Caucasian males seems disproportionately higher than the use by African-American and Hispanic children.²⁴⁴ Another recent article that examined the ADHD literature with reference to African-American children arrived at these conclusions: although African American youths have a tendency to be rated by parents and teachers as having more ADHD symptoms than Caucasian youth, they are diagnosed with the disorder by health professionals at only two-thirds the rate of their Caucasian counterparts.²⁴⁹ The authors suggest that that this less frequent receipt of ADHD diagnoses in the former group may be attributable to a lack of information on the part of parents, a lack of access to appropriate health care services or a lack of willingness to seek out services.²⁴⁹

Geographic variation in the prevalence of stimulant medication use, evaluated using a prescription claim database (restricted to activity in 1999), was observed even after controlling for age and gender – specifically, relative to children living in the Western region of the U.S., children living in the Midwest and South were significantly more likely to use stimulant treatment.²⁵⁰ Those living in areas with some proximity to urban areas were also found to be more likely to receive stimulant treatment.²⁵⁰ Other relevant predictors of use of stimulants for ADHD among 5-14 year olds were male gender, living in a higher income community and living in a community with large proportion of Caucasians.²⁵⁰ In support of these findings, the results of another study that looked at variation between areas in the U.S. in terms of their per-capita psychostimulant consumption showed that most variables that were significantly associated with greater per-capita use of ADHD medications served as proxies for county affluence (e.g. higher per-capita income, lower unemployment).²⁵¹ The latter study obtained county-level data for the year 2000 on psychostimulant use from the Drug Enforcement Administration's Automation of Reports and Consolidated Orders System (ARCOS) database, which tracks the flow of controlled substances.²⁵¹ A 2001 study of the annual prevalence of use of psychotherapeutic drugs by preschoolers (2-4 years old) with Medicaid insurance, assessed by means of large dataset of seven state Medicaid programs, revealed that 67.3 percent (N = 6319) of psychotherapeutic drug use by this group was accounted for by stimulants (broken down by type: 58.3 percent MPH, 60.7 percent amphetamines and 0.7 percent other).³³

In the case of adults, a study of pharmacy claims data for a large population of commercially insured Americans, measuring ADHD treatment prevalence and drug use from 2000-05 reported that in 2005, 0.8 percent of adults (aged 20 years and older) used ADHD medications; with no difference in use between the genders, though younger adults (ages 20-44 years) were more

likely to use ADHD medications than older adults.²⁵² During this period of time, treatment prevalence increased 11.8 percent per year for the population as a whole, with variations by age and gender – among adults, for instance, growth in the prevalence of treatment use was most prominent among women (increased 18.1 percent per year for women vs. 12.6 percent per year for men).²⁵² A 2005 publication reported a prevalence of 2.9 percent for Narrow ADHD and 16.4 percent for Broad ADHD in a random sample (using random digit dialing) of 966 adults (>18 years) in the community.²⁵³ As part of a larger telephone survey, respondents were asked about each DSM-IV symptom of ADHD, with a narrow diagnosis constructed to estimate the prevalence of adult ADHD among those who presented strong evidence of ADHD in both childhood and adulthood and a broader diagnosis serving to estimate the screening prevalence.²⁵³

Brief Summary, U.S.

- An increase in the use of pharmacological treatment(s) for ADHD occurred in the early 1990s. This increase seems to have plateaued in the late 1990s-early 2000s.
- Some differences by ethnicity/race in the likelihood of receiving a diagnosis and/or treatment for ADHD have been uncovered (Caucasian >Hispanic- and African-American children).
- Some regional variation between States in treatment use has also been recorded.

Canada. Canadian data from cycles of the National Longitudinal Survey of Children and Youth (NLSCY) showed that among children aged 2-11 years, the overall prevalence of MPH use was low (<2 percent from 1994-95 to 1998-99), noting an increase in use among girls and among those aged 6-11 years.³² Another study using data from cycles 1(1994-95) and 2 (1996-97) found that in the same age group, boys were 4.6 times more likely than girls (across all age categories) to use MPH, with the highest prevalence of use among 7 to 9-year olds.²⁵⁴ However, the overall prevalence of use of MPH was also deemed to be relatively low, ranging from 0.09 percent to 3.89 percent in 2-11 year olds from the first cycle.²⁵⁴

To consider variation by province, a study of patterns of use and prescribing of MPH in youth aged 19 years or less using linked administrative and health databases in B.C. for the period 1990-96 reported an increase from 1.9 per 1000 children in 1990 to 11.0 per 1000 in 1996 in the number of children who had received at least one prescription.²⁶ MPH use was found to be slightly higher (RR: 1.17, 95 percent CI: 1.14-1.21) among individuals in the lowest two socioeconomic quintiles (least privileged) relative to the highest three quintiles.²⁶ Paediatricians and psychiatrists wrote 23 percent and 21 percent of all prescriptions, respectively, whereas General Practitioners (GPs) wrote 56 percent of all prescriptions and 41 percent of the initial prescriptions.²⁶ Using computerized administrative records of physician visits and prescriptions, a cohort of 4787 Manitoba children (up to the age of 19 years) diagnosed with ADHD within a 24-month period (1994-96) or prescribed psycho-stimulant treatment over a 12-month period (1995-96) was assembled in order to calculate estimates of ADHD diagnosis and use of stimulants at the provincial level.²⁹ Overall, 1.52 percent of Manitoba children were noted to have received a medical diagnosis of ADHD and 0.89 percent, to have received stimulant medication.²⁹ Among those who received a diagnosis, 58.6 percent were treated with medication. On average, the peak age to receive a diagnosis and medication was between 7-9 years of age,

with males much more likely to be both diagnosed and treated with stimulants in each age group.²⁹ Lastly, these outcomes were found to vary according to physician speciality - children in Manitoba appeared more likely to be diagnosed and treated by a pediatrician than by a GP or psychiatrist.²⁹

A recent publication compared patterns of stimulant use in the provinces of B.C. and Manitoba (by those less than 19 years of age) using population-based administrative prescription medication data for the years 1997-2003.²⁵⁵ Important differences were detected - though psychostimulant prescription rates were nearly identical in the two provinces in the late 1990s and increased over the next 6 years, the increase in use in Manitoba was more than 3-fold the increase observed in B.C. children.²⁵⁵ Next, in 2003, psychostimulant use in Manitoba was greatest in the 11-14 year age group, whereas in B.C., it was highest among 15-18 year olds.²⁵⁵ Use was found to have decreased among children aged 6-10 years in B.C. between 1997 and 2003, whereas in Manitoba, all three categories (6-10, 11-14, 15-18 years of age) experienced an increase.²⁵⁵ A suggested explanation of more discriminate diagnosing and prescribing by B.C. physicians was given for these discrepancies.²⁵⁵

Brief Summary, Canada.

- There was a relatively low prevalence of MPH use in the early 1990s by those <11 years old.
- There appears to be a gender difference in treatment use, boys > girls.
- There was a much larger increase in treatment use by children in Manitoba vs. B.C. during the years 1997-2003.

Europe. Observing time period trends in the United Kingdom (U.K.), a population-based study conducted to estimate the prevalence of psychotropic drug prescriptions in children and adolescents (<19 years) between 1992 and 2001 in primary care settings revealed that stimulant prescriptions (mostly MPH) rose significantly from 0.03 per 1000 (95 percent CI: 0.02-0.04) in 1992 to 2.9 per 1000 (2.52-3.32) in 2001, a 96-fold increase.²⁵⁶ Of note, 2.4 percent of stimulant prescriptions were made to children <6 years of age and a higher proportion of boys received stimulants than girls.²⁵⁶ Next, using the same large, population-based database (GPRD, patients were between 15-21 years of age at this point and had had a minimum of one stimulant prescription and 1 year of research-data available), the prevalence of prescribing averaged across all age groups of ADHD medications was found to have increased eightfold, from 0.26 per 1000 patients in 1999 to 2.07 per 1000 in 2006.¹⁹⁶

In the Netherlands, a large increase in the use of psychostimulants during the years 1996-2006 was documented in those less than 19 years old using a pharmacy prescription database.²⁵⁷ The use of psycho-stimulants increased in boys (overall, irrespective of age) from 4.5 percent (95 percent CI: 3.8-5.3) in 1996 to 31.1 percent (95 percent CI: 29.8-32.5) in 2006 and for girls, from 0.7 percent (95 percent CI: 0.5-1.1) to 8.1 percent (95 percent CI: 7.4-8.8), respectively.²⁵⁷ The group that experienced the largest increase in use was boys aged 10-19 years and the male to female prevalence ratio declined from 6.4 in 1996 to 3.8 in 2006.²⁵⁷ It should be pointed out, however, that the UK studies used population-based sample(s), whereas this one used a

pharmacy prescription database (made up only of individuals who take pharmaceuticals), which may possibly account for the larger estimates in the latter study.

Notable differences in the prevalence of psychotropic medication use in youth (0-19 years) emerged in a cross-national comparison between Germany, the Netherlands and the U.S., using administrative claims data for the year 2000 (for insured enrollees in selected large health insurance systems from the three nations). The annual prevalence of any psychotropic medication in youth was significantly greater in the US in 2000 (6.7 percent) than in either of Germany or the Netherlands (2.0 percent and 2.9 percent, respectively).²⁵⁸ Keeping provider type factors in mind, GPs prescribe most of the psychotropic drugs in Western Europe whereas in the U.S., pediatricians tend to fulfill that role for youths.²⁵⁸ In addition, the number of child psychiatrists per capita in Western Europe is low relative to the U.S., which may also account for some prescribing differences.²⁵⁸

Brief Summary, Europe

- Increases in the prevalence of psychostimulant treatment use were documented in both the U.K. and Netherlands from 1990-onwards in those <19 years of age.
- There appears to be a gender difference in the prescriptions for psychostimulant treatment, boys > girls.
- Relative to the U.S., psychotropic medication use in youths was much lower in Germany and the Netherlands in 2000.

Other World Regions. Between the years 1988 and 1993 in Western Australia (WA) and New South Wales, a significant increase in the use of stimulants for ADHD in youths up to the age of 16 years was noted.²⁵⁹ In contrast, an analysis of new psychostimulant prescriptions in South Australia during the period 1990-2000 for ≈5000 youths up to the age of 18 years observed that despite a significant rise in prescriptions up to the year 1995, the rate then declined.²⁶⁰ At the end of the year 2000, the rate of children and adolescents, aged 2-17 years, on stimulant medication for ADHD was 11.3 per 1000 (1.1 percent) of the population aged 2-17 years in New South Wales.²⁶¹ In terms of socio-demographic profile, the rate of treatment was highest among 10-yr olds (19.9 per 1000 aged 10 years) and the majority of those receiving stimulant treatments were male.²⁶¹ An examination of treatment with psychostimulants for ADHD in children aged 3-17 years during the year 2004 in the same region (WA) using whole population based administrative pharmacy data concluded that the prevalence of treatment with stimulants for this cohort was 2.4 percent with age-specific prevalence as high as 3.5 percent.²⁶² The male to female ratio of stimulant treatment was 4:1.²⁶² Prevalence increased rapidly from ages 3-8 years, remained high until a peak at 14 years and declined rapidly thereafter, signifying that children between the ages of 8-14 have the highest levels of treatment. Most (89.3 percent). children received their prescriptions from pediatricians.²⁶²

Lastly, a longitudinal, population-based investigation of MPH use for the treatment of ADHD among children up to the age of 18 years in Israel from 1998-2004 found a rapidly increasing rate of MPH use among Israeli children during this time frame, with the increase being more pronounced in girls.²⁶³ The overall 1-year prevalence estimate of MPH use in the whole group increased from 0.7 percent in 1998 to 2.5 percent in 2004.²⁶³

Brief Summary, Other World Regions. **Some increases in stimulant use for ADHD in youth were noted in areas of Australia from 1988-93, though another region observed a decline after 1995.**

- Stimulant treatment in males > females.
- An increase in MPH use for the treatment of ADHD was also documented in Israel youth between the years 1998 and 2004.

Key Considerations, Overall

- Clinical identification and treatment appear to vary considerably by geographic area.
- In addition to the factors pointed out in the prevalence section (which are also relevant here, relating to identification), a major item with respect to comparability of diagnoses and treatment of ADHD across geographic regions and different time periods is the data source – for instance, how each of the study groups are defined and who they represent. In order to draw meaningful conclusions about the nature of the relationships of interest, this factor needs to be taken into account for any comparisons to be valid.
- Context and cultural overlay influence how ADHD is understood from country to country, and thus how it is treated
- Underlying prevalence does not appear to vary much between nations and regions, once differences in methodologies for ascertainment are taken into account
- Rates of diagnosis vary considerably due to cultural context, time period, access to health care services, and provider type, as well as measurement and classification, among other factors; they also vary among regions within the United States
- Appreciation of the combined neuro-developmental and environmental etiologies and magnitude of impairment due to the condition has increased over the past 4 decades.

Discussion

Summary of the Evidence

This systematic review examined three questions regarding the effectiveness and safety of interventions for persons with Attention Deficit Hyperactivity Disorder (ADHD). We investigated safety and efficacy of interventions for preschool children with disruptive behavior disorders including those at high risk for ADHD. We investigated long term effectiveness of interventions, with a special focus on safety of pharmacologic interventions, for persons of all ages with ADHD, and we report on variability in prevalence, clinical identification and treatment for ADHD, in the United States and elsewhere.

Overall we found that the most information about long-term outcomes applies to boys aged 7 to 9 years at intervention. Preschoolers with diagnosed ADHD, girls, teenagers, and adults have rarely been the focus of intervention research. In general, safe and effective interventions have been identified. Parent behavior training for preschoolers is efficacious and benefits appear to last, however many parents drop out of treatment. Medications can be efficacious in preschoolers but are not as well tolerated as in children over 6 years and in adults. In addition to psychostimulant medications, two additional pharmacologic agents, ATX and guanfacine, have been studied that appear effective and safe for one or more years at a time, with differing adverse event profiles. Classroom teacher based interventions can improve academic and classroom behavior outcomes for both preschoolers and primary school children, but difficulties re-emerge 1 to 2 years following discontinuation of the intervention. For subgroups of children additional benefit may derive from combined medication and behavioral interventions, but not for all. There remains a lack of clarity about how long treatment may be required, of what type and for whom. For some, incremental improvement accrues with continued intervention over years; for others, medication interventions can be discontinued without relapse. However, these observations are difficult to evaluate due to absence of information regarding co-interventions.

A survey of the research in community samples suggests that clinical identification and treatment of ADHD has increased since the early 1990s and varies widely by geography. Prevalence estimates for school age ADHD vary primarily due to method of measurement, definition of disorder and informant. Among older adolescents and adults many fewer prevalence studies are available. Little information is available regarding clinical identification and treatment for large-scale populations except for studies using administrative databases where use of medications may indicate both identification and treatment. Alternative or additional interventions are not represented.

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Key Question 1. Among Children Less than 6 Years of Age with Attention Deficit Hyperactivity Disorder or Disruptive Behavior Disorder, What are the Effectiveness and Adverse Event Outcomes Following Treatment?

Twenty-eight randomized controlled trials (RCTs) investigating parent behavior training in children with disruptive behavior disorders are available, most comparing interventions to wait list controls. Among these studies we chose those using uniform outcome measures of child behavior difficulties and parent efficacy, and performed meta-analyses. The descriptive review of the studies showed that parent behavioral interventions are an efficacious treatment option for preschoolers with disruptive behavior disorders. The meta-analyses confirmed that both child behavior parent efficacy improve to a clinically significant degree. Among these RCTs, eight examined measures of ADHD symptoms. Seven of the eight studies documented improvements in these symptoms as well. Some studies utilized blinded observations of child and parent interactions and identified improved child compliance and improved parenting strategies. Self-directed, group, and individual variants of parenting interventions are generally equally effective, though group therapy may be more cost-effective when compared to individual therapy. The primary barrier to effectiveness is that parents do not attend or do not complete the recommended numbers of sessions, and this could interfere with optimal benefit.

Extension studies suggest that the benefits shown post intervention are maintained. However these studies lack a control group since most RCTs used wait list controls and the comparison families received intervention following the prescribed period of waiting. In addition, the extension studies show high levels of attrition. Therefore the possibility exists that natural maturation or child development would also lead to improvement over extended periods of time.

Five studies examined multi-component home and school or daycare based interventions designed specifically for preschoolers or kindergarten children with ADHD or those at high risk for ADHD and disruptive behavior disorders. Two studies examined comprehensive home and school behavior training in comparison to community care or a structured parent education program in a population of children with little socio economic burden. In this population, behavior and school readiness improved following both the multi-component and comparison interventions. Few children received medication. In contrast, a combination parent training and teacher consultation program showed definite benefit in comparison to treatment as usual for a low socioeconomic Head Start community. A final study examined a kindergarten treatment classroom intervention in comparison to parent training, combined parent training and treatment classroom and no treatment control. This population included both families on public assistance and those not on public assistance. The treatment classroom appeared to be the primary beneficial intervention with little additional improvement noted for those in parent training. However, the relative benefits of the treatment classroom diminished over 2 years.

There are a few short-term studies, examining psychostimulant use in preschoolers, most with small sample sizes. Of these only one small study⁷³ compares medication directly with parent training and the combination of medication and parent training. The medication dose it examines is low compared with doses suggested by other studies. The sample size was very small perhaps

due to attrition (16 /26 children completing interventions), precluding usual statistical analysis for controlled trials examining efficacy. There is one randomized controlled study, with a more robust sample size (N = 165), that offers the best evidence of both efficacy and safety, the preschool ADHD Treatment Study (PATS). Following clinical consensus, all 303 families with children eligible for the study initially participated in a 10 session parent behavior training program. The next phase was an open label safety lead in phase followed by a 5 week multiple dose randomized crossover titration trial to examine dose effects, including adverse events (N = 165). After identifying the child's best dose, a 4 week parallel RCT, compared best dose to placebo. One hundred and forty children entered a 10 month open label extension study. The research program offered excellent evidence that MPH is both efficacious and generally safe for treatment of ADHD symptoms.⁸⁴ However, additional analyses identify that children do not improve in all domains, parents report increases in mood and anxiety symptoms, while clinicians identify global improvement and teachers note improved social skills.⁸¹ Children experience more adverse events than older groups, and many families do not maintain adherence.²⁴ The most common adverse event resulting in withdrawal from the study was irritability. Growth rates are slowed over 1 year's time,⁸³ and children with multiple co-morbidities do more poorly on medication than those who have a less complicated presentation.⁸²

Key Question 2. Among People 6 Years of Age or Older With Attention Deficit Hyperactivity Disorder, What are the Effectiveness and Adverse Event Outcomes Following 12 Months or More of Any Combination of Follow-up or Treatment, Including, but not Limited to, 12 Months or More of Continuous Treatment?

Among the studies available examining extended outcomes following treatment, many examined pharmacologic agents. Three studies were placebo controlled discontinuation studies or relapse prevention studies.^{92,95,96} In general pharmacologic agents continue to control the symptoms of ADHD after 12 months of use, with benefits maintained. The different agents demonstrate different adverse event profiles, such that adverse events may be a primary reason for choosing one agent over another. The following offers details about effectiveness and safety by specific agent.

Psychostimulants

Psychostimulants continue to provide control of ADHD symptoms and are generally well tolerated for months to years at a time. Concerns about exacerbation of tics with stimulants appear to be unfounded, although sample size in studies of tics remains small and may result in type II error. Some of the long-term research summarizes information based on short-acting formulations of psychostimulants, requiring multiple doses daily. The Barbaresi⁸⁷ study for instance reports that methylphenidate (MPH) is better tolerated than dextroamphetamine. However, direct comparison of once-daily agents, for example, OROS MPH and MAS XR is

difficult, as the Hoare et al., 2005 study⁸⁹ of OROS MPH included adolescents and those with ADHD inattentive type, whereas the McGough et al., 2005 study⁹⁴ of MAS XR sample had more than 90 percent with ADHD, combined type. Comparison could be read as suggestive that OROS MPH is better tolerated than MAS XR, however both studies had 15 percent of participants withdraw because of adverse events. Also the methods for collecting adverse events may have been more sensitive in McGough et al.,⁹⁴ as they were collected by both spontaneous reports and by investigator inquiry. It is also possible that the Hoare et al., study⁸⁹ offered participants relatively less effective dose, thereby diminishing the likelihood of adverse events. The agents have not been compared in the same trial and therefore it is not possible to make direct comparisons of effectiveness and tolerability.

Atomoxetine

Industry sponsored trials show that ATX is both safe and effective for ADHD symptoms over 12 to 18 months. The research examining its use considers global functional assessments as well as ADHD symptom change. Relative to studies of other agents the research offers direct comparison with placebo for examination of relapse prevention, offering strong evidence of effectiveness and safety in children and teens.^{95,96,102} Adler et al.,⁸⁸ offer the only study of pharmacologic intervention over extended time period in adults with ADHD. The relapse prevention studies offer both evidence of effectiveness and safety, but also evidence that some individuals maintain benefit despite discontinuation of medication following 12 months of use.

Guanfacine

Industry sponsored trials of GXR show it to be effective and generally safe. Parents report benefit in reduced ADHD symptoms and global improvement for a substantial number of children and teens with ADHD. Somnolence, headache and fatigue appear to interfere with its use but these adverse events diminish following several months of treatment, although this may be due to discontinuation by those who do not tolerate the agent. Tolerance appears to be improved with concurrent administration of psychostimulants. Monitoring of cardiac status may be indicated as there are rare reports of significant bradycardia, junctional escape complexes and intraventricular delay.

We examined studies regarding three areas of adverse events that required use of articles that were not clinical trials comparing two or more interventions. These were studies examining growth rates in comparison to standardized norms, and rates of hospital and emergency department use for cardiac events and cerebrovascular events, such as cerebrovascular accidents (CVAs) and Transient Ischemic attacks (TIAs).

Growth

Medications used for ADHD appear to have a small but distinct dose-related impact on rates of growth for children with ADHD. Limitations in the studies include small sample size, and

relatively short duration of studies which interfere with clarification regarding final adult height following years of medication use.

Cardiac Events

Rates of hospital admission for cardiac reasons are similar to rates in the general population. Rates of emergency department use were 20 percent higher for those with ADHD who use stimulant medication compared to those who do not.¹⁰⁶ Rates were comparable among those using methylphenidate and amphetamines. Use of concurrent bronchodilators, antidepressants or antipsychotics, age 15 to 20 years, and history of cardiac problems were associated with increased use of emergency departments.¹⁰⁷

Cerebrovascular Events

There was no increased rate of incidents of CVAs or TIAs between groups prescribed ATX or psychostimulants. However the combined ADHD medication cohort exhibited a higher hazard ratio (HR) (3.44, 95 percent CI 1.13 – 10.60) for TIAs compared with the general population after adjusting for baseline risk factors. A similar pattern was not observed for CVAs. These results do not support an increased risk of cerebrovascular events for users of ATX over psychostimulants. However users of ADHD medications may be at higher risk of TIAs than the general population.¹⁰⁸

Psychostimulant Medication Compared with Combination of Psychostimulant Medication and Psychosocial and/or Behavior Treatment

Three cohorts were identified that examined stimulant medication and/or combined medication and psychosocial or behavioral treatment. One of these was a study in China¹⁴³ while two were in North America,^{120-122,142} including the followup cohort extension study of the Multimodal treatment study of ADHD (MTA study), the largest RCT to date examining combinations of interventions.¹²² The results from these three cohorts indicate that both medication and combined medication and behavioral treatment are effective in treating ADHD plus Oppositional Defiance Disorder (ODD) symptoms in children, and also anxiety, primarily boys aged 7-9 of normal intelligence with combined type of ADHD, especially during the first 2 years of treatment. Overall, the MTA study suggests that combined therapy may have a slight advantage over medication management during the first 14 months, and a clear advantage over behavior treatment,^{127,129} especially for children with multiple co-morbidities.²⁶⁴ However, combined treatment is equivalent to medication alone in controlling ADHD and ODD symptoms for up to 2 years if the child shows an early favourable response to medication.¹³⁹ The MTA study also suggests that these two strategies may be superior to psychosocial/behavioral treatment alone or community care during the first 2 years,^{120,122,137} although psychosocial/behavioral treatment is equally effective as treatments with medication for ADHD children with co-morbid anxiety disorder during the first 14 months.¹²⁸ Combination therapy and medication management are

effective in reducing ODD during the first 2 years of treatment,¹³⁹ and superior to psychosocial/behavioral treatment and Community Care.^{120,122} It appears that psychosocial/behavioral treatment reduces the risk of substance use for 10 months following intervention, but the effect disappears by 22 months.¹³⁴ No treatment strategy is clearly superior in reducing other co-morbid psychiatric disorders at 14 months or 3 years.^{132,133}

Combining medication with behavioral/psychosocial treatment may reduce the dose of medication required, and may retain patients in treatment.¹⁴³ In So's study involving Chinese children, the mean daily dose of stimulant medication was less than half that used in the MTA study. From Abikoff's 2004 study, it may be cost-effective to treat stimulant-responsive children free of learning and conduct problems with medication alone.¹³⁸ Treatment with medication, intensive behavioral treatment or combination of the two can reduce negative parenting, but combined treatment may be the most effective in improving positive parenting.^{123-125,141}

Using intention to treat analyses, the MTA study suggests loss of superiority of any individual intervention 2 years after treatment has ended. However, secondary analyses such as mixed effects models, propensity score analysis and growth mixture model analysis have provided additional findings. These secondary studies document that most children with ADHD receiving any of the interventions, generally maintained improvement up to 8 years, while a small proportion began to worsen after the interventions discontinued. On the other hand while most of the children experienced improved symptoms and functioning, they did not reach levels of functioning comparable to non-clinical community peers.¹³⁶

We also examined cohort studies that followed children for multiple years since initial treatment. The outcomes and time frames varied extensively across studies. Except for Biederman (2006) and Wilens' (2008) group which studied an exclusively female cohort, all others studied an exclusively or predominantly male sample. Although any conclusions can only be seen as preliminary, it appears that stimulant medication might protect against psychiatric disorders (ODD, CD, depression, anxiety disorder) in the long term (at 10 years). Some studies suggest that stimulant medication reduces substance use disorders in late adolescence or adulthood^{152,157,158} while one paper reported no benefit.¹⁵⁵ Two studies suggested stimulant medication may protect against nicotine use.^{151,158} Treatment with stimulant medication, especially at an earlier age, may delay onset of smoking and reduce substance use disorder.^{153,156,157} Given the challenges inherent in pursuing long term outcomes studies, with lack of ability to control for co-interventions and significant life events, such information can only be seen as hypothesis generating.

We found three reports on two cohorts that examined academic achievement as the primary outcome following classroom-based interventions. Other studies reported on academic outcome as one of multiple secondary outcome measures. The review of the academic outcomes with long-term followup of treatment interventions revealed benefits, albeit limited, with medication interventions in some domains. Combining psycho-behavioral and academic skills interventions with medication offers no additional gains from medication alone, at least for children with ADHD without comorbid learning disabilities. Interventions for academic skills in classroom-based programs result in academic enhancement but the findings support the need for sustained intervention to improve academic functioning over time.

Key Question 3. How do A) Underlying Prevalence of ADHD, and B) Rates of Diagnosis (Clinical Identification) and Treatment for ADHD Vary by Geography, Time Period, Provider Type, and Socio-demographic Characteristics?

According to a recent comprehensive systematic review and meta-regression analysis that encompassed studies from all areas of the world, the worldwide pooled prevalence estimate of ADHD among those 18 years of age or younger is 5.29 percent (95 percent CI: 5.01-5.56).¹⁴ Though a significant amount of variability was noted in the comparison of prevalence estimates across world regions, results seemed to indicate that once methodological differences of studies were controlled for, geographic location explained very little of the variability.¹⁴ In fact, after this step, only significant differences were detected between studies carried out in North America and Africa and the Middle East.¹⁴ The requirement of impairment for the diagnosis, diagnostic criteria, and source of information, then, were the main sources of variability in the pooled prevalence estimate of ADHD.¹⁴

Most studies show that more boys than girls have ADHD, and children in the age group 5 to 10 years show the highest prevalence. In addition some studies suggest children from lower socioeconomic status (SES) demonstrate higher levels of symptoms. Research detailing prevalence in other age groups world-wide is generally lacking, with few studies examining prevalence among preschoolers, adolescents, or adults. These are age groups where diagnostic consensus is less clear, making the task of identifying cases difficult. There is a general lack of uniform protocol for eliciting information about prevalence, including research choices about informants, measurement instruments, and definition of cases across geographic areas.

Despite the inherent difficulties with case identification on a community-wide basis, information about clinical identification and treatment available through administrative data and health surveys document that pharmacological use of psychostimulants for ADHD increased throughout the early to mid 1990s, but appears to have slowed in the late 1990s and early 2000s in the United States.^{27,28,246} Similarly in Canada and in Europe, psychostimulant use for children with ADHD increased throughout the 1990s and early 2000s, although rates of use are lower in Germany and the Netherlands than in the United States.^{255,258} In general, more boys than girls are treated and in the United States, more Caucasians than Hispanic or African Americans receive medication treatment once identified.^{244,249} There are geographic disparities among services offered in the United States as well with more children in the Midwest and South receiving psychostimulants relative to the West, and more children in urban rather than rural centers.²⁵⁰ In addition, children living in more affluent communities are more likely to receive psychostimulants.²⁵¹

Limitations, Preschool Interventions

Very few RCTs offer information about parent training interventions designed specifically for preschoolers with ADHD. Despite this, eight of the parent training intervention studies, documented improvement in ADHD symptoms. While it appears that parent training benefits

may last several years, no extension study included untreated comparison groups, and attrition over the followup period ranged from 24 percent at 18 months⁵⁷ to 54 percent at 3 to 6 years,^{41,52} limiting interpretation of the results.

The five studies examining combined parent training and school or daycare interventions for children with ADHD suggest that adding classroom teacher consultation may be important for children in low SES communities, but this does not offer additional benefit for families with educated parents who live in communities with resources. It was also noted that the benefits of the classroom treatment disappeared after 2 years. The other studies did not provide comparable information regarding long term maintenance of benefit.

Investigations of psychostimulant medication use in preschoolers are generally very small samples and short term trials. The PATS study addresses a number of important methodological and clinical concerns, examining the potential additional benefit of medication following a series of 10 parent behavior training sessions. Careful attention to details regarding adverse events and impact of these on medication adherence offers clear information about long term effectiveness and safety as well. Interestingly clinicians documented improved global functioning concurrently with parents noting increased mood problems. While parent and teacher ADHD symptom scales measuring dysfunction noted improvement, those measuring strengths as well as weaknesses in behavior showed no overall behavioral benefit from the addition of stimulant medication. The PATS study offers information about both the potential benefits and limitations of stimulant medication use in young children. Limitations are that younger children experience more dose related adverse events than older children, that stimulants interfere with rates of growth, and that parents that may agree with ongoing use following titration especially in light of the findings that presence of three or more comorbid conditions and psychosocial adversity interfered with the effectiveness of adding psychostimulant medication to parent training. Only 54 percent of those enrolled in the study opted to enter the medication titration component following parent training, suggesting parent preferences play an important role in providing optimum care for young children with ADHD.

Future work should examine the appropriate place of parent behavior training as a specific intervention for ADHD in preschoolers. A focus of such studies should include different SES and ethnocultural groups, as well as presence of comorbid conditions in the children. Adverse events are not discussed in reports of parent training trials. Outcomes examined should include global functioning and school readiness as well as behavior symptom counts. Specific attention to the circumstances surrounding parent attrition from parent training is warranted as that appears to be a primary barrier to success. Additional awareness and understanding of parent preferences may be especially important in this age group.

Limitations, Extended Studies

Studies conducted over long periods of time face challenges in controlling for many confounders which may affect the outcomes studied. Several of these longer term studies either did not include, at baseline, representatives from lower SES at risk for psycho-social adversity, or those who were less able to be contacted for followup. Some studies did not systematically collect or

report important confounders, such as socioeconomic demographics, family psychiatric history, childhood abuse, adherence to treatment, or co-interventions. The retrospective studies face problems with recall and documentation bias, which prospective longitudinal studies face as well if the time intervals between data collection are lengthy. An important challenge is documentation of treatment adherence and co-interventions, both formal and informal, which affect treatment outcomes.

A considerable limitation to evaluating academic outcomes following interventions is that classroom-based or teacher consultation based interventions are by nature difficult to investigate, as it can be challenging to coordinate cross-sector research and to develop informative comparison interventions that are ethically acceptable. In addition, few of the studies reviewed controlled for learning disabilities and IQ, important confounding factors for academic outcomes in an ADHD population. Additional aspects to consider in future studies will be the challenges inherent in coordinating and tracking the co-interventions offered in school settings along with those offered through health care settings.

The most commonly studied population for the extended interventions studies were children, primarily boys, aged 7-9 years, with combined type ADHD at the time of documented treatment. It is not clear whether the same intervention outcomes apply to community samples across different geographical regions and cultures, and to both genders, other ADHD subtypes and different age groups. In addition, for the most rigorous studies, there was no comparison group of children with untreated ADHD as this would be an ethical challenge. It is therefore difficult to be fully confident that the improvements seen over time were due to treatment effects rather than subsequent co-interventions, maturational or other unmeasured effects.

Limitations, Prevalence and Health Services Studies

The ascertainment of the prevalence of ADHD across all age categories in the population is necessary in order to appreciate the burden that the condition poses and subsequently, to ascertain unmet need, and devise services to aid in alleviating the burden. There are several methodological factors that influence the calculation of prevalence estimates – namely, the diagnostic criteria employed, along with informant type and the data source.²⁶⁵ As underlined by the recent systematic review/meta-regression of worldwide prevalence of ADHD, key methodological differences between studies accounted for much of the variability in the pooled prevalence estimate, highlighting the need for a standardized, methodological approach in order to improve comparability of estimates and epidemiological trends reported over time and in different geographical areas.

To date, the prevalence of ADHD among both adolescents and adults is not well delineated in the literature. Adolescents tend to be subsumed under children, though the burden in this age group may well be different and/or incorrectly approximated by current diagnostic methods. It is also unclear whether the diagnostic criteria are appropriate for use with adults. University-aged individuals with ADHD may be worth examining further, as a special group. Other special populations that warrant further interest include diverse cultural groups and/or ethnic minorities, and other vulnerable groups such as immigrants, and families of low SES.

To develop an understanding of who is identified and treated for ADHD in community practice, the types of data used most frequently were administrative and prescription databases. The former type of database is limited in the sense that it represents only those with health insurance, whereas the latter takes into account only those who use prescription medication. Nevertheless, each provides a depiction of what happens in community practice rather than in the context of an academic research setting, with regard to diagnosis and/or treatment use for ADHD. Similar to epidemiology studies for prevalence, issues of case identification, informant and quality of interventions and outcome measures limit interpretations of the results. For the purposes of understanding who is receiving what kind of treatment, a significant shortcoming of the current literature is a lack of information on other forms of treatment for ADHD besides the use of psychostimulants or other medications. This renders the task of capturing all aspects of treatment use difficult, assuming that some less prominent types of treatment are used for ADHD. In addition to addressing this gap, more attention should be paid to uncovering whether or not certain groups (e.g. those of lower SES, ethnic minorities, those living in more isolated or rural areas) are being under-recognized and/or undertreated for ADHD as some studies have suggested that disparities exist.

Conclusions and Recommendations for Future Research

Key Question 1

The evidence available for interventions in preschoolers with disruptive behavior disorders supports the use of parent behavior training as an effective intervention both for oppositional behaviors and for ADHD symptoms where measured, with no adverse events reported. The largest barrier to successful completion of the intervention is parent attrition. Preliminary efforts to examine modes of service delivery to accommodate parent preferences suggest such adjustments do not interfere with its effectiveness as long as the program is delivered as designed. For preschoolers, psychostimulant medications are also generally safe and efficacious for improving behavior and can provide benefits in addition to Parent Training. However, adverse events, especially irritability and moodiness can lead to discontinuation over extended periods of time, and use for several months to a year impacts growth rate to a small degree. The addition of school-based interventions to parent training appears to be more useful for disadvantaged populations, although benefits diminish following discontinuation of the intervention.

Areas for future research should include:

- Investigations of parent preferences regarding behavior training are needed to determine if parent completion rates for training can be improved.
- Some studies adjusted the parent behavior training to address ADHD specifically, but other interventions also showed improvement in measured ADHD symptoms without adjustment. Evaluation is required regarding the need for specific adjustments to assist children with ADHD.
- One study found that a structured parent education program offered the same benefits as combined parent behavior training and school consultation for middle income families. Further investigation is required of the role of psychoeducation interventions in the continuum of ADHD care, as this may be a cost-effective intervention option.
- The role of teacher consultation or classroom interventions deserves additional evaluation in the context of cross-sectoral research combining health care and education interventions for preschool children at high risk of ADHD.
- Developing methods to investigate long-term outcomes of preschool interventions including appropriate comparison groups is required.
- Investigate the optimal circumstances for adding medication in the treatment for preschool children with ADHD, including which subgroups, for how long, and in conjunction with what additional interventions.

Key Question 2

The long term effectiveness and safety of several psychostimulants, ATX and guanfacine XR have been examined prospectively in children and adolescents over the age of 6 years. All of these agents are efficacious for control of inattention and overactivity for extended periods of time, and few serious adverse events are noted. Fewer individuals discontinue psychostimulants and ATX than guanfacine XR due to adverse events. Placebo controlled discontinuation trials are

few, one in children receiving amphetamine, and two others after 1 year and again after 2 years of use in children receiving ATX. These trials suggest that some individuals continue to benefit and others no longer benefit, following 12, 15 or 24 months of continuous treatment with medication.

Evaluation of long term outcomes following interventions for ADHD is complex due to multiple patterns of services used. The best data is available through the 8 year followup of the MTA study. By 3 years after initiation no single intervention group showed superior benefit likely due to individuals obtaining a complex range of interventions in the community. The majority of children who received an intervention were maintaining improvements in functioning, although they were not improved enough to match non-clinical comparison groups. A small proportion returned to previous levels of poor functioning over time. There was no clear relationship identified between duration of medication use and outcomes. Other cohort studies suggest that long-term use of medication improves grade retention and academic achievement, and may lessen onset of substance use disorders as well as oppositional defiant, conduct, anxiety and depressive disorders.

Areas for future research should include:

- Extension studies of pharmacological agents that include placebo controlled relapse prevention trials, as these offer information about individuals no longer requiring continued use of medication.
- Interventions in subgroups not commonly investigated to this point in time, specifically, individuals with primarily inattentive subtype of ADHD, girls, teenagers, university students and adults. Other groups of interest are those with psychiatric comorbidities, and different racial or ethnic groups, or low socioeconomic circumstances.
- Little specific information is available regarding outcomes for those with comorbid learning disabilities, language impairments, reading or mathematics disorders.
- The definition of interventions as “psychosocial and /or behavioral” is highly inclusive and based on the intensive intervention used in the MTA study that included parent behavior training, a summer behavior treatment program for the child and consultation with the school teacher following the summer intervention. The individual aspects of this program require “unpacking” and matching to the subgroup of ADHD and comorbid condition that data suggested would most likely benefit. Evaluation of the separate components will optimize the match between what the child needs and what intervention he/she receives.
- Understanding the role of academic interventions or combined medication and academic interventions with an emphasis on long-term academic outcomes is important, as maximizing educational success is often an important long term treatment goal.
- Use of standardized outcome measures such as global impairment scales or quality of life scales would be useful to compare study outcomes from different cohorts.
- The challenges of lengthy studies are many, and include systematic data collection, retention of participants, and identification of appropriate comparison groups.

Key Question 3

A systematic review and meta-regression placed the worldwide pooled prevalence estimate of ADHD among those 18 years of age or younger at 5.29 percent (95 percent CI: 5.01-5.56),¹⁴ with more boys than girls identified and the highest rates of disorder occurring in the 5 to 10 year old age group. Primary sources of variability were identified as methodological rather than geographic, and include differences in requirements for impairment, diagnostic criteria, and source of information. Fewer studies are available that document prevalence in adult, adolescent or preschool age groups, which likely reflects a lack of clarity regarding current diagnostic criteria in these groups. Information about clinical identification and treatment available through administrative and prescription data and health surveys, documents that psychostimulant use for ADHD increased throughout the early to mid 1990s, but has slowed in the late 1990s and early 2000s in the United States. Disparities are noted with more boys than girls treated and more Caucasians than Hispanic or African Americans receiving medication treatment once diagnosed in the United States. Rates of identification and treatment also vary from state to state. Non-pharmacologic interventions are not documented. For direct geographic or time period comparisons to be informative, data sources and methods of identifying cases and documenting interventions should be comparable.

Areas for future research should include:

- Prevalence data regarding ADHD in subpopulations of adolescents, and adults. In some areas of the world information about ADHD prevalence among university students is needed.
- Standardized methods of data collection, case identification and outcomes measurement in epidemiologic surveys and administrative databases is required.
- There is a need for more research on patterns of service use; to improve our understanding of health system, educational system, health insurance, provider, family and child factors that influence the distribution, access and receipt of treatment for ADHD.
- Cross sector coordination of health services, mental health services and education databases is uniquely required in the area of ADHD.

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Abbreviations

Abbreviation	Definition
%ile	percentile
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-C	Attention Deficit Hyperactivity Disorder - Combined type
ADHD-HI	Attention Deficit Hyperactivity Disorder- Hyperactive Impulsive
ADHD-I	Attention Deficit Hyperactivity Disorder- Inattentive
AE	Adverse Events
AHRQ	Agency for Healthcare Research and Quality
amph	amphetamine
ARCOS	Automation of Reports and Consolidated Orders System
ATX	atomoxetine
B.C.	British Columbia
BELLA	Mental Health Module (German)
BP	Blood Pressure
bpm	Beats per minute
C p/t	Conners parent/teacher
CBCL	Child Behavior Checklist
CBM	Curriculum-based measurement
CC	Community Care
CD	Conduct Disorder
CER	Comparative Effectiveness Review
CGI-IS	Clinical Global Impressions-Impairment scale
CHP-C	Challenging Horizon Program and Consultation
CHQ	child health questionnaire
CI	Confidence interval
cm	centimeter
CP	classroom performance
CT	clinical trial
CVAs	Cerebrovascular Accidents
d/c'd	discontinued
DAWBA	Development and Well-Being Assesment
DBD	Disruptive Behavior Disorder
DEX	dextamphetamine
diff	difference
DISC-IV	Diagnostic Interview Schedule for Children Version IV
DISC-IV-P	Diagnostic Interview Schedule for Children Version IV – Prevalence
DR	dose related
DSM	Diagnostic and Statistical Manual of Metal Disorders
DSM IV	Diagnostic and Statistical Manual of Mental Disorders 4 th edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders 3 rd edition - revision
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders 4 th edition – text revision
ECBI	Early Child Behavior Inventory
ECG	Electrocardiograph
ED	Emergency Department
EMBASE	Excerpta Medical Database
EPC	Evidence-based Practice Center
Eric	Education Resources Information Center
F/U	followup
FBB-HKS/ADHS	German ADHD Rating Scale

Abbreviation	Definition
FDA	Food & Drug Administration
freq	frequency
GP	General Practitioner
GPA	Grade Point Average
GPRD	General Practice Research Database
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
GXR	Guanfacine extended release
HR	Haert Rate
ICD	International Classification of Diseases
IDAI	Intensive Data-based Academic Intervention
IQ	Intelligence Quotient
IR	immediate release
IYPP	Incredible Years Parenting Program
kg	kilogram
KiGGS	The German Health Interview and Examination Survey for Children and Adolescents
KQ	Key Question
K-SADS-E	Kiddie - Schedule for Affective Disorders and Schizophrenia - Expressive
levo	levoamphetamine
LT	long-term
MAS	Mixed Amphetamine Salts
MAS XR	mixed amphetamine salts extended release
MCI	Multi-component Intervention
MEPS	Medical Expenditure Panel Survey
mg	milligram
mmHg	Millimeters of Mercury
MPH	methylphenidate
MTA	Multimodal Treatment Study of Children with ADHD
NAMCS	National Ambulatory Medical Care Survey
NC	non-compliance
NCHS	National Survey of Child Health
NFPP	New Forest Parenting Program
NIMH	National Institute for Mental Health
NLSCY	National Longitudinal Study of Children and Youth
ODD	Oppositional Defiant Disorder
OLE	Open Label Extension
OROS MPH	once a day methylphenidate
PATS	Preschool ADHD Treatment Study
PCIT	Parent-Child Interaction Therapy
PE	Parent Education
PICOT	population, intervention, comparison, treatment
PSOC	Parent Sense of Competency
PT	Parent behavior training
Q	Question
QTc	Q T Interval
RCR	retrospective chart review
RCT	Randomized Controlled Trial
RR	Relative Risk
RS IV	Rating Scale version IV
SADS	The Schedule for Affective Disorders and Schizophrenia
SD	Standard Deviations

Abbreviation	Definition
SDQ	Strengths and Difficulties Questionnaires
SE	Side Effect
SES	Socio-economic status
SET-PC	Supportive Expressive Therapy – Parent Child
SMD	Standardized Mean Difference
SNAP-IV	Swanson, Nolan and Pelham
SRS	Systematic Review Software
stim	stimulant
STP	summer treatment program
t.i.d.	ter in die (three times per day)
TDAI	Traditional Data-based Academic Intervention
TEP	Technical Expert Panel
TIAs	Transient Ischemic Attacks
TOO	Task Order Officer
Triple P	Positive Parenting of Preschoolers
U.K.	United Kingdom
U.S.A.	United States of American
VADPRS	Vanderbilt ADHD Diagnostic Parent Rating Scale
VARTRS	Vanderbilt ADHD Teacher Rating Scale
vs	versus
WA	Western Australia
yr	year

APPENDIXES

APPENDIX A

Search Strategies

ADHD Treatment Search Strategies

OVID-Medline

May 31 2010

1. "attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/ or conduct disorder/
2. minimal brain d?sfuction*.tw,sh.
3. (attention deficit* or adhd).ti.
4. addh.tw.
5. or/1-4
6. Hyperkinesis/
7. Impulsive Behavior/
8. Child Behavior Disorders/
9. aggression/ or agonistic behavior/
10. inattent*.tw.
11. Impulse Control Disorders/
12. (disruptive adj4 disorder?).tw.
13. or/6-12
14. limit 13 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)")
15. exp *Mental Disorders/
16. (attention deficit* or adhd).tw.
17. hyperactiv*.tw.
18. inattent*.tw.
19. Impulsive Behavior/
20. or/16-19
21. 15 and 20
22. 5 or 21
23. limit 22 to yr="1997 -Current"
24. 14 or 23
25. Drug Therapy/ae, co, ct, mo [Adverse Effects, Complications, Contraindications, Mortality]
26. (side effect? or adverse or harm?).tw.
27. atomoxetine.tw.
28. guanfacine.tw.
29. Lisdexamfetamine.tw.
30. Vyvanse.tw.
31. exp Central Nervous System Stimulants/ae, ct, po, to [Adverse Effects, Contraindications, Poisoning, Toxicity]
32. ritalin.tw.
33. or/25-32
34. (attention deficit* or adhd).tw.
35. 33 and 34
36. 24 or 35
37. (comment or editorial or letter).pt.
38. 36 not 37
39. review.pt,sh.

40. 38 and 39
41. meta-analysis.pt,ti,ab,sh.
42. (meta anal\$ or metaanal\$).ti,ab,sh.
43. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ti.
44. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ab.
45. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
46. (medline or embase or cochrane).ti,ab.
47. or/44-46
48. review.pt,sh.
49. 47 and 48
50. 41 or 49 or 43 or 42
51. 38 and 50
52. 40 not 51
53. 38 not 52
54. limit 53 to humans
55. limit 54 to english language

OVID-Embase

May 31 2010

1. attention deficit disorder/
2. minimal brain d?sfuction*.tw,sh.
3. (attention deficit* or adhd).ti.
4. addh.tw.
5. or/1-4
6. hyperactivity/
7. disruptive behavior/
8. conduct disorder/
9. oppositional defiant disorder/
10. hyperkinesia/
11. aggression/ or aggressiveness/ or anger/ or bullying/ or hostility/
12. impulsiveness/
13. inattention.tw.
14. (disruptive adj4 disorder?).tw.
15. or/6-14
16. limit 15 to (infant or child or preschool child <1 to 6 years>)
17. exp *behavior disorder/
18. hyperactiv*.tw.
19. hyperactivity/
20. inattent*.tw.
21. (attention deficit* or adhd).tw.
22. hyperkine*.tw.
23. hyperkinesia/
24. impulsiveness/
25. or/18-24
26. 17 and 25
27. 5 or 26

28. limit 27 to yr="1997 -Current"
29. 16 or 28
30. limit 29 to human
31. limit 30 to (book or book series or conference paper or editorial or letter or note)
32. 30 not 31
33. review.pt,sh.
34. 32 and 33
35. meta analysis/
36. meta-analysis.ti,ab.
37. (meta anal\$ or metaanal\$).ti,ab.
38. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ti.
39. ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ab.
40. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
41. (medline or embase or cochrane).ti,ab.
42. or/39-41
43. review.pt,sh.
44. 42 and 43
45. or/35-38
46. 45 or 44
47. 32 and 46
48. 34 not 47
49. 32 not 48
50. limit 49 to english language

OVID-PsycINFO

May 31 2010

1. attention deficit disorder/ or attention deficit disorder with hyperactivity/
2. minimal brain d?sfunction*.tw,sh.
3. (attention deficit* or adhd).ti.
4. addh.tw.
5. or/1-4
6. conduct disorder/
7. aggressive behavior/
8. impulsiveness/
9. exp impulse control disorders/
10. oppositional defiant disorder/
11. distractability/
12. attention span/
13. hyperkinesis/
14. inattent*.tw.
15. (disruptive adj4 disorder?).tw.
16. or/6-15
17. limit 16 to childhood
18. exp *behavior problems/ or *behavior disorders/
19. (attention deficit* or adhd).tw.
20. 18 and 19

21. exp "side effects (treatment)"/
22. (side effect? or adverse or harm?).tw.
23. or/21-22
24. 19 and 23
25. 5 or 20
26. limit 25 to yr="1997 -Current"
27. 17 or 24 or 26
28. limit 27 to human
29. limit 28 to english language
30. limit 29 to (chapter or "column/opinion" or "comment/reply" or editorial or letter or review-book)
31. 29 not 30

OVID-Cochrane Central

May 31, 2010

- 1 "attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/ or conduct disorder/
- 2 minimal brain d?sfuction*.tw,sh.
- 3 (attention deficit* or adhd).ti.
- 4 addh.tw.
- 5 or/1-4
- 6 Hyperkinesis/
- 7 Impulsive Behavior/
- 8 Child Behavior Disorders/
- 9 aggression/ or agonistic behavior/
- 10 inattent*.tw.
- 11 Impulse Control Disorders/
- 12 (disruptive adj4 disorder?).tw.
- 13 or/6-12
- 14 limit 13 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)") [Limit not valid; records were retained]
- 15 exp *Mental Disorders/
- 16 (attention deficit* or adhd).tw.
- 17 hyperactiv*.tw.
- 18 inattent*.tw.
- 19 Impulsive Behavior/
- 20 or/16-19
- 21 15 and 20
- 22 5 or 21 (1799)
- 23 limit 22 to yr="1997 -Current"
- 24 14 or 23
- 25 Drug Therapy/ae, co, ct, mo [Adverse Effects, Complications, Contraindications, Mortality]
- 26 (side effect? or adverse or harm?).tw.
- 27 atomoxetine.tw.
- 28 guanfacine.tw.

29 Lisdexamfetamine.tw.
30 Vyvanse.tw.
31 exp Central Nervous System Stimulants/ae, ct, po, to [Adverse Effects, Contraindications,
Poisoning, Toxicity]
32 ritalin.tw.
33 or/25-32
34 (attention deficit* or adhd).tw.
35 33 and 34
36 24 or 35

ERIC ADHD Search – May 31, 2009

((**Thesaurus Descriptors:**"*Attention Deficit Disorders*") or (**Thesaurus Descriptors:**"*Attention Deficit Hyperactivity Disorder*") or (**Thesaurus Descriptors:**"*Hyperactivity*") or (**Keywords:**"*attention deficit*") or (**Keywords:***ADHD*) or (**Keywords:***inattention*) and (**Thesaurus Descriptors:**"*Self Control*") and (**Publication Type:**"Journal Articles" OR **Publication Type:**"ERIC Publications" OR **Publication Type:**"Information Analyses" OR **Publication Type:**"Numerical Quantitative Data" OR **Publication Type:**"Reference Materials General" OR **Publication Type:**"Reports Evaluative" OR **Publication Type:**"Reports General" OR **Publication Type:**"Reports Research" OR **Publication Type:**"Translations")

ADHD Prevalence Search Strategies

OVID-Medline

March 25 2010

1. ((prescription or administrative or insurance or claims) adj3 (data or database? or claims)).tw.
2. "Databases, Factual"/
3. *Physician's Practice Patterns/
4. Physician's Practice Patterns/sn, td [Statistics & Numerical Data, Trends]
5. insurance claim reporting/ or "insurance claim review"/
6. Epidemiology/
7. Drug Utilization/sn, td [Statistics & Numerical Data, Trends]
8. off-label.tw.
9. "Off-Label Use"/st, sn [Standards, Statistics & Numerical Data]
10. *"Pharmacoepidemiology"/
11. Pharmacoepidemiology/st, sn, td [Standards, Statistics & Numerical Data, Trends]
12. "Drug Utilization Review"/
13. utilization.tw.
14. health surveys/ or population surveillance/ or health care surveys/
15. (trend? or pattern? or rate? or prevalence).ti.
16. ((national or regional or prescribing or prescripion or diagnos*) adj3 (trend? or rate? or pattern? or variation? or prevalence)).tw.
17. Drug Prescriptions/sn, td [Statistics & Numerical Data, Trends]
18. or/1-17
19. *Methylphenidate/tu [Therapeutic Use]
20. exp *Amphetamines/tu [Therapeutic Use]
21. exp *Central Nervous System Stimulants/tu [Therapeutic Use]
22. exp *Psychotropic Drugs/tu [Therapeutic Use]
23. *Attention Deficit Disorder with Hyperactivity/ep [Epidemiology]
24. exp *Antipsychotic Agents/tu [Therapeutic Use]
25. off-label.tw.
26. "Off-Label Use"/
27. *"Pharmacoepidemiology"/
28. Pharmacoepidemiology/st, sn, td [Standards, Statistics & Numerical Data, Trends]
29. *Drug Utilization/sn, td [Statistics & Numerical Data, Trends]
30. "Drug Utilization Review"/
31. or/19-30
32. limit 31 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)")
33. "attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/ or conduct disorder/
34. minimal brain d?sfuction*.tw,sh.
35. (attention deficit* or adhd).ti.
36. addh.tw.
37. or/33-36
38. Hyperkinesis/
39. Impulsive Behavior/
40. Child Behavior Disorders/

41. aggression/ or agonistic behavior/
42. inattent*.tw.
43. Impulse Control Disorders/
44. (disruptive adj4 disorder?).tw.
45. or/38-44
46. limit 45 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)")
47. 37 or 46
48. 18 and 47
49. 32 or 48
50. exp *Attention Deficit Disorder with Hyperactivity/di, ep [Diagnosis, Epidemiology]
51. 49 or 50
52. limit 51 to english language
53. limit 52 to yr="1980 -Current"
54. limit 53 to (comment or congresses or editorial or letter or news)
55. 53 not 54

OVID-Embase

March 25 2010

1. *clinical practice/
2. ((prescription or administrative or insurance or claims) adj3 (data or database? or claims)).tw.
3. factual database/
4. health insurance/
5. pharmacoepidemiology/
6. exp *epidemiology/
7. *"drug use"/ or *drug preference/ or *"off label drug use"/ or *prescription/
8. off-label.tw.
9. health survey/
10. (trend? or pattern? or rate? or prevalence).ti.
11. ((national or regional or prescribing or prescripton or diagnos*) adj3 (trend? or rate? or pattern? or variation? or prevalence)).tw.
12. utilization.tw.
13. "billing and claims"/
14. *geographic distribution/
15. *drug utilization/
16. "utilization review"/
17. trend study/
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. *methylphenidate/
20. methylphenidate/dt
21. exp *central nervous system agents/dt [Drug Therapy]
22. *attention deficit disorder/ep [Epidemiology]
23. *"drug use"/ or *drug preference/ or "off label drug use"/ or *prescription/
24. pharmacoepidemiology/
25. "utilization review"/
26. trend study/

27. or/19-26
28. limit 27 to preschool child <1 to 6 years>
29. attention deficit disorder/
30. minimal brain d?sfuction*.tw,sh.
31. (attention deficit* or adhd).ti.
32. addh.tw.
33. or/29-32
34. hyperactivity/
35. disruptive behavior/
36. conduct disorder/
37. oppositional defiant disorder/
38. hyperkinesia/
39. aggression/ or aggressiveness/ or anger/ or bullying/ or hostility/
40. impulsiveness/
41. inattention.tw.
42. (disruptive adj4 disorder?).tw.
43. or/34-42
44. limit 43 to (infant or child or preschool child <1 to 6 years>)
45. 33 or 44
46. 18 and 45
47. 28 or 46
48. *attention deficit disorder/ep, pe
49. 47 or 48
50. limit 49 to (human and english language)
51. limit 50 to yr="1980 -Current"
52. limit 51 to (book or book series or conference paper or editorial or letter or note or proceeding)
53. 51 not 52

OVID-PsycINFO

March 26 2010

1. *clinical practice/
2. ((prescription or administrative or insurance or claims) adj3 (data or database? or claims)).tw.
3. exp databases/
4. exp health insurance/
5. epidemiology/
6. "prescribing (drugs)"/
7. *drug therapy/
8. *drug usage/
9. off-label.tw.
10. exp questionnaires/ or exp surveys/
11. ((national or regional or prescribing or prescripton or diagnos*) adj3 (trend? or rate? or pattern? or variation? or prevalence)).tw.
12. utilization.tw.
13. utilization reviews/
14. *human sex differences/

15. *age differences/
16. *demographic characteristics/
17. (trend? or pattern? or rate? or prevalence).ti.
18. *health care utilization/
19. or/1-18
20. psychotropic.tw.
21. *methylphenidate/
22. exp *cns stimulating drugs/
23. exp *neuroleptic drugs/
24. "prescribing (drugs)"/
25. *drug therapy/
26. *drug usage/
27. off-label.tw.
28. or/20-27
29. limit 28 to (140 infancy or 160 preschool age)
30. attention deficit disorder/ or attention deficit disorder with hyperactivity/
31. minimal brain d?sfuction*.tw,sh.
32. (attention deficit* or adhd).ti.
33. addh.tw.
34. or/30-33
35. conduct disorder/
36. aggressive behavior/
37. impulsiveness/
38. exp impulse control disorders/
39. oppositional defiant disorder/
40. distractability/
41. attention span/
42. hyperkinesis/
43. inattent*.tw.
44. (disruptive adj4 disorder?).tw.
45. or/35-44
46. limit 45 to (140 infancy or 160 preschool age)
47. 34 or 46
48. 19 and 47
49. 29 or 48
50. limit 49 to english language
51. limit 50 to human
52. limit 51 to yr="1980 -Current"
53. limit 52 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract" or (chapter or "column/opinion" or "comment/reply" or dissertation or editorial or encyclopedia entry or letter or obituary or review-book or review-software & other))
54. 52 not 53

Appendix B

Forms

Level 1 Title and Abstract Screening Form

1. Should this report be excluded for any of the following reasons?

- ☐ Not English
- ☐ Not a full report of a study (meeting abstract or review or opinion or guideline etc)
- ☐ Published before 1997
- ☐ None of the above

2. Does this report describe outcomes (positive or negative) for any treatment for ADHD, or Disruptive Behavior Disorder, or Oppositional Defiant Disorder (ODD), or Conduct Disorder (CD), or for those at risk for ADHD?

- ☐ Yes
- ☐ Cannot tell
- ☐ No

3. Does this report present results for children <6 years of age, OR for those of any age when the combination of treatment and follow-up is at least 12 months?

- ☐ Yes
- ☐ Cannot tell
- ☐ No

ADHD Level 1 Screening Guide

Question 1.

This question is to remove papers for reasons of the publication characteristics rather than the study characteristics. Only one choice is possible, so please go in order of the answers.

Not English: If the abstract is not English, if there is another language listed at the end of the title in square brackets, check not English. If the journal name seems to be a foreign language, do not check Not English, because some of those are published in English.

Not a full report: If this is a letter to the editor, a proceedings from a meeting, or in some other way, you know that it is not a full report of a study, check Not a full report.

Published before 1997: Check the year in the Citation line at the top of the page. If there is no year given (or it is really strange, such as pre 1960), do not check this line.

Question 2.

This question is to remove citations that are examining only a population that is not included in our review. We initially were looking for just those with ADHD, but have expanded that to include those who have symptoms of ADHD or who were treated for ADHD. Please be inclusive here by answering Cannot tell if you are unsure.

The report must describe outcomes for the treatment. This means that changes due to the treatment should be measured in some way, or differences between one treatment and another should have the results presented.

Question 3.

We are not studying all ADHD populations, only those less than 6 years of age and those of any age if they were treated and followed for a year or more. This will be difficult to tell from the abstract, but if enough information is there, answer Yes or No. If there is no mention of age, or length of follow-up, answer Cannot tell. If it is a paper that examines the adult outcomes of childhood treatment, answer Yes.

Level 2 Title and Abstract Screening Form

1. What is the study design described in this report?

- ☐ RCT or CCT
- ☐ Case-control
- ☐ Cohort/longitude
- ☐ Cross-sectional
- ☐ Before-after [[STOP NOW]]
- ☐ Review/meta-analysis [[STOP NOW]]
- ☐ Case report [[STOP NOW]]
- ☐ Other [[STOP NOW]]
- ☐ Cannot tell

2. What is the diagnosis of the treatment population?

- ☐ ADHD or ADD
- ☐ Disruptive Behavior Disorder (including Oppositional Defiant Disorder – ODD, and ☐ ☐ Conduct Disorder- CD)
- ☐ Aggressiveness, hyperactivity, inattentiveness, impulsivity
- ☐ At risk for ADHD
- ☐ Cannot tell
- ☐ Other related
- ☐ None of the above [[STOP NOW]]

3. What comparisons between included populations have outcomes reported in this study?

Included populations are: Attention Deficit Hyperactivity Disorder (ADHD), Attention Deficit Disorder (ADD), Disruptive Behavior Disorder, Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), at risk for ADHD (aggressive, hyperactive, inattentive, impulsive).

- ☐ Two or more different treatments or two or more different timing or dose of same treatment
- ☐ One part treated and one part given placebo
- ☐ On part treated and one part no treatment
- ☐ Other for included population
- ☐ None of the above included population
- ☐ Cannot tell

Level 3 Full Text Screening Form

1. What is the population for which treatment outcomes are reported?

- ☐ ADHD by DSM or ICD diagnoses
- ☐ Disruptive Behavior Syndrome (included ODD and CD)
- ☐ At risk for ADHD- aggressive, inattentive, hyperactive, temper tantrums, etc
- ☐ Two or more of the above conditions
- ☐ Cannot tell
- ☐ None of the above

2. What treatment or intervention is applied to population described in Question 1?

- ☐ Drug/pharmacological
- ☐ Psychosocial or Behavioral
- ☐ Parent training
- ☐ School or group based intervention
- ☐ Combination or two or more of above treatments
- ☐ Unsure
- ☐ None of the Above

3. Were outcomes reported for two or ore treatment groups (any treatment, placebo, control, waitlist etc) of the included population?

“Treatment” can be drug psychosocial, behavioral, or a combination.

“Outcomes” can be for a treatment compared to:

- i) another dose or different timing or the same treatment?
- ii) another treatment?
- iii) another type of treatment?
- iv) placebo treatment?
- v) no treatment?
- vi) wait list?

- ☐ Yes
- ☐ No
- ☐ Unsure

4. Are Treatment results reported for:

- ☐ Children less than 6 years of age, separately from any subjects great or equal to 12 months
- ☐ A population of any age where the diagnosis of ADHD was by ICD or DSM criteria, AND the combination of treatment and follow-up was greater than or equal to 12 months?
- ☐ Both of above
- ☐ None of the above

Full Text Sorting Level

1. New exclusion status of paper.

- ☐ Include
- ☐ Include, but not useful
- ☐ Exclude for population, >5y without ADHD dx or <6y without included behavior disorder dx
- ☐ Exclude for intervention, no treatment or no comparison of treatments on at least two included population groups
- ☐ Exclude for outcomes, age is >5y and treatment + follow-up is less than 12 months
- ☐ Exclude other –specify

2. Does this paper compare outcomes for children <6 years with an included diagnosis, treated at least two different ways?

- ☐ Yes
- ☐ No

3. Does this paper compare outcomes for subjects >5 years, diagnosed with ADHD, or <6 years with and included diagnosis treated at least two different ways with treatment + follow-up 12 months or longer?

- ☐ Yes
- ☐ No

QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES

COMPONENT RATINGS

A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

- 1 Very likely
- 2 Somewhat likely
- 3 Not likely
- 4 Can't tell

(Q2) What percentage of selected individuals agreed to participate?

- 1 80 - 100% agreement
- 2 60 – 79% agreement
- 3 less than 60% agreement
- 4 Not applicable
- 5 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

B) STUDY DESIGN

Indicate the study design

- 1 Randomized controlled trial
- 2 Controlled clinical trial
- 3 Cohort analytic (two group pre + post)
- 4 Case-control
- 5 Cohort (one group pre + post (before and after))
- 6 Interrupted time series
- 7 Other specify _____
- 8 Can't tell

Was the study described as randomized? If NO, go to Component C.

No Yes

If Yes, was the method of randomization described? (See dictionary)

No Yes

If Yes, was the method appropriate? (See dictionary)

No Yes

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

C) CONFOUNDERS

(Q1) Were there important differences between groups prior to the intervention?

- 1 Yes
- 2 No
- 3 Can't tell

The following are examples of confounders:

- 1 Race
- 2 Sex
- 3 Marital status/family
- 4 Age
- 5 SES (income or class)
- 6 Education
- 7 Health status
- 8 Pre-intervention score on outcome measure

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?

- 1 80 – 100% (most)
- 2 60 – 79% (some)
- 3 Less than 60% (few or none)
- 4 Can't Tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

D) BLINDING

(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?

- 1 Yes
- 2 No
- 3 Can't tell

(Q2) Were the study participants aware of the research question?

- 1 Yes
- 2 No
- 3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

E) DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?

- 1 Yes
- 2 No
- 3 Can't tell

(Q2) Were data collection tools shown to be reliable?

- 1 Yes
- 2 No
- 3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

F) WITHDRAWALS AND DROP-OUTS

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?

- 1 Yes
- 2 No
- 3 Can't tell
- 4 Not Applicable (i.e. one time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).

- 1 80 -100%
- 2 60 - 79%
- 3 less than 60%
- 4 Can't tell
- 5 Not Applicable (i.e. Retrospective case-control)

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3
			Not Applicable

G) INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?

- 1 80 -100%
- 2 60 - 79%
- 3 less than 60%
- 4 Can't tell

(Q2) Was the consistency of the intervention measured?

- 1 Yes
- 2 No
- 3 Can't tell

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?

- 4 Yes
- 5 No
- 6 Can't tell

H) ANALYSES

(Q1) Indicate the unit of allocation (circle one)

community organization/institution practice/office individual

(Q2) Indicate the unit of analysis (circle one)

community organization/institution practice/office individual

(Q3) Are the statistical methods appropriate for the study design?

- 1 Yes
- 2 No
- 3 Can't tell

(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?

- 1 Yes
- 2 No
- 3 Can't tell

GLOBAL RATING

COMPONENT RATINGS

Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

A	SELECTION BIAS	STRONG	MODERATE	WEAK
		1	2	3
B	STUDY DESIGN	STRONG	MODERATE	WEAK
		1	2	3
C	CONFOUNDERS	STRONG	MODERATE	WEAK
		1	2	3
D	BLINDING	STRONG	MODERATE	WEAK
		1	2	3
E	DATA COLLECTION METHOD	STRONG	MODERATE	WEAK
		1	2	3
F	WITHDRAWALS AND DROPOUTS	STRONG	MODERATE	WEAK
		1	2	3

Quality Assessment Tool for Quantitative Studies

Dictionary

The purpose of this dictionary is to describe items in the tool thereby assisting raters to score study quality. Due to under-reporting or lack of clarity in the primary study, raters will need to make judgments about the extent that bias may be present. When making judgments about each component, raters should form their opinion based upon information contained in the study rather than making inferences about what the authors intended. Mixed methods studies can be quality assessed using this tool with the quantitative component of the study.

A) SELECTION BIAS

(Q1) Participants are more likely to be representative of the target population if they are randomly selected from a comprehensive list of individuals in the target population (score very likely). They may not be representative if they are referred from a source (e.g. clinic) in a systematic manner (score somewhat likely) or self-referred (score not likely).

(Q2) Refers to the % of subjects in the control and intervention groups that agreed to participate in the study before they were assigned to intervention or control groups.

B) STUDY DESIGN

In this section, raters assess the likelihood of bias due to the allocation process in an experimental study. For observational studies, raters assess the extent that assessments of exposure and outcome are likely to be independent. Generally, the type of design is a good indicator of the extent of bias. In stronger designs, an equivalent control group is present and the allocation process is such that the investigators are unable to predict the sequence.

Randomized Controlled Trial (RCT)

An experimental design where investigators randomly allocate eligible people to an intervention or control group. A rater should describe a study as an RCT if the randomization sequence allows each study participant to have the same chance of receiving each intervention and the investigators could not predict which intervention was next. If the investigators do not describe the allocation process and only use the words 'random' or 'randomly', the study is described as a controlled clinical trial.

See below for more details.

Was the study described as randomized?

Score YES, if the authors used words such as random allocation, randomly assigned, and random assignment.

Score NO, if no mention of randomization is made.

Was the method of randomization described?

Score YES, if the authors describe any method used to generate a random allocation sequence.

Score NO, if the authors do not describe the allocation method or describe methods of allocation such as alternation, case record numbers, dates of birth, day of the week, and any allocation

procedure that is entirely transparent before assignment, such as an open list of random numbers of assignments.

If NO is scored, then the study is a controlled clinical trial.

Was the method appropriate?

Score YES, if the randomization sequence allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which intervention was next. Examples of appropriate approaches include assignment of subjects by a central office unaware of subject characteristics, or sequentially numbered, sealed, opaque envelopes.

Score NO, if the randomization sequence is open to the individuals responsible for recruiting and allocating participants or providing the intervention, since those individuals can influence the allocation process, either knowingly or unknowingly.

If NO is scored, then the study is a controlled clinical trial.

Controlled Clinical Trial (CCT)

An experimental study design where the method of allocating study subjects to intervention or control groups is open to individuals responsible for recruiting subjects or providing the intervention. The method of allocation is transparent before assignment, e.g. an open list of random numbers or allocation by date of birth, etc.

Cohort analytic (two group pre and post)

An observational study design where groups are assembled according to whether or not exposure to the intervention has occurred. Exposure to the intervention is not under the control of the investigators. Study groups might be non-equivalent or not comparable on some feature that affects outcome.

Case control study

A retrospective study design where the investigators gather 'cases' of people who already have the outcome of interest and 'controls' who do not. Both groups are then questioned or their records examined about whether they received the intervention exposure of interest.

Cohort (one group pre + post (before and after))

The same group is pretested, given an intervention, and tested immediately after the intervention. The intervention group, by means of the pretest, act as their own control group.

Interrupted time series

A time series consists of multiple observations over time. Observations can be on the same units (e.g. individuals over time) or on different but similar units (e.g. student achievement scores for particular grade and school). Interrupted time series analysis requires knowing the specific point in the series when an intervention occurred.

Other:

One time surveys or interviews

C) CONFOUNDERS

By definition, a confounder is a variable that is associated with the intervention or exposure and causally related to the outcome of interest. Even in a robust study design, groups may not be balanced with respect to important variables prior to the intervention. The authors should indicate if confounders were controlled in the design (by stratification or matching) or in the analysis. If the allocation to intervention and control groups is randomized, the authors must report that the groups were balanced at baseline with respect to confounders (either in the text or a table).

D) BLINDING

(Q1) Assessors should be described as blinded to which participants were in the control and intervention groups. The purpose of blinding the outcome assessors (who might also be the care providers) is to protect against detection bias.

(Q2) Study participants should not be aware of (i.e. blinded to) the research question. The purpose of blinding the participants is to protect against reporting bias.

E) DATA COLLECTION METHODS

Tools for primary outcome measures must be described as reliable and valid. If ‘face’ validity or ‘content’ validity has been demonstrated, this is acceptable. Some sources from which data may be collected are described below:

Self reported data includes data that is collected from participants in the study (e.g. completing a questionnaire, survey, answering questions during an interview, etc.).

Assessment/Screening includes objective data that is retrieved by the researchers. (e.g. observations by investigators).

Medical Records/Vital Statistics refers to the types of formal records used for the extraction of the data.

Reliability and validity can be reported in the study or in a separate study. For example, some standard assessment tools have known reliability and validity.

F) WITHDRAWALS AND DROP-OUTS

Score **YES** if the authors describe BOTH the numbers and reasons for withdrawals and drop-outs.

Score **NO** if either the numbers or reasons for withdrawals and drop-outs are not reported.

Score **NOT APPLICABLE** if the study was a one-time interview or survey where there was not follow-up data reported.

The percentage of participants completing the study refers to the % of subjects remaining in the study at the final data collection period in all groups (i.e. control and intervention groups).

G) INTERVENTION INTEGRITY

The number of participants receiving the intended intervention should be noted (consider both frequency and intensity). For example, the authors may have reported that at least 80 percent of the participants received the complete intervention. The authors should describe a method of measuring if the intervention was provided to all participants the same way. As well, the authors should indicate if subjects received an unintended intervention that may have influenced the outcomes. For example, co-intervention occurs when the study group receives an additional intervention (other than that intended). In this case, it is possible that the effect of the intervention may be over-estimated. Contamination refers to situations where the control group accidentally receives the study intervention. This could result in an under-estimation of the impact of the intervention.

H) ANALYSIS APPROPRIATE TO QUESTION

Was the quantitative analysis appropriate to the research question being asked?

An intention-to-treat analysis is one in which all the participants in a trial are analyzed according to the intervention to which they were allocated, whether they received it or not. Intention-to-treat analyses are favoured in assessments of effectiveness as they mirror the noncompliance and treatment changes that are likely to occur when the intervention is used in practice, and because of the risk of attrition bias when participants are excluded from the analysis.

Component Ratings of Study:

For each of the six components A – F, use the following descriptions as a roadmap.

SELECTION BIAS

Strong: The selected individuals are very likely to be representative of the target population (Q1 is 1) **and** there is greater than 80% participation (Q2 is 1).

Moderate: The selected individuals are at least somewhat likely to be representative of the target population (Q1 is 1 or 2); **and** there is 60 - 79% participation (Q2 is 2). ‘Moderate’ may also be assigned if Q1 is 1 or 2 and Q2 is 5 (can’t tell).

Weak: The selected individuals are not likely to be representative of the target population (Q1 is 3); **or** there is less than 60% participation (Q2 is 3) **or** selection is not described (Q1 is 4); and the level of participation is not described (Q2 is 5).

B) DESIGN

Strong: will be assigned to those articles that described RCTs and CCTs.

Moderate: will be assigned to those that described a cohort analytic study, a case control study, a cohort design, or an interrupted time series.

Weak: will be assigned to those that used any other method or did not state the method used.

C) CONFOUNDERS

Strong: will be assigned to those articles that controlled for at least 80% of relevant confounders (Q1 is 2); **or** (Q2 is 1).

Moderate: will be given to those studies that controlled for 60 – 79% of relevant confounders (Q1 is 1) **and** (Q2 is 2).

Weak: will be assigned when less than 60% of relevant confounders were controlled (Q1 is 1) **and** (Q2 is 3) **or** control of confounders was not described (Q1 is 3) **and** (Q2 is 4).

D) BLINDING

Strong: The outcome assessor is not aware of the intervention status of participants (Q1 is 2); **and** the study participants are not aware of the research question (Q2 is 2).

Moderate: The outcome assessor is not aware of the intervention status of participants (Q1 is 2); **or** the study participants are not aware of the research question (Q2 is 2).

Weak: The outcome assessor is aware of the intervention status of participants (Q1 is 1); **and** the study participants are aware of the research question (Q2 is 1); **or** blinding is not described (Q1 is 3 and Q2 is 3).

E) DATA COLLECTION METHODS

Strong: The data collection tools have been shown to be valid (Q1 is 1); **and** the data collection tools have been shown to be reliable (Q2 is 1).

Moderate: The data collection tools have been shown to be valid (Q1 is 1); **and** the data collection tools have not been shown to be reliable (Q2 is 2) **or** reliability is not described (Q2 is 3).

Weak: The data collection tools have not been shown to be valid (Q1 is 2) **or** both reliability and validity are not described (Q1 is 3 and Q2 is 3).

F) WITHDRAWALS AND DROP-OUTS - a rating of:

Strong: will be assigned when the follow-up rate is 80% or greater (Q1 is 1 and Q2 is 1).

Moderate: will be assigned when the follow-up rate is 60 – 79% (Q2 is 2) **OR** Q1 is 4 or Q2 is 5.

Weak: will be assigned when a follow-up rate is less than 60% (Q2 is 3) or if the withdrawals and drop-outs were not described (Q1 is No or Q2 is 4).

Not Applicable: if Q1 is 4 or Q2 is 5.

Appendix C

Excluded Studies

Evaluation of the first 3 years of the Fast Track prevention trial with children at high risk for adolescent conduct problems. *J Abnorm Child Psychol* 2002 Feb;30(1):19-35.
Exclude: Did not compare two included treatments

Alternative treatments for attention deficit hyperactivity disorder. [French, English]. *Paediatrics and Child Health* 8(4)(pp 243-246), 2003 Date of Publication: Apr 2003 2003;(4):243-6.
Exclude: Not an eligible population

The Effects of the Fast Track Program on Serious Problem Outcomes at the End of Elementary School. *Journal of Clinical Child and Adolescent Psychology* 2004 Dec;33(4):650-61.
Exclude: Not an eligible population

Aarskog D, Fevang FO, Klove H, et al. The effect of the stimulant drugs, dextroamphetamine and methylphenidate, on secretion of growth hormone in hyperactive children. *The Journal of Pediatrics* 1977;90(1):136-9.
Exclude: Did not compare two included treatments

Abikoff H, Gittelman R. Does Behav Ther normalize the classroom behavior of hyperactive children? *Archives of General Psychiatry* 41(5)(pp 449-454), 1984 Date of Publication: 1984 1984;(5):449-54.
Exclude: Did not compare two included treatments

Abikoff H, Gittelman R. The normalizing effects of methylphenidate on the classroom behavior of ADDH children. *Journal of Abnormal Child Psychology* 13(1)(pp 33-44), 1985 Date of Publication: 1985 1985;(1):33-44.
Exclude: Did not compare two included treatments

Abramson PR, Abramson SD. A factorial study of a multidimensional approach to aggressive behavior in black preschool age children. *J Genet Psychol* 1974 Sep;125(1st:Half):Half-6
Exclude: Not an eligible population

Ackerman PT, Dykman RA, Holcomb PJ, et al. Methylphenidate effects on cognitive style and reaction time in four groups of children. *Psychiatry Res* 1982;7(2):199-213.
Exclude: Did not compare two included treatments

Ackerman PT, Dykman RA, Holcomb PJ, et al. Effects of high and low dosages of methylphenidate in children with strong and sensitive nervous systems. *Pavlovian Journal of Biological Science* 18(1)(pp 36-48), 1983 Date of Publication: 1983 1983;(1):36-48.
Exclude: Did not compare two included treatments

Ackerman PT, Holcomb PJ, Dykman RA. Effects of reward and methylphenidate on heart rate response

morphology of augmenting and reducing children. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology* 1984;1(4):301-16.
Exclude: Did not compare two included treatments

Ad-Dab'bagh Y, Greenfield B, Milne-Smith J, et al. Inpatient treatment of severe disruptive behaviour disorders with risperidone and milieu therapy. *Can J Psychiatry* 2000 May;45(4):376-82.
Exclude: No eligible outcomes presented

Adams D, Allen D. Assessing the need for reactive behaviour management strategies in children with intellectual disability and severe challenging behaviour. *Journal of Intellectual Disability Research* 45(4)(pp 335-343), 2001 Date of Publication: 2001 2001;(4):335-43.
Exclude: Did not compare two included treatments

Adler L, Dietrich A, Reimherr FW, et al. Safety and tolerability of once versus twice daily atomoxetine in adults with ADHD. *Ann Clin Psychiatry* 2006 Apr;18(2):107-13.
Exclude: Did not compare two included treatments

Adler L, Wilens T, Zhang S, et al. Retrospective safety analysis of atomoxetine in adult ADHD patients with or without comorbid alcohol abuse and dependence. *Am J Addict* 2009 Sep;18(5):393-401.
Exclude: No eligible outcomes presented

Ahmann PA, Waltonen SJ, Olson KA, et al. Placebo-controlled evaluation of Ritalin side effects. *Pediatrics* 1993 Jun;91(6):1101-6.
Exclude: Did not compare two included treatments

Ahmann PA, Theye FW, Berg R, et al. Placebo-controlled evaluation of amphetamine mixture-dextroamphetamine salts and amphetamine salts (Adderall): efficacy rate and side effects. *Pediatrics* 2001 Jan;107(1):E10
Exclude: Did not compare two included treatments

Aird RB, Yamamoto T. Behavior disorders of childhood. *Electroencephalography & Clinical Neurophysiology* 1966 Aug;21(2):148-56.
Exclude: Not an eligible population

Akhondzadeh S, Tavakolian R, Davari-Ashtiani R, et al. Selegiline in the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2003 Aug;27(5):841-5.
Exclude: Did not compare two included treatments

Akhondzadeh S, Mohammadi MR, Khademi M. Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial [ISRCTN64132371].

BMC Psychiatry 2004 Apr 8;4:9

Exclude: Did not compare two included treatments

Alderton HR, Hoddinott BA. A controlled study of the use of thioridazine in the treatment of hyperactive and aggressive children in a children's psychiatric hospital. Canadian Psychiatric Journal 1964;9(3):239-47.

Exclude: Did not compare two included treatments

Alexandris A, Lundell FW. Effect of thioridazine, amphetamine and placebo on the hyperkinetic syndrome and cognitive area in mentally deficient children. Can Med Assoc J 1968;98(2):92-6.

Exclude: Did not compare two included treatments

Alger I. Attention-deficit hyperactivity disorder; AIDS in children and adolescents. Hospital and Community Psychiatry 40(12)(pp 1222-1223), 1989 Date of Publication: 1989 1989;(12):1222-3.

Exclude: Not an eligible population

Alhambra MA, Fowler TP, Alhambra AA. EEG biofeedback: A new treatment option for ADD/ADHD. Journal of Neurotherapy 1995;1(2):39-43.

Exclude: Did not compare two included treatments

Allakhverdiev AR, Horunzheva Y, Kadyrova KG. Influence of functional biocontrol on brain non-specific systems in children with neurotic hyperkinesis. Hum Physiol 1995 Jul;21(4):341-3.

Exclude: Not an eligible population

Allen KE, Henke LB, Harris FR, et al. Control of hyperactivity by social reinforcement of attending behavior. J Educ Psychol 1967 Aug;58(4):231-7.

Exclude: Not an eligible population

Aman MG, Sprague RL. The state-dependent effects of methylphenidate and dextroamphetamine. Journal of Nervous & Mental Disease 1974 Apr;158(4):268-79.

Exclude: Did not compare two included treatments

Aman MG, Werry JS. Methylphenidate in children: Effects upon cardiorespiratory function on exertion. International Journal of Mental Health 1975;4(1-2):119-31.

Exclude: Did not compare two included treatments

Aman MG, Mitchell EA, Turbott SH. The effects of essential fatty acid supplementation by Efamol in hyperactive children. Journal of Abnormal Child Psychology 15(1)(pp 75-90), 1987 Date of Publication: 1987 1987;(1):75-90.

Exclude: Did not compare two included treatments

Aman MG, Marks RE, Turbott SH, et al. Clinical effects of methylphenidate and thioridazine in intellectually subaverage children. J Can Acad Child Adolesc Psychiatry 1991 Mar;30(2):246-56.

Exclude: Did not compare two included treatments

Aman MG, Kern RA, McGhee DE, et al. Fenfluramine and methylphenidate in children with mental retardation and attention deficit hyperactivity disorder: laboratory effects. J Autism Dev Disord 1993;23(3):491-506.

Exclude: Did not compare two included treatments

Aman MG, Kern RA, McGhee DE, et al. Fenfluramine and methylphenidate in children with mental retardation and ADHD: clinical and side effects. J Can Acad Child Adolesc Psychiatry 1993 Jul;32(4):851-9.

Exclude: No eligible outcomes presented

Aman MG, De Smedt G, Derivan A, et al. Double-blind, placebo-controlled study of risperidone for the treatment of disruptive behaviors in children with subaverage intelligence. Am J Psychiatry 2002 Aug;159(8):1337-46.

Exclude: Did not compare two included treatments

Aman MG, Armstrong S, Buican B, et al. Four-year follow-up of children with low intelligence and ADHD: a replication. Res Dev Disabil 2002 Mar;23(2):119-34.

Exclude: Did not compare two included treatments

Aman MG, Hollway JA, Leone S, et al. Effects of risperidone on cognitive-motor performance and motor movements in chronically medicated children. Res Dev Disabil 2009 Mar;30(2):386-96.

Exclude: No eligible outcomes presented

Aman MG, Marks RE, Turbott SH, et al. Methylphenidate and thioridazine in the treatment of intellectually subaverage children: Effects on cognitive-motor performance. J Can Acad Child Adolesc Psychiatry 1991 Sep;30(5):816-24.

Exclude: Did not compare two included treatments

Ambrosino SV, De Fonte TM. A psychoeducational study of the hyperkinetic syndrome. Psychosomatics: Journal of Consultation Liaison Psychiatry 1973 Jul;14(4):207-13.

Exclude: Did not compare two included treatments

Amery B, Minichiello MD, Brown GL. Aggression in hyperactive boys: Response to d-amphetamine. Journal of the American Academy of Child Psychiatry 23(3)(pp 291-294), 1984 Date of Publication: 1984 1984;(3):291-4.

Exclude: Did not compare two included treatments

Amon KL, Campbell A. Can Children with AD/HD Learn Relaxation and Breathing Techniques through Biofeedback Video Games? Australian Journal of Educational & Developmental Psychology 2008;8:72-84.

Exclude: Did not compare two included treatments

Anastopoulos AD, Shelton TL, Dupaul GJ, et al. Parent training for attention-deficit hyperactivity disorder: Its impact on parent functioning. Journal of Abnormal Child Psychology 21(5)(pp 581-596), 1993 Date of Publication: 1993 1993;(5):581-96.

Exclude: Did not compare two included treatments

Anderson K, Barabasz M, Barabasz A, et al. Efficacy of Barabasz's instant alert hypnosis in the treatment of ADHD with neurotherapy. *Child Study Journal* 2000;30(1):51-62.
Exclude: Did not compare two included treatments

Anderson RP, Halcomb CG, Gordon W, et al. Measurement of attention distractibility in LD children. *Academic Therapy* 1974;9(5):261-6.
Exclude: Not an eligible population

Angold A, Erkanli A, Egger HL, et al. Stimulant treatment for children: a community perspective. *J Can Acad Child Adolesc Psychiatry* 1984;39(8):975-84.
Exclude: No eligible outcomes presented

Arbuthnot J, Gordon DA. Behavioral and cognitive effects of a moral reasoning development intervention for high-risk behavior-disordered adolescents. *J Consult Clin Psychol* 1986;54(2):208-16.
Exclude: Not an eligible population

Ardoin SP, Martens BK. Testing the ability of children with attention deficit hyperactivity disorder to accurately report the effects of medication on their behavior. *J Appl Behav Anal* 2000;33(4):593-610.
Exclude: Did not compare two included treatments

Arnett PA, Fischer M, Newby RF. "The effect of Ritalin on response to reward and punishment in children with ADHD": Addendum. *Child Study Journal* 1996;26(2):161
Exclude: Not an eligible population

Arnett PA, Fischer M, Newby RF. The effect of Ritalin on response to reward and punishment in children with ADHD. *Child Study Journal* 1996;26(1):51-70.
Exclude: Did not compare two included treatments

Arnold LE, Wender PH, McCloskey K, et al. Levoamphetamine and dextroamphetamine: comparative efficacy in the hyperkinetic syndrome. Assessment by target symptoms. *Arch Gen Psychiatry* 1972;27(6):816-22.
Exclude: Did not compare two included treatments

Arnold LE, Kiriluk V, Corson SA, et al. Levoamphetamine and dextroamphetamine: differential effect on aggression and hyperkinesis in children and dogs. *Am J Psychiatry* 1973;130(2):165-70.
Exclude: Not an eligible population

Arnold LE, Abikoff HB, Cantwell DP, et al. National Institute of Mental Health Collaborative Multimodal Treatment Study of Children with ADHD (the MTA). Design challenges and choices. *Arch Gen Psychiatry* 1997 Sep;54(9):865-70.
Exclude: No eligible outcomes presented

Arnold LE, Pinkham SM, Votolato N. Does zinc moderate essential fatty acid and amphetamine treatment of attention-deficit/hyperactivity disorder? *J Child Adolesc Psychopharmacol* 2000;10(2):111-7.
Exclude: Not an eligible population

Arnold LE, Lindsay RL, Conners CK, et al. A double-blind, placebo-controlled withdrawal trial of dexamethylphenidate hydrochloride in children with attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2004;14(4):542-54.
Exclude: Did not compare two included treatments

Arnold LE, Chuang S, Davies M, et al. Nine months of multicomponent behavioral treatment for ADHD and effectiveness of MTA fading procedures. *J Abnorm Child Psychol* 2004 Feb;32(1):39-51.
Exclude: No eligible outcomes presented

Arnold LE, Aman MG, Cook AM, et al. Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. *J Can Acad Child Adolesc Psychiatry* 2006 Oct;45(10):1196-205.
Exclude: Did not compare two included treatments

Arnold LE, Amato A, Bozzolo H, et al. Acetyl-L-carnitine (ALC) in attention-deficit/hyperactivity disorder: a multi-site, placebo-controlled pilot trial. *J Child Adolesc Psychopharmacol* 2007 Dec;17(6):791-802.
Exclude: Did not compare two included treatments

Arnold LE. Vestibular and visual rotational stimulation as treatment for attention deficit and hyperactivity. *Am J Occup Ther* 1985 Feb;39(2):84-91.
Exclude: Did not compare two included treatments

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Exclude: Not an eligible population

Arnold LE, Amato A, Bozzolo H, et al. Acetyl-L-carnitine in attention-deficit/hyperactivity disorder: A multi-site, placebo-controlled pilot trial. *J Child Adolesc Psychopharmacol* 2007 Dec;17(6):791-801.
Exclude: Did not compare two included treatments

Arnold SC, Forehand R. A comparison of cognitive training and response cost procedures in modifying cognitive styles of impulsive children. *Cognitive Therapy and Research* 2(2)(pp 183-187), 1979 Date of Publication: 1979 1979;2(2):183-7.
Exclude: No eligible outcomes presented

Atkins MS, Frazier SL, Birman D, et al. School-based mental health services for children living in high poverty urban communities. *Administration & Policy in Mental Health* 2006 Mar;33(2):146-59.
Exclude: Not an eligible population

Augenbraun B, Reid HL, Friedman DB. Brief intervention as a preventive force in disorders of early childhood. *Am J Orthopsychiatry* 1967 Jul;37(4):697-702.
Exclude: Not an eligible population

Augimeri LK, Farrington DP, Koegl CJ, et al. The SNAPTM Under 12 Outreach Project: Effects of a community based program for children with conduct problems. *Journal of Child and Family Studies* 2007 Dec;16(6):799-807.

Exclude: Not an eligible population

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Exclude: Did not compare two included treatments

August GJ, Lee SS, Bloomquist ML, et al. Dissemination of an evidence-based prevention innovation for aggressive children living in culturally diverse, urban neighborhoods: the Early Risers effectiveness study. *Prevention Science* 2003 Dec;4(4):271-86.

Exclude: Did not compare two included treatments

August GJ, Egan EA, Realmuto GM, et al. Four years of the early risers early-age-targeted preventive intervention: Effects on aggressive children's peer relations. *Behav Ther* 34(4)(pp 453-470), 2003 Date of Publication: Sep 2003 2003;(4):453-70.

Exclude: No eligible outcomes presented

Bailey V. Cognitive-behavioral therapies for children and adolescents. *Advances in Psychiatric Treatment* 7(3)(pp 224-232), 2001 Date of Publication: 2001 2001;(3):224-32.

Exclude: Not an eligible population

Baker-Henningham H, Walker S. A qualitative study of teacher's perceptions of an intervention to prevent conduct problems in Jamaican pre-schools. *Child Care Health Dev* 2009 Sep;35(5):632-42.

Exclude: No eligible outcomes presented

Bakermans-Kranenburg MJ, van IJzendoorn MH, Mesman J, et al. Effects of an attachment-based intervention on daily cortisol moderated by dopamine receptor D4: a randomized control trial on 1- to 3-year-olds screened for externalizing behavior. *Development & Psychopathology* 2008;20(3):805-20.

Exclude: No eligible outcomes presented

Bakken RJ, Paczkowski M, Kramer HP, et al. Effects of atomoxetine on attention-deficit/hyperactivity disorder in clinical pediatric treatment settings: a naturalistic study. *Current Medical Research & Opinion* 2008 Feb;24(2):449-60.

Exclude: No eligible outcomes presented

Baldwin RW, Kenny TJ. Thioridazine in the management of organic behavior disturbances in children. *Current Therapeutic Research, Clinical & Experimental* 1966 Aug;8(8):373-7.

Exclude: Not an eligible population

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Exclude: Did not compare two included treatments

Ballinger CT, Varley CK, Nolen PA. Effects of methylphenidate on reading in children with attention deficit disorder. *American Journal of Psychiatry* 141(12)(pp 1590-1593), 1984 Date of Publication: 1984 1984;(12):1590-3.

Exclude: Did not compare two included treatments

Balthazor MJ, Wagner RK, Pelham WE. The specificity of the effects of stimulant medication on classroom learning-related measures of cognitive processing for attention deficit disorder children. *J Abnorm Child Psychol* 1991;19(1):35-52.

Exclude: Did not compare two included treatments

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Exclude: Did not compare two included treatments

Banaschewski T, Bismans F, Ziegler H, et al. Evaluation of sensorimotor training in children with ADHD. *Perceptual & Motor Skills* 2001 Feb;92(1):137-49.

Exclude: Did not compare two included treatments

Banerjee S, Ayyash HF. Does atomoxetine increase the risk of aggression and hostility in children with attention deficit hyperactivity disorder? *Archives of Disease in Childhood Education & Practice* 2008 Aug;93(4):131-2.

Exclude: No eligible outcomes presented

Banerjee S. Use of atomoxetine in children and adolescents with ADHD. *Progress in Neurology and Psychiatry* 13(2)(pp 18-20), 2009 Date of Publication: 2009 2009;(2):18-20.

Exclude: Did not compare two included treatments

Barcai A. The emergence of neurotic conflict in some children after successful administration of dextroamphetamine. *J Child Psychol Psychiatry* 1969 Dec;10(4):269-76.

Exclude: Not an eligible population

Barkley RA. The effects of methylphenidate on various types of activity level and attention in hyperkinetic children. *J Abnorm Child Psychol* 1977 Dec;5(4):351-69.

Exclude: Did not compare two included treatments

Barkley RA, Cunningham CE. Stimulant drugs and activity level in hyperactive children. *Am J Orthopsychiatry* 1979 Jul;49(3):491-9.

Exclude: Did not compare two included treatments

Barkley RA, Cunningham CE. The effects of methylphenidate on the mother-child interactions of

hyperactive children. *Arch Gen Psychiatry* 1979 Feb;36(2):201-8.

Exclude: Did not compare two included treatments

Barkley RA, Strzelecki E, Karlsson J, et al. Effects of age and ritalin dosage on the mother-child interactions of hyperactive children. *J Consulting Clin Psychol* 52(5)(pp 750-758), 1984 Date of Publication: 1984 1984;(5):750-8.

Exclude: No eligible outcomes presented

Barkley RA, McMurray MB, Edelbrock CS, et al. The response of aggressive and nonaggressive ADHD children to two doses of methylphenidate. *J Am Acad Child Adolesc Psychiatry* 28(6)(pp 873-881), 1989 Date of Publication: 1989 1989;(6):873-81.

Exclude: Did not compare two included treatments

Barkley RA. Hyperactive girls and boys: Stimulant drug effects on mother-child interactions. *J Child Psychol Psychiatry* 30(3)(pp 379-390), 1989 Date of Publication: 1989 1989;(3):379-90.

Exclude: Did not compare two included treatments

Barkley RA, McMurray MB, Edelbrock CS, et al. Side effects of methylphenidate in children with attention deficit hyperactivity disorder: a systemic, placebo-controlled evaluation. *Pediatrics* 1990 Aug;86(2):184-92.

Exclude: Did not compare two included treatments

Barkley RA, Dupaul GJ, McMurray MB. Attention deficit disorder with and without hyperactivity: clinical response to three dose levels of methylphenidate. *Pediatrics* 1991;87(4):519-31.

Exclude: Did not compare two included treatments

Barkley RA, Fischer M, Newby RF, et al. Development of a multimethod clinical protocol for assessing stimulant drug response in children with attention deficit disorder. *J Clin Child Psychol* 1988 Mar;17(1):14-24.

Exclude: Did not compare two included treatments

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Exclude: Did not compare two included treatments

Barnett R, Maruff P, Vance A, et al. Abnormal executive function in attention deficit hyperactivity disorder: the effect of stimulant medication and age on spatial working memory. *Psychol Med* 2001 Aug;31(6):1107-15.

Exclude: Did not compare two included treatments

Barratt ES, Kent TA, Bryant SG, et al. A controlled trial of phenytoin in impulsive aggression. *J Clin Psychopharmacol* 1991;11(6):388-9.

Exclude: Not an eligible population

Barrera M, Jr., Biglan A, Taylor TK, et al. Early elementary school intervention to reduce conduct problems: a randomized trial with Hispanic and non-Hispanic

children. *Prevention Science* 2002 Jun;3(2):83-94.

Exclude: Not an eligible population

Barry RJ, Clarke AR, Hajos M, et al. Acute atomoxetine effects on the EEG of children with Attention-Deficit/Hyperactivity Disorder. *Neuropharmacology* 57(7-8)(pp 702-707), 2009 Date of Publication: December 2009 2009;(7-8):702-7.

Exclude: Did not compare two included treatments

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Exclude: Did not compare two included treatments

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Exclude: Did not compare two included treatments

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Exclude: No eligible outcomes presented

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Exclude: Did not compare two included treatments

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Exclude: Did not compare two included treatments

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Exclude: Not an eligible population

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Exclude: Did not compare two included treatments

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Exclude: Did not compare two included treatments

Bedard AC, Martinussen R, Ickowicz A, et al. Methylphenidate improves visual-spatial memory in children with attention-deficit/hyperactivity disorder. *J Can Acad Child Adolesc Psychiatry* 2004 Mar;43(3):260-8.
Exclude: Did not compare two included treatments

Behan J, Fitzpatrick C, Sharry J, et al. Evaluation of the Parenting Plus Programme. *Irish Journal of Psychology* 2001;22(3-4):238-56.
Exclude: Did not compare two included treatments

Belanger SA, Vanasse M, Spahis S, et al. Omega-3 fatty acid treatment of children with attention-deficit hyperactivity disorder: A randomized, double-blind, placebo-controlled study. *Paediatrics and Child Health* 14(2)(pp 89-98), 2009 Date of Publication: 2009 2009;(2):89-98.
Exclude: Did not compare two included treatments

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Exclude: Did not compare two included treatments

Bellgrove MA, Hawi Z, Kirley A, et al. Association between dopamine transporter (DAT1) genotype, left-sided inattention, and an enhanced response to methylphenidate in attention-deficit hyperactivity disorder. *Neuropsychopharmacology* 2005 Dec;30(12):2290-7.
Exclude: Did not compare two included treatments

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Exclude: Did not compare two included treatments

Bennett DE, Zentall SS, French BF, et al. The Effects of Computer-Administered Choice on Students With and Without Characteristics of Attention-Deficit/Hyperactivity Disorder. *Behavioral Disorders* 2006 Feb;31(2):189-203.
Exclude: Did not compare two included treatments

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Exclude: Not an eligible population

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