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Psychopharmacological and Other Treatments in Preschool Children with Attention-Deficit/ Hyperactivity Disorder: Current Evidence and Practice

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Abstract

Objective: This article reviews rational approaches to treating attention-deficit/hyperactivity disorder (ADHD) in preschool children, including pharmacological and nonpharmacological treatments. Implications for clinical practice are discussed.
Data Sources: We searched MEDLINE, PsychINFO, Cumulative Index to Nursing & Allied Health, Educational Resources Information Center, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects for relevant literature published in English from 1967 to 2007 on preschool ADHD. We also reviewed the references cited in identified reports.
Study Selection: Studies were reviewed if the sample included at least some children younger than 6 years of age or attending kindergarten, the study participants had a diagnosis of ADHD or equivalent symptoms, received intervention aimed at ADHD symptoms, and included a relevant outcome measure.
Data Extraction: Studies were reviewed for type of intervention and outcome relevant to ADHD and were rated for the level of evidence for adequacy of the data to inform clinical practice.
Conclusions: The current level of evidence for adequacy of empirical data to inform clinical practice for short-term treatment of ADHD in preschool children is Level A for methylphenidate and Level B for parent behavior training, child training, and additive-free elimination diet.

Introduction

Attention deficit/hyperactivity disorder (ADHD) frequently begins between 2 and 4 years of age (Connor 2002; Egger and Angold 2006). It is associated with significant impairment in terms of emotional distress for the preschool child and the caregivers (DuPaul et al. 2001), expulsion from daycare or early education settings (Blackman 1999), demands on the caregiver's time, exclusion from family events, and accident proneness and other safety concerns (Lahey et al. 2004; Rappley et al. 1999). Children with ADHD have comorbid mental health and chronic health problems and are frequent users of the healthcare system (Rappley et al. 2002). As shown by several prospective longitudinal follow up studies, behavior problems in preschool children persist to school-age years and continue to be associated with significant impairment (Campbell and Ewing 1990; Campbell et al. 2000; Egeland et al. 1990; Fischer et al. 1984; Lahey et al. 2004; Lavigne et al. 1998; McGee et al. 1991; Richman et al. 1982). In a recent study, 79.2% of the preschool children who met full diagnostic criteria for ADHD and 34.5% of the preschool children who met criteria in one situation only at initial assessment continued to meet full ADHD diagnostic criteria and exhibited global academic and social impairment three years later (Lahey et al. 2004).

Impairment from ADHD and persistence of problems at later ages underscores the need for early intervention in preschool children with ADHD (Beckwith 2000; Bierman et al. 2007; Campbell 2002; Conduct Problems Prevention Research Group 1999; Elliot et al. 2002; Petras et al. 2008; Shure et al. 2001). Recently, the Preschool Psychopharmacology Working Group (PPWG) reviewed pharmacologi-

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cal treatment studies in preschool children and proposed treatment algorithms for preschool psychiatric disorders (Gleason et al. 2007), however the nonpharmacological treatments for ADHD were not reviewed in detail. The primary objective of this paper is to review rational approaches to pharmacological and nonpharmacological treatment of ADHD in preschoolers and the implications for clinical practice. For the purposes of this paper, we define preschool age as prior to starting formal schooling, i.e., first grade. Hence, we reviewed studies that included children in kindergarten and/or younger than 6 years of age. The Food and Drug Administration (FDA) provides additional demarcation for children younger than 6 years. Most of the pharmacological agents for treatment of ADHD are approved by the FDA only for children older than 6 years (with the exception of amphetamines), and the FDA considers their use in children younger than 6 years as "off-label."

Methods and Review

We searched MEDLINE, PsychINFO, Cumulative Index to Nursing & Allied Health, Educational Resources Information Center, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects for relevant literature on treatment of preschool ADHD. We also reviewed the references cited in identified reports to locate other relevant studies. Due to limited literature in this area, we reviewed both controlled and non-controlled studies. The reviewed studies met the following inclusion criteria: Published in English in the past 40 years (between 1967 to 2007); included at least some children younger than 6 years of age and/or attending kindergarten who had a diagnosis of ADHD; or exhibited behavior problems that are part of the ADHD diagnostic criteria, involved intervention aimed at ADHD symptoms, and included an outcome measure to monitor ADHD symptoms. To determine the level of evidence to inform clinical practice, we adapted the International Psychopharmacology Algorithm Project criteria (Jobson and Potter 1995) previously used by Judice and Mayes (2003) to categorize psychopharmacology treatments in preschool children. Since most of the reviewed child training studies were single case design experiments (state of current evidence for child training studies), based on the Task Force on Promotion and Dissemination of Psychological Procedures guidelines (Task Force on Psychological Intervention Guidelines 1995) previously used by Chorpita et al. (2002) to assess efficacy of psychosocial treatment studies in children and adolescents, we modified the criteria to include single case design experiments in addition to randomized controlled trials.

A treatment was considered to have evidence at Level A, if it demonstrated a significant difference on an ADHD outcome variable in a sample of preschoolers with a Diagnostic and Statistical Manual (DSM) diagnosis of ADHD in at least two randomized controlled trials (RCT) or two series of single case design experiments comparing randomly assigned active treatment to a comparison treatment or placebo. A treatment was considered to have evidence at Level B, if it demonstrated a significant difference on an ADHD outcome variable in a sample of preschoolers with a DSM diagnosis of ADHD in one RCT, two or more RCTs with mixed results, or one series of single case design experiments comparing randomly assigned active treatment to a comparison treatment or placebo. Level C was assigned to a treatment to indicate that data were based on uncontrolled trials, case reports, retrospective chart reviews, or informed clinical opinion.

Treatment of Preschool Attention-Deficit/ Hyperactivity Disorder

Here we review the current available evidence for psychopharmacological and nonpsychopharmacological interventions (psychosocial and alternative treatments) and clinical implications for preschool children with ADHD. Prior to starting any treatment, it is important to conduct a comprehensive assessment that is contextually relevant and takes into account the rapid developmental changes occurring during preschool years. Because a comprehensive discussion of the assessment process for diagnosing ADHD in preschool children is beyond the scope of this paper, the reader is referred to several excellent reviews addressing preschool nosology, diagnosis, and assessment (Angold et al. 2004; Campbell 2002; Carter et al. 2004; Egger and Angold 2006; Emde et al. 1993; Task Force on Research Diagnostic Criteria: Infancy and Preschool 2003). In general, a multi-method and multi-informant evaluation extending over multiple appointments to assess symptomatology and impairment in multiple environments and caregiving contexts is recommended (Carter et al. 2004; Gleason et al. 2007). A combination of diagnostic interviews and parent and teacher rating scales, with psychometric data in preschoolers, are commonly employed to aid in the diagnostic and assessment process. Examples of the parent and teacher rating scales include Conners' Rating Scales-Revised (CRS-R) (Conners 2001), Swanson, Nolan and Pelham (SNAP) rating scale (Swanson 1992), Child Behavior Checklist-$1\frac{1}{2}$ (CBCL-$1\frac{1}{2}$) (Achenbach and Rescorla 2000), and ADHD Rating Scale (ADHD-RS) (DuPaul 1998; Gimpel and Kuhn 2000). The Preschool Age Psychiatric Assessment (PAPA) (Egger et al. 2006) is a reliable and valid semi-structured diagnostic parent-interview that is widely used in research studies of preschool pathology. However, clinical settings may find the cost and length of the PAPA training and administration to be a barrier for its use in routine clinical practice. Nonetheless, adequate history, mental status examination, and collateral information are important for developing an appropriate treatment plan that addresses the biopsychosocial issues specific to each family.

Psychopharmacological treatment

There are several challenges to psychopharmacological treatment of preschool children with ADHD. Preschool age is a period of continued rapid neuronal maturation including synaptic remodeling and construction. Cortical synaptic density reaches its maximum at age 3 and is substantially modified by the pruning process from ages 3 to 7 years (Huttenlocher 1990). Cerebral metabolic rate peaks between 3 and 4 years of age (Chugani 1987). Aminergic systems play an important role in neurogenesis, neuronal migration, axonal outgrowth, and synaptogenesis (Coyle 1997) and are also the

targets of action for many psychopharmacological agents as indicated by studies in preclinical models. Thus, clinicians are faced with a dilemma. On one hand, whether it is prudent to recommend exposing the rapidly developing brain of a preschool child to psychopharmacological agents. On the other hand, clinicians also need to consider the consequences of an untreated disorder. Early exposure to adverse environmental circumstances and stress has been shown to result in long-lasting impact on the brain and emotional regulation of animals and humans (Graham et al. 1999; Matthews 2002; Nemeroff 2004).

Information about the use of psychopharmacological agents for treatment of ADHD is available mostly for school age children. In school age children, psychostimulants are the mainstay of treatment for ADHD; nonstimulant psychopharmacological agents are frequently recommended as a second-line treatment if a school age child's ADHD symptoms do not adequately respond to stimulants (Dulcan and Benson 1997). Recently, a nonstimulant psychopharmacological agent, atomoxetine, has been shown to be a safe and effective treatment of ADHD in school age children (Kratochvil et al. 2004; Michelson et al. 2001). Comparatively, there is limited information on the use of psychopharmacological agents for treatment of ADHD in preschool children. No pharmacokinetic and dose finding studies to identify dosage and frequency of drug administration in preschool children are available. Until recently, clinicians were left to extrapolate findings from older children to preschool children. However, medications used in older children may have specific toxicities in preschool children (Wigal et al. 2006), and there may be differences in efficacy in preschool children compared to school age children (Greenhill et al. 2006). Additionally, extrapolation to preschool children of data collected in older children is not always possible due to differences in development.

There are over 250 published studies of psychopharmacological agents in school age children with ADHD (Wilens et al. 2002). In contrast, there are a total of 24 published reports (blinded and open-label studies) on the use of psychopharmacological agents involving over 495 preschool children with ADHD. Of the 24 published reports (Tables 1 and 2), 20 published reports are on the use of stimulants, 2 published case reports on the use of $\alpha 2$ agonists, 1 published case report on the use of atomoxetine, and 1 published case report on the use of fluoxetine in preschool children with ADHD.

Psychostimulant studies. Of the 20 published studies on the use of stimulants in preschool children, 12 double-blind group treatment studies (one parallel groups, 10 crossover and 1 ABA design) included 417 preschool children treated with methylphenidate (MPH). Two double-blind MPH/placebo crossover studies included both preschool and older children, but did not specify the number of preschool participants (Barkley 1988; Fischer and Newby 1991); and one blinded time series treated one preschool child with dextroamphetamine (Speltz et al. 1988). The remaining five published reports are open-label studies or case reports involving a total of 61 preschool children treated with MPH or dextroamphetamine (Alessandri and Schramm 1991; Byrne et al. 1998; Cohen et al. 1981; Ghuman et al. 2001; Stiefel and Dossetor 1998).

Twelve of the fifteen blinded MPH studies treated typically developing preschool children with ADHD; seven studies included only preschool children (Barkley 1988; Conners 1975; Firestone et al. 1998; Greenhill et al. 2006; Musten et al. 1997; Schleifer et al. 1975; Short et al. 2004; Speltz et al. 1988), while the other six studies included both preschool and older children (Barkley et al. 1988; 1985; 1984; Chacko et al. 2005; Cunningham et al. 1985; Fischer and Newby 1991). Of the other two studies, one included a mixture of inpatient or outpatient preschool and school age children with ADHD who were either typically developing or had autism or other developmental disorders (Mayes et al. 1994), and the one remaining blinded study treated preschool children with developmental disorders (Handen et al. 1999). The diagnostic procedure used most frequently included a combination of clinical interview and dimensional rating scales. With the exception of the recent PATS study, sample size was small ranging from 11–59, duration of the psychostimulant trials ranged from 3–9 weeks, and stimulant dose ranged from 0.15–0.6 mg/kg. Mixed outcomes were reported for efficacy. Based on direct observation of the preschool children's nursery school behavior, one study reported no improvement with MPH compared to placebo (Schleifer et al. 1975). Positive response to MPH was reported by other investigators in 80%–83% of typically developing preschool children (Conners 1975; Greenhill et al. 2006; Short et al. 2004) and 71%–73% of preschool children with developmental disorders (Handen et al. 1999). Data on side effect profile in preschool children was also divergent. Rates of side effects ranged from minimal or clinically negligible (Conners 1975) to 89% in typically developing preschool children (Schleifer et al. 1975) and 45%–50% in preschool children with developmental disorders (Handen et al. 1999; Mayes et al. 1994). Dysphoria, crying, whining, irritability, and solitary play were more frequently reported in preschool children than seen in older children.

The 6-site PATS study randomized 165 preschool children (3–5.5 years) diagnosed with ADHD in a placebo-controlled, double-blind crossover design, to one week each of 4 MPH doses (1.25 mg, 2.5 mg, 5 mg and 7.5 mg TID) and placebo. With the exception of the lowest MPH dose, improvements in parent- and teacher-rated ADHD symptoms were reported with MPH compared to placebo; the 7.5 mg TID dose was found to be the most effective. The effect sizes (Cohen's d) in the intent-to-treat sample ranged from 0.4–0.8 and were smaller than those reported for school age children treated with MPH (Greenhill et al. 2006). Interestingly, secondary analyses of the PATS efficacy data showed that preschoolers with ADHD with no or one comorbid disorder (primarily oppositional defiant disorder [ODD]) had treatment responses (Cohen's $d = 0.89$ and 1.00, respectively) at the same level as found in school age children (Ghuman et al. 2007). Preschoolers with 2 comorbid disorders had moderate treatment response (Cohen's $d = 0.56$) and preschoolers with 3 or more comorbid disorders did not respond to MPH (Ghuman et al. 2007). However, caution is needed in the generalization of the findings as there were only 15 preschoolers (9% of the sample) with 3 or more comorbid disorders compared to 150 preschoolers with two comorbid disorders ($n = 34$, 21% of the sample), one comorbid disorder ($n = 69$, 42% of the sample) or no comorbid disorders ($n = 47$, 28% of the sample). In addition to decreased appetite, stomach ache,

Table 1. Published Blinded Studies of Stimulant Treatment of Attention-Deficit/Hyperactivity Disorder in Preschool Children

Authors	*Age Range (Mean ± SD)*	*N/* ***n < 6 years***	*Procedure for ADHD Diagnosis*	*Intervention Medication/ Dose*	*Study Design/ Duration*	*Outcome Assessment (for ADHD and disruptive behaviors)*	*Study Outcome*	*Side Effects/Safety*
Conners, 1975	<6 years (57.7 ± 13.2 months)	59/**59**	Clinical interview, parent questionnaire	(MPH 11.8 mg/day (1.5 mg/kg/day)	Double-blind, 2 parallel groups (MPH, placebo)/ 6 weeks	Parent Behavior Rating Scale, Global Clinical Improvement Rating, measures of vigilance, seat activity & impulsivity	Significant clinical improvement (93% improved on MPH, 11.5% improved on placebo) as rated by the physician on the Global Clinical Improvement Rating, significant reduction in restlessness and disruptive behavior as rated by the parents on the Parent Behavior Rating Scale. Measures of vigilance, seat activity & impulsivity did not show significant difference between MPH and placebo	Minimal side effects, trend towards elevated blood pressure in the MPH group
Schleifer et al., 1975	40–58 months (49 ± months[1])	26/**26**	Clinical interview	MPH 2.5–30 mg/day on a qd or bid schedule	Double-blind, crossover (placebo & MPH "optimal dose")/ 4–6 weeks	Nursery school observation, Hyperactivity Rating Scale measures of reflectivity-impulsivity, field independence and motor impulsivity	Improvement based on caregiver report, no improvement on nursery school observation or psychological measures	Dysphoria, social withdrawal, poor appetite, difficulty getting to sleep
Barkely et al., 1984	48–119 months (60.8 ± 7.6 months)	54/**18**	Clinical interview, Conners' Rating Scale-Parent (CRS-P), WWPARS	MPH 0.15 mg/kg bid, 1.5 mg/kg bid	Double-blind, crossover (placebo & 2 MPH doses)/ 3 weeks	Mother-child interaction	Significant improvement in child compliance and off-task behavior with MPH, "normalizing" effect of MPH on mother-child interactions	More frequent side effects on high MPH dose than low dose or placebo
Barkley et al., 1985	5–9 years (89 months[1])	60/**12**	Psychiatric assessment, CRS-P, Werry Weiss Peters Activity Rating Scale (WWPARS), Home Situations Questionnaire (HSQ)	MPH 0.3 mg/kg bid. 0.7 mg/kg bid	Double-blind, crossover (placebo & 2 MPH doses)/ 4 weeks	Mother-child interaction during free play and task periods	Child compliance and length of sustained compliance improved with the higher dose during the task period, drug effects did not differ during free play or across age levels	Greater number of side effects on MPH compared to placebo

Cunningham et al., 1985	4–6 years (68 months[1])	42/**12**	Clinical diagnosis CRS-P	Single dose of MPH 0.15 mg/kg, 0.50 mg/kg	Double-blind, crossover (placebo & 2 MPH doses)/ 4 sessions	Videotaped observations during freeplay, co-operative task, and simulated school setting	↓ actometer readings & ↑ on-task behavior during the simulated school setting, linear dose response, optimal ↓ in controlling and domineering interactions observed at 0.15 mg/kg dose with no incremental benefit on 0.50 mg/kg dose	Side effects were not monitored
Barkley, 1988	31–59 months (46.8 ± 6.7 months)	27/**27**	Clinical interview, CRS-P, WWPARS, HSQ	MPH 0.15 mg/kg bid, 1.5 mg/kg bid	Triple-blind, crossover (placebo & 2 MPH doses)/ 3 weeks	Mother-child interaction	↑ rates of compliance and length of sustained compliance with maternal commands, and on task behavior on higher dose during the task period	Trend for more frequent side effects on MPH compared to placebo
Barkley, at al., 1988	5–12 years (8.5 ± 2.3 years)	23/**not specified**	Semistructured parent interview, CRS-P or CRS-Teacher (CRS-T)	MPH 0.3 mg/kg bid, 0.5 mg/kg bid	Double-blind, crossover (placebo & 2 MPH doses)/ 3 weeks	Gordon Diagnostic System (GDS) for vigilance and impulse control, playroom observation during a restricted academic situation, CRS-P, CRS-T, HSQ, School Situations Questionnaire (SSQ)	80% of the children responded positivly to MPH on parent and teacher ratings of hyperactivity and disruptive behaviors, and ↓ off-task and hyperacctivity ratings during playroom observation (restricted academic situation). Significant main drug effects for 16 of the 31 outcome measures, mostly on teacher ratings and observations during the restricted academic situation, both doses were equally effective	No difference in the number or severity of side effects. Two children discontinued the study due to development of tics in response to the medication and were excluded from the study analysis
Speltz et al., 1988[2]	51 months	1/**1**	Clinical interview, CRS-T	Dextroamphet-amine (DEX) 2.5 mg bid DEX 5 mg bid and Day Program	Double-blind time series (placebo & 2 DEX doses in counter-balanced order)/ 11 weeks	Daily observations of 15-minute work periods and 20-minute free play for frequency of on-task behavior, and teacher ratings of aggressive and disruptive behaviors and reports of side effects	↓ off-task and aggressive behavior on DEX compared to placebo Behavior gains maintained at follow up 2 years later	↑ whining, listlessness, solitary play, stomachache ↓ appetite, more frequent during 5 mg bid dose

(*continued*)

TABLE 1. PUBLISHED BLINDED STUDIES OF STIMULANT TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN PRESCHOOL CHILDREN (*CONT'D*)

Authors	*Age Range (Mean ± SD)*	*N/ **n < 6 years***	*Procedure for ADHD Diagnosis*	*Intervention Medication/ Dose*	*Study Design/ Duration*	*Outcome Assessment (for ADHD and disruptive behaviors)*	*Study Outcome*	*Side Effects/Safety*
Fischer & Newby, 1991	2–17 years (8.9 ± 2.9 years)	161/**not specified**	Semistructured parent interview, CRS-P, CRS-T, Child Behavior Checklist (CBCL), Teacher Rating Form (TRF)	MPH 0.2 mg/kg & 0.4 mg/kg BID	Double-blind crossover (placebo & 2 MPH doses)/ 3 weeks	CRS-P, CRS-T, HSQ SSQ, reaction time, GDS viligance task	Significant positive medication response on parent and teacher ratings of hyperactivity and laboratory measures of viligance and off-task behaviors, higher dose was most effective	No side effects reported
Mayes et al., 1994[3]	2–13 years (7.1 years[1])	69/**14**	Clinical interview	MPH 7.5–30 mg/day on a tid schedule	Double-blind, ABA (placebo & MPH "optimal dose")/3 weeks	Conners' 10-item ADHD Parent Rating Scale	79.4% improved on MPH based parent ratings on the Conners' scale	50.7% experienced side effects irritability, ↓ appetite, lethargy
Musten et al., 1997; Firestone et al., 1998	48–70 months (58.1 ± 8.2 months)	31/**31**	Diagnostic Interview for Children and Adults-Parents (DICA-P), Swanson, Nolan and Pelham checklist (SNAP), CRS-P, attention task	MPH 0.3 mg/kg bid, 0.5 mg/kg bid	Double-blind, crossover (placebo & 2 MPH doses)/ 3 weeks	Parent-child interaction tasks, CRS-P, GDS Delay and Vigilance Tasks	↑ attention and on-task during laboratory observation, ↓ impulsivitiy and hyperactivity as rated by parents on the CRS-P, no improved in compliance to parent requests	10% experienced severe side effects: social withdrawal, sadness. ↑ number & ↑ severity of side effects with the higher dose
Handen et al., 1999[4]	48–71 months (58.9 ± 8.2 months)	11/**11**	Clinical interview, Preschool Behavior Questionaire (PBQ), CRS-P	MPH 0.3 mg/kg/dose & 0.6 mg/kg/dose qd to tid	Double-blind, crossover (placebo & 2 MPH doses)/ 3 weeks	CRS-T, PBQ, direct behavior observation	72.7% improved on MPH based on at-least 40% reduction in teacher ratings of hyperactivity and inattention, significant improvement on clinic-based observations of activity level and compliance, more improvement on the higher dose	45% experienced side effects (social withdrawal and irritability); side effects more frequent at the higher dose

Short et al., 2004	<6 years (63 months[1])	28/**28**	Diagnostic Interview Schedule for Children-Parent (DISC-P) or clinical interview, Conners' Abbreviated Symptoms Questionnaire (CASQ), ADHD Rating Scale (ADHD-RS)	MPH 5 mg, 10 mg, 15 mg bid or mixed amphetamine salts (MAS; Adderall) 5 mg, 10 mg & 15 mg qd	Double-blind, crossover (placebo & 2 or 3 MPH or MAS doses)/ 3–4 weeks	ASQ, ADHD-RS, HSQ	Improved parent and teacher ratings of ADHD on either stimulant by at least 1 SD in 82% of the children and by 2 SD in 50% of the children. Clinical ratings of normalized behavior on best dose in 82% of the children	↓ appetite, crying & rebound effects
Chacko et al., 2005	5–6 years (6.1 ± 0.57 months)	36/**14**	Structured parent interview, parent and teacher Disruptive Behavior Disorder rating scales	MPH 0.3 mg/kg & 0.6 mg/kg bid and Behavior Modification System in a Summer Treatment Program	Double-blind, crossover (placebo & 2 MPH doses)/ 8 weeks	Point system, classroom rules, productivity and accuracy of class work	Improved classroom behavior for following rules and non-compliance and class work completion on both MPH doses compared to placebo, little incremental improvement in classroom measures on the higher MPH dose compared to the lower MPH dose. 28% children improved with classroom behavioral intervention & showed no incremental benefit of MPH	↓ appetite
Greenhill et al., 2006	3–5.5 years (53 ± 8 months)	165/**165**	Clinical assessment for DSM-IV diagnosis of ADHD, unanimous consensus by the panel of investigators, CRS-P, CRS-T	MPH 1.25 mg, 2.5 mg, 5.0 mg, 7.5 mg tid	Double-blind, crossover (placebo & 4 MPH doses) after 10 weeks of parent training/ 5 weeks	Swanson, Kotkin, Atkins, M-Flynn, and Pelham (SKAMP), Conners, Loney and Milch (CLAM) rating scales	Significant ↓ in parent- and teacher-rated ADHD symptoms on the 3 higher doses	↓ appetite stomachache, and sleep difficulties, ↑ rates of social withdrawal and lethargy, ↓ growth velocity, 8.3% discontinued due to MPH side effects

[1]SD not provided.
[2]Individualized weekly parent training sessions, classroom behavior management program and social skills training group were also administered concurrently.
[3]Included inpatient or outpatient preschool and school age children with autism, other developmental disorders or no developmental disorders.
[4]Included preschool children with mental retardation.
ADHD = attention-deficity/hyperactivity disorder; MPH = methylphenidate.

Table 2. Published Open-label Studies of Stimulant Treatment of Attention-Deficit/Hyperactivity Disorder in Prechool Children

Authors	*Age Range (Mean ± SD)*	*N/**n** < **6 years***	*Diagnostic Procedure for Eligibility*	*Medication/ Dose*	*Study Design/ Duration*	*Outcome Assessment (for ADHD and disruptive behaviors)*	*Study Outcome*	*Side Effects/Safety*
Cohen et al., 1981	Kindergarten aged[1]	24/**24**	Clinical interview, Connors' Rating Scale-Teacher (CRS-T)	MPH 10–30 mg/day	Three randomized parallel groups (MPH, Cognitive Behavior Management [CBM], and CBM + MPH), open-label treatment/ 10 weeks	Cognitive and motor impulsivity tasks, parent and teacher behavior rating scales, classroom observation	No treatment effect in any of the groups	4 of the 14 (29%) children on MPH stopped medication due to side effects and were reassigned to either CBT or no treatment
Alessandri & Scharmm, 1991	50 months	1/**1**	Clinical interview, Connors' Rating Scale-Parent (CRS-P)	DEX 2.5 mg bid	Open-label A-B-A-B reversal design/ 16 weeks	Blinded ratings of off-task behavior, level of cognitive play and social participation during structured activity and unstructured play; teacher rated PBQ, CRS-T	↓ off-task behavior, ↑ attention, ↑ developmentally appropriate goal-directed, organized and symbolic play, & improved social functioning on direct observation ratings of behavior during structured activity and unstructured play	↑ solitary & parallel play
Byrne et al., 1998	62 months[1]	8/**8**	Clinical interview, Continuous Performance Test for Preschoolers—Visual (CPTP-V), CPT-Auditory (A), CRS-P, CBCL	MPH 15–20 mg/day or DEX 7.5–15 mg/day on qd-tid schedule	Open-label/ 5 months	CPTP-V, CPT-A, CRS-P, Child Behavior Checklist (CBCL)	↑ attention & social relations, ↓ problem behaviors	No information
Stiefel & Dossetor, 1998	5 years	1/**1**	Clinical interview	DEX 5 mg bid	Open-label/ 4 years	Clinical assessment	Improved behavior	Initial problem with reduced appetite and getting to sleep ameliorated with time
Ghuman et al., 2001	40–70 months (56.4 ± (9.6 months)	27/**27**	Clinical interview	MPH 0.55 mg/kg/day or DEX 0.43 mg/kg qd-qid	Chart review/ 24 months	Clinical Global Impressions-Severity (CGI-S) and CGI-Improvement	74% experienced improvement at 3 months and 70% at 12 and 24 months	63% experienced side effects; poor appetite, stomachache, irritability, dysphoria, sleep disturbance, headache, dull/tired; 11% stopped stimulants due to side effects

[1]Mean age not provided.
MPH = methylphenidate; DEX = dextroamphetamine.

and sleep difficulties usually seen in school age children, increased rates of social withdrawal and lethargy were reported especially at higher doses. A higher discontinuation rate (8.3%) due to MPH side effects was reported in the PATS study than the 0.5% discontinuation rate in the National Institute of Mental Health (NIMH) Multimodal Treatment of ADHD (MTA) study with school-age ADHD children (Wigal et al. 2006). Compared with the Center for Disease Control (CDC) norms, the preschool children with ADHD in the PATS were 2.0 cm taller and 1.8 kg heavier at baseline. A 20% less than expected annual height gain (−1.38 cm/year) and 55% less than expected annual weight gain (−1.32 kg/year) was reported for the children who continued MPH for a year in the open-label follow up phase (Swanson et al. 2006). Decrease in weight velocity was evident at the end of the 5-week double-blind crossover phase. Most preschoolers with ADHD were able to maintain improvement over 10 months of open-label follow up treatment (Vitiello et al. 2007).

Two of the open-label stimulant studies were prospective open-label treatment trials, two were case reports, and one was a retrospective chart review. Positive response to stimulants (MPH or dextroamphetamine) was reported in four of the open-label studies; one prospective treatment trial reported no treatment effect and reported a 30% discontinuation rate due to MPH adverse effects (Cohen et al. 1981).

Non-stimulant studies. The two published case reports of open-label treatment with α2 agonists in 5 preschool children with ADHD reported improvement in hyperactive and impulsive behavior (Cesena et al. 1995; Lee 1997), one published case report of open-label treatment with atomoxetine in 10 preschool children reported improvement in hyperactive, impulsive and inattentive symptoms (Kratochvil et al. 2007), and one published case report of open-label treatment with fluoxetine in one preschool child with ADHD reported improvement in attention span (Campbell et al. 1995) (Table 3).

Prescribing patterns. Despite controversy and scarcity of empirical information regarding dose guidelines, safety, and efficacy, psychopharmacological agents are being prescribed to preschool children.

This is a serious public health concern and was identified as a research priority by the Surgeon General (National Institutes of Health 2000; US Public Health Service 2000) and the White House (Pear 2000).

In 1994, 226,000 MPH prescriptions were written for children under 6 years of age (US Food and Drug Administration 1997). A three-fold increase in MPH use in 2–4 year old children was reported from 1991–1995 (Zito et al. 2000); Marshall (2000) reported that 150,000 to 200,000 children between the ages of 2 and 4 years were estimated to be taking MPH. Outpatient prescription data from 7 state Medicaid programs revealed 67.3% stimulant and 26% α-agonist use in 2001 in 2–4 year old children treated with psychotropic agents (Zito et al. 2007).

Pre-school children with ADHD symptoms are more often treated with stimulants in the community than with any other drug. Those not treated with stimulants, are often given other psychotropic medications, including those that have not been shown to have any efficacy in ADHD, such as selective serotonin reuptake inhibitors (SSRIs) (Rappley et al. 2002) and those with some efficacy for ADHD but leading to severe long-term adverse events (e.g., tardive dyskinesia), such as neuroleptics (Minde 1998; Rappley et al. 2002). Health Maintenance Organization (HMO) and Medicaid database surveys in 1995 showed frequent use of psychotropic medications in preschool children diagnosed with ADHD. Frequency of psychotropic drug prescription in 1–3 year old children diagnosed with ADHD (N = 223) in the Michigan Medicaid system was 57% (n =127) compared to 26% (n = 47) for psychosocial intervention (Rappley et al. 1999). Psychotropic medications alone as a sole intervention strategy were utilized in 40% children (n = 89); comparatively psychosocial intervention as a sole treatment was utilized in only 9% (n = 21). Stimulants were prescribed for 93.7%, α2 agonists for 44.9%, tricyclic antidepressants for 33.1%, neuroleptics for 15.7%, and SSRIs for 11% of the preschool children receiving psychotropic medications. More than half of the children received treatment for longer than 6 months. Medication monitoring was inadequate—for 75 children (59%) follow-up visits occurred every 3 months and for 25 children (19%) at intervals greater than 6 months (Rappley et al. 2002).

Summary of psychopharmacological treatments. There is evidence for short-term efficacy and long-term effectiveness and tolerability of psychostimulants, especially MPH, in preschool children with ADHD. Response is reported to be less robust and response rate is reported to be lower in preschool children with ADHD compared to older children. Preschool children with ADHD are sensitive to developing more side effects especially at higher doses and have unique adverse effect profile including more irritability and mood changes. This sensitivity to stimulant adverse effects may be a limiting factor in achieving an adequate and/or robust response in preschool children with ADHD. Only open-label information is available regarding effectiveness and tolerability of one non-stimulant, atomoxetine, in preschool children with ADHD. Additionally, pharmacological interventions may be effective in reducing core ADHD symptoms such as impulsivity, overactivity, and inattention among preschool children with ADHD (Greenhill et al. 2006); however, there is little evidence to suggest that psychostimulants improve long-term interpersonal relationships known to be important in predicting outcomes for children displaying disruptive behaviors (Coie and Dodge 1998; Pelham et al. 1998; Rubin et al. 2006). Moreover, no information is available about long-term safety and effects of psychopharmacological agents on brain development in preschool children.

Psychosocial treatments

Concerns about the short- and long-term safety of psychopharmacological agents especially on the developing brain of preschool children, coupled with ethical, societal, and political beliefs about manipulating behavior through medication and perceived overprescription (Jensen et al. 1999) often lead families and providers to favor other interventions for preschoolers (Dulcan and Benson 1997). In this section, we will review current evidence for success of psychosocial treatments in preschool children with ADHD.

There is evidence from studies in school-age children that long-term behavioral improvements may require psychoso-

Table 3. Published Reports of Non-Stimulant Treatment of Attention-Deficit/Hyperactivity Disorder in Preschool Children

Authors	*Age Range (Mean ± SD)*	*N/**n** < **6 years***	*Procedure for Eligibility*	*Diagnostic Medication/ Dose*	*Study Design/ Duration*	*Outcome Assessment (for ADHD and disruptive behavior)*	*Study Outcome*	*Side Effects/Safety*
Campbell et al., 1995	3 years	1/**1**	Clinical interview	Fluoxetine 10 mg qd	Open-label/ 6 weeks	Clinical assessment	Improved attention even-tempered, ↓ aggression	No significant side effects
Cesena et al., 1995[1]	56 months (4.8 years)	1/**1**	Clinical interview	Clonidine 0.025 mg tid	Open-label/ 5 months	ASQ, Clinical Global Impressions (CGI) ADHD	Normalization of hyperactivity & attention on teacher ASQ, improved sleep	Sedation early in treatment, was resolved later in the course of treatment
Lee, 1997	31–42 months	4/**4**	Clinical interview, Child Behavior Checklist (CBCL)/2/3, Connors' Rating Scale-Parent (CRS-P)	Guanfacine 0.25 mg bid-1.25 mg/day	Open-label/ 2–6 months	Clinical assessment	↓ impulsive hyperactive and aggressive behavior, ↓ tantrums, improved mother-child relations	Sedation and transient benign chest pain
Kratchovil et al., 2007	5–6 years (6.1 ± 0.58 years)	22/**10**	Diagnostic Interview Schedule for Children-4 (DISC-4), clinical interview, ADHD Rating Scale (ADHD-RS)	Atomoxetine 10–45 mg/day qd or bid	Open-label/ 8 weeks	ADHD-RS, CGI	Improved ADHD-RS scores and CGI	Mood lability, reduced appetite, weight loss (mean = 1.04 ± 0.8 kg)

[1]Child's ADHD symptoms were seen as manifestation of HIV encephalopathy.
ADHD = attention-deficit/hyperactivity disorder.

cial interventions (Ialongo et al. 1993). Inhibitory processes play a critical role in impaired functioning in children with ADHD (Barkley 1997; Barkley 1998; Barkley 2003; Nigg 2001; Nigg 2003; Quay 1997) and these, although rudimentary, are developing rapidly during the preschool period (Davidson et al. 2006; Diamond and Taylor 1996; Espy et al. 1999; Garon et al. 2008; Jones et al. 2003; Rueda et al. 2005). Psychosocial interventions targeting key executive functions, especially inhibitory processes, may be particularly helpful (Diamond et al. 2007; Dowsett and Livesey 2000).

Limited psychosocial intervention research has been conducted with preschool samples of children formally diagnosed with ADHD (Bryant et al. 1999; McGoey et al. 2002); however, there is considerable evidence that parent, child, and parent-child interventions can reduce problem behaviors in young children displaying a range of disruptive behaviors, including excessive hyperactivity and inattention as reviewed in the following section. We have grouped the psychosocial intervention studies into those that train parents in behavioral techniques and use the parents as the primary agent of change, and those that train children in a classroom setting to reduce problematic behaviors.

Parent training. Among psychosocial interventions, parent training to help parents learn and implement behavioral treatment has the strongest evidence base showing positive effects for school age children with ADHD (Chorpita and Daleiden 2002). For preschool children with ADHD, parent training in behavior management is an especially helpful and the most appropriate psychosocial intervention (Stanley and Stanley 2005; Webster-Stratton et al. 2001). When children are young, parents have an enormous impact on their child's behavior (Capage et al. 1998; Eyberg et al. 1995; Funderburk et al. 1998; Hembree-Kigin and McNeil 1995) creating a window of opportunity to teach parents how to be positive and consistent in their parenting responses, help reduce noncompliant and aggressive behaviors, and help their child persist at a difficult task and provide successful experiences for their child, thus reducing risk for continued problems in later years. Parent behavior training programs for preschool children have been modeled after efficacious programs developed with older children (Anastopoulos et al. 1993; Dishion and McMahon 1998), and draw upon both social-learning and attachment theories to varying extent. Parent training programs may include sessions with parents, parent-child dyad, or a combination of parent sessions and work with the parent-child dyad to improve parent-child relationship, and increase the child's prosocial behaviors and decrease negative behaviors.

There are 15 published reports of parent behavior training treatment trials (either controlled, case series or case reports) that monitored outcomes in ADHD symptoms in preschool children with a DSM diagnosis of ADHD or preschool children displaying ADHD symptoms (Tables 4 and 5). However, there was a wide variation in the study design, type of control groups, inclusion criteria, diagnostic measures, type of psychosocial intervention, method of intervention delivery, and outcome measures employed in the studies. Nine studies used a randomized parallel groups design with control groups ranging from wait-list, community treatment, combination treatment to minimal treatment (Barkley et al. 2000; Bor et al. 2002; Corrin 2004; Jones et al. 2007; McGoey et al. 2005; Pisterman et al. 1992; 1989; Sonuga-Barke et al. 2001; Strayhorn and Weidman 1989; Strayhorn and Weidman 1991) and six studies did not employ any control group (Chang et al. 2004; Danforth 1999; Drash et al. 1976; Erhardt and Baker 1990; Henry 1987; Huang et al. 2003). Eight of the nine controlled studies included only preschool children and four of these eight studies selected the preschoolers based on a DSM diagnosis of ADHD through clinical or structured parent interview (Bor et al. 2002; Pisterman et al. 1992; 1989; Sonuga-Barke et al. 2001), and the other four selected preschoolers based on a rating scale cutoff. The ninth controlled study included both preschool-age and school-age children with a DSM diagnosis of ADHD. Sample sizes ranged from 20-50 per group. Most studies employed group-training sessions except for three studies that employed individual training sessions with the parents (Bor et al. 2002; Henry 1987; Sonuga-Barke et al. 2001). Training was conducted over 8–12 sessions, each parent training session lasting 1–3 hours. Most studies included both teaching/modeling sessions with the parents and work with the parent-child dyad with the exception of one study that included parent training sessions only (Jones et al. 2007), one study that included parent and/or child training sessions separately (Corrin 2004) and two studies that included only didactic teaching sessions with the parents (Barkley et al. 2000; Huang et al. 2003). Outcome assessments varied among the studies and included parent ratings of ADHD and disruptive behaviors, and direct behavior observation by independent raters for on-task behavior, child compliance with maternal commands, and parent-child interaction quality during structured play.

Improvements in ADHD symptoms were reported in three of the eight controlled studies that included only preschool children (Jones et al. 2007; Sonuga-Barke et al. 2001; Strayhorn and Weidman 1989) and only one of these studies (Sonuga-Barke et al. 2001) was in preschoolers formally diagnosed with ADHD. Preschoolers diagnosed with ADHD (N = 78) were randomized to 8 weeks of parent training, parent counseling and support, or a wait-list group (Sonuga-Barke et al. 2001). Improvements in ADHD symptoms were reported with parent training compared to the other two conditions; positive effects were maintained at 6 month follow-up. No improvement in hyperactive, impulsive and/or inattentive symptoms on parent ratings or direct observation was reported in the remaining 5 controlled studies that included only preschool children. Improvements in ADHD symptoms were also reported in most of the non-randomized non-controlled case series (Drash et al. 1976; Erhardt and Baker 1990; Huang et al. 2003).

With the exception of Barkley et al (2000), most investigators reported improvements in parenting skills, parenting style of interaction, and child compliance. Barkley et al. (2000) reported poor treatment response with parent behavior training in kindergarteners (N = 158) who met dimensional rating scale cutoff criteria for hyperactive, impulsive, inattentive, and aggressive behavior. The kindergarteners were assigned to one of four treatment groups: parent training only, classroom day treatment only, a combined condition, or a no treatment control group. The parent training intervention produced no effects.

There may be several reasons for the poor treatment response in this study. Inclusion criteria for the study were

Table 4. Published Controlled Studies of Psychosocial Treatments in Preschool Children with Attention Deficit Hyperactivity Disorder: Parent Training

Authors	*Age range in years (Mean age ± SD)*	*N/**n** < **6** **years***	*Procedure for ADHD Diagnosis; Inclusion Criteria*	*Psychosocial intervention*	*Study Design/ Duration*	*Outcome Assessment (for ADHD and disruptive behaviors)*	*Study Outcome*
Strayhorn & Weidman, 1989; 1991	2–5 (3.9[1])	96/**96**	No clinical assessment, parent questionnaire based on DSM III-R diagnostic criteria; At-risk for behavior problems (complaints of ADHD, disruptive behaviors or emotional difficulties, low socioeconomic status), 40% parents endorsed ≥ 8 of 14 ADHD symptoms	Group parent training and individual sessions work with the parent-child dyad	Two randomized parallel groups: parent behavior training (PBT) or minimal treatment control group, open-label treatment/ 12 sessions	Parent and teacher ratings on ADHD, compliance, and internalizing symptoms on the Behar Preschool Behavior Questionnaire; direct observation of parent and child behaviors, parenting practices	Improvement in the PBT group in parent-rated ADHD and internalizing symptoms, and child and parent behaviors on direct observation. No improvement in teacher ratings, or verbal ability measures. Improved parent behavior correlated positively with improved child behavior Improvement in teacher-rated classroom behavior at 1 year follow-up
Pisterman et al., 1989	3–6 (4.15 ±0.78)	50/**50**	Structured screening interview, >1 SD on the Conners' Hyperactivity Index; DSM-III criteria for ADDH	Group parent training and 2 individual sessions with the parent-child dyad	Two randomized parallel groups: immediate treatment or delayed treatment group, open-label treatment/ 12 weeks	Parent ratings on the Conners' Hyperactivity Index, direct behavioral assessment of child attention, child compliance and parental style of interaction	No treatment effect on child attention or parent-rated Conners' Hyperactivity Index. Improvement in the immediate treatment group in child compliance; improved parental style of interaction. Outcome reported only for 46 of the 50 randomized children; four children (8%) dropped out after group assignment. Five children received methylphenidate during the study. Improvement maintained at 3 month follow up

Pisterman et al., 1992	3–6 (3.9 ± 0.62)	57/**57**	Semi-structured screening interview, cutoff threshold for parent or teacher Swanson, Nolan and Pelham (SNAP) rating scale and Conners' Hyperactivity Index; DSM-III criteria for ADDH	Group parent training and 2 individual sessions with the parent-child dyad	Two randomized parallel groups: immediate treatment or delayed treatment group, open-label treatment/ 12 weeks	Direct behavioral assessment of child attention, child compliance and parental style of interaction	No treatment effect on child attention on direct observation Improvement in child compliance and parental style of interaction in the immediate treatment group. Outcome reported only for 45 of the 57 randomized children; 12 children (21%) dropped out after group assignment with a higher drop-out rate for less educated parents. Four children received stimulants during the study. Improvement maintained at 3 month follow up
Barkley et al., 2000; Shelton et al., 2000	4.5–6 (4.8 ± 0.5)	158/**158**	Diagnostic Interview Schedule for Children-Parent (DISC-P), Conners' rating Scale-Parent (CRS-P); Cutoff dimensional threshold for Hyperactive, Oppositional &/or Conduct Problem factors on CRS-P, no clinical diagnosis of ADHD required for inclusion, 66% children met ADHD criteria on the DISC-P	10 weekly group parent training sessions followed by 6 monthly booster sessions, special treatment classroom	Four randomized parallel groups; Parent Training (PT) Special Treatment Classroom (STC), combined (PT and STC) or no treatment control groups, open-label treatment/ 9 months (school year)	DISC-P, parent and teacher ratings of child behavior on Child Behavior Checklist (CBCL), Home Situations Questionnaire (HSQ), School Situations Questionnaire (SSQ), Self-Control Rating Scale (SCRS); Continuous Performance Test (CPT); parent self-report on parenting practices and competence; clinic observation for disruptive behavior and parent-child interaction; and classroom observation	No improvement and poor attendance in the PT group. STC produced improvement in parent ratings of adaptive behavior, teacher ratings of social skills, attention and aggression; and classroom observation ratings of externalizing behavior. No improvement in academic achievement or parent ratings of home behavior; and no improvement in laboratory measures of attention, impulse control or parent-child interaction in any of the treatment groups. No difference in the groups at 2 year follow-up

(*continued*)

Table 4. Published Controlled Studies of Psychosocial Treatments in Preschool Children with Attention Deficit Hyperactivity Disorder: Parent Training *(Cont'd.)*

Authors	*Age range in years (Mean age ± SD)*	*N/**n** < **6 years***	*Procedure for ADHD Diagnosis; Inclusion Criteria*	*Psychosocial intervention*	*Study Design/ Duration*	*Outcome Assessment (for ADHD and disruptive behaviors)*	*Study Outcome*
Snuga-Barke et al., 2001	3[2]	78/**78**	Structured clinical interview (Parental Account of Childhood Symptoms (PACS), Werry-Weiss-Peters Activity Scale (WWPAS); Cuttoff threshold for the ADHD Hyperkinesis scale of the PACS and cutoff threshold on the WWPAS	Eight 1-hour weekly in-home individual parent training sessions and work control with the mother-child dyad	Three randomized parallel groups: parent training (PT), parent counseling and support (PC&S) or waiting-list (WLC) groups, open-label treatment/ 8 weeks	Clinician ratings of ADHD based on parent interview using the PACS; play observation for attention/parent self-engagement: Parenting report on the Satisfaction and Parenting Efficacy scales of the Parental Sense of Competence (PSOC) scale	PT more effective than PC&S and WLC in improving ADHD symptoms both on parent interview and play observation, and improvement in mothers' sense of well-being Improvement maintained at 23 weeks
Bor et al., 2002	3–4 (3.42 ± 0.31)	87/**87**	Structured diagnostic interview, Eyberg Child Behavior Inventory (ECBI); DSM IV diagnosis of ADHD, >90th percentile on the Inattentive Behavior subscale of the ECBI and at least 1 family adversity factor	Ten 60–90-minute individual sessions (7 parent training sessions and 3 parent-child sessions) for the Standard and 12 for the Enhanced Behavior Family Intervention (SBFI and EBFI)	Three randomized parallel groups: SBFI, EBFI, waitlist (WL) control group. open-label treatment/ 15–17 weeks	Parent ratings on the ECBI, Parent Daily Report (PDR), Parenting Sense of Competency (PSOC) scale, Parenting Scale (PS), Parent Problem Checklist (PPC), observation of mother-child behavior	No treatment effect on parent-rated inattentive behavior. Improvement in parent-reported child behavior problems, dysfunctional parenting, and parental competence with both SBFI and EBFI; significantly less observed child negative behavior with EBFI; no difference in SBFI and EBFI conditions. Outcome reported only for 63 of the 87 randomized children; 24 children did not complete intervention and post-assessment. Gains maintained at 1-year follow-up
Corrin, 2004	4.5–8.5 (6.6 ± 1.25)	55/**9**	Structured parent interview, CRS-P; DSM diagnosis of ADHD	Ten weekly group child and parent training sessions	Two randomized parallel groups: child group training or combined parent and child training, open-label label treatment/ 10 weekly sessions	CBCL, CRS-P, HSQ	Improvement in CRS-P Hyperactivity scale in both treatment groups, 17 children were on stimulant medication

McGoey et al., 2005	3–5 (4.04 ± 0.72)	57/**57**	Semi-structured parent interview for DSM-IV criteria for ADHD, and cutoff threshold for parent and teacher Hyperactivity or Inattention subscale of the CRS; at-risk for ADHD	Multi-component intervention including 12 weekly group parent training sessions & 9 monthly booster sessions, preschool consultation, and medication consultation as needed	Two randomized parallel groups: Early Intervention (EI) or a Community Treatment Control (CTC) group, open-label treatment/ 12 months	Preschool and Kindergarten Behavior Scales (PKBS), direct observation of classroom behavior and parent-child interaction, Medical Outcomes and Service Utilization, Consumer knowledge ratings	No treatment effect reported on parent- and teacher-rated Attention problems/Overactivity subscale of the PKBS, improvement in on-task performance, compliance, self-control, and social skills; increased positive parenting behaviors, reductions in negative parent behavior, and positive changes in family coping were seen in both groups. Outcome reported for completers (21 out of the 30 children (70%) randomized to EI) only. Four children were prescribed stimulants or clonidine.
Jones et al., 2007; 2008	3–4 (3.86 ± 0.51)	79/**79**	No clinical assessment, cutoff threshold for parent Hyperactivity subscale of the Strengths and Difficulties Questionnaire (SDQ); cutoff threshold for parent problem or intensity subscale of the ECBI and Hyperactivity subscale of the SDQ	Twelve 2.5 hour-weekly Incredible Years Basic Parent Training (IY-BPT) group sessions and weekly telephone calls	Two randomized parallel groups: IY-BPT or waitlist (WL) control group, open-label treatment/ 12 weeks	Parent ratings on the Conners' Abbreviated Parent Rating Scale (CAPRS), and Child Deviance (negative and destructive behavior and non-compliance) subscale score of the Dyadic Parent-Child Interaction Coding System (DPICS) based on observation of mother-child behavior	Parents reported greater reduction on the CAPRS scores in the IY-BPT group compared to the WL group, and improvement was significant even after controlling for co-occurring conduct problems as measured by the Child Deviance subscale scores of the DPICS Gains maintained at 6 months, 12 months and 18 months post-intervention.

[1]SD not provided.
[2]Mean age not provided.
ADHD = attention-deficity/hyperactivity disorder; ADDH = attention-deficit disorder with hyperactivity.

Table 5. Published Non-controlled Studies of Psychosocial Treatments in Preschool Children with Attention Deficit Hyperactivity Disorder: Parent Training

Authors	*Age range in years Mean age ± SD)*	*N/**n** < **6** **years***	*Procedure for ADHD Diagnosis & Inclusion Criteria*	*Psychosocial intervention*	*Study Design/ Duration*	*Outcome Assessment (for ADHD and disruptive behaviors)*	*Study Outcome*
Drash et al., 1976	2–4.8 (2.8[1])	5/**5**	Clinical diagnosis of ADHD	Weekly 3-hour parent classes (two mother-child pairs also received direct training), child group training in a classroom setting	Case series, prospective, no control group. open-label treatment/ 9 months	Parent-rated Behar Preschool Behavior Questionnaire (BPBQ), direct behavior observation during group classroom situation and a standardized task completion activity	Parent-rated BPBQ Hyperactivity and Distractibility subscale scores, decreased from 90th percentile to 52nd percentile, high rates of compliance rates across settings Two children received psychotropic medication
Henry, 1987	4.5–10.5 (7.3[1])	6/**n < 6 years not specified**	DSM- III diagnosis of ADHD by a psychiatrist and a psychologist, stabilized on psychostintulant medication	Four 20-minute symbolic modeling sessions with the child followed by six 60-minute combined symbolic modeling and parent training sessions administered	Case study, prospective, no control group, open-label treatment/ 10 weeks	Parent Conners' Symptom Questionnaire, observation of child compliance to parental task during a structured task	3/5 children improved on the parent ratings of the Conners' Symptom Questionnaire. A combination of medication, symbolic modeling and parent training was more effective than a combination of medication and symbolic modeling or medication alone in reducing noncompliance. Parent training for time-out procedure was most effective. Combined symbolic modeling and medication was not any more effective than medication alone. Gains maintained at 6 months
Erhardt and Baker, 1990	5.2–5.8	2/**2**	Diagnosed as being hyperactive by the pediatrician. parent score of >15 on the Abbreviated Symptom Questionnaire (CASQ)	Six 2-hour group parent training and four 1-hour individual consultation and parent-child interactive sessions	Case study, prospective, no control group, open-label treatment/ 10 sessions	Parent ratings on the CASQ, Iowa Conners' Rating Scale. Werry-Weiss-Peters Activity Scale (WWPAS), Child Behavior Checklist (CBCL)	Improved parental ratings of hyperactivity, tantrums, aggression, compliance and social functioning

Danforth, 1999	4.0 (Twins)	2/**2**	DSM IV diagnosis of ADHD and oppositional defiant disorder (ODD), clinical diagnosis by the referring pediatrician	Eight 1-hour weekly parent training sessions using the Behavior Management Flow Chart	Case study, prospective, no control group, open-label treatment/ 8 sessions	Conners' Rating Scale-Parent (CRS-P), CBCL, Parent Daily Report telephone checklist, direct observation of mother-child interaction	CRS-P Hyperactive Index T scores decreased from 80 to 50 for one twin and remained unchanged for the other twin; increased compliance and decreased aggressive behavior on direct observation of mother-child interaction
Huang et al., 2003	3–6 (5.42 1.1)	23/**23**	Diagnosis of ADHD on Barkley's semistructured interview questionnaire	Nine 1-hour weekly group parent training sessions and 1 booster session 4 weeks later	Prospective, no control treatment condition, open-label treatment/ 10 sessions	Disruptive Behavior Rating Scale-Parent Form, Child Attention Profile, and Home Situations Questionnaire	Improved parental ratings for ADHD and ODD symptoms, significant decline in the severity of symptoms and problem behaviors at home. Outcome reported for completers (n = 14, 61% of the recruited sample) only Four children were also taking stimulants during the trial
Chang et al., 2004	4–6 (6 ± 0.8)	8/**8**	DSM IV diagnosis of ADHD by 2 child psychiatrists	Eight 2-hour weekly group parent training and joint parent-child social skills training group sessions	No control group/ 8 sessions	No information provided regarding how outcome assessment was conducted	Parents reported improved ADHD behaviors in 3 (37.5%) children; improvement in emotional expression/regulation, less parental frustration and increased satisfaction regarding child's behavior at home.

[1]SD not provided.
ADHD = attention-deficit/hyperactivity disorder.

based on a rating scale cutoff and no clinical or structured diagnostic interviews were conducted for a diagnosis of ADHD. Most important, neither the children's caregivers nor their teachers had indicated impaired functioning in the kindergartners included in the study. There is evidence that psychosocial treatment approaches have greater impact on those children rated with higher levels of problems (Kellam et al. 1998; Wilson and Lipsey 2007). Furthermore, only 25% of the parents attended more than four parent behavior training sessions, and, finally, the parent behavior training was delivered in a didactic format.

Parent-Child Interaction Therapy (PCIT) (Eyberg 1988), a related yet distinct parent behavior training program, is an evidence-based intensive intervention for preschool children with disruptive behavior disorders. Parents are trained in behavioral management techniques within a play-therapy context; the therapist works with the parent-child dyad and provides "live" interactive coaching and immediate feedback to change interaction patterns within the dyad. A number of studies have reported positive effects of PCIT on outcomes for young children with externalizing problems, reducing hyperactive as well as disruptive behavior and improving compliance with maintenance of gains 6 years later (Hood and Eyberg 2003).

Although PCIT has not been used specifically to treat ADHD in preschoolers, many studies of PCIT included preschool children who met DSM diagnostic criteria for ADHD and reported benefit in parent- and/or teacher-rated ADHD symptoms (Eisenstadt 1993; Eyberg et al. 2001; Nixon 2001).

Child training. There have been a few studies in which behavioral management techniques have been applied within the preschool setting to treat individual preschool children presenting with hyperactive, inattentive and disruptive behaviors. We identified four published case series (Billings and Wasik 1985; Bornstein and Quevillon 1976; Bryant and Budd 1982; McGoey and DuPaul 2000) and two single-case reports (Allen et al. 1967; McCain and Kelley 1993) in preschool children with ADHD symptoms in which child training was conducted within the context of the classroom setting and ADHD outcomes were assessed with direct observation using a within-subject comparison design (Table 6). There was a wide variation in the inclusion criteria and the procedure used for ADHD diagnosis, study design, behavior techniques and outcome measures employed in the studies.

Only one study utilized a combination of a structured diagnostic interview with the parent and dimensional threshold on a rating scale for ADHD (McGoey and DuPaul 2000), one study included children who were given a diagnosis of ADHD prior to their study participation with no confirmation of the diagnosis by the study investigators (McCain and Kelley 1993), and four studies included children based on teacher complaints of hyperactive, inattentive, or disruptive behaviors. The two single-case reports and one case series (McCain and Kelley 1993) employed a reversal design, and three of the case series employed multiple baselines across subjects.

The sample sizes were small ranging from 1–4 children. Behavioral techniques used in the studies included self-instructional training to encourage on-task behavior in three studies, and shaping procedure with contingent reinforcement and/or response cost was employed to decrease hyperactive, disruptive, and impulsive behavior in three studies. Information regarding treatment integrity was reported only in one study (McGoey and DuPaul 2000) Treatment effect on number of activity changes, on-task behavior, and disruptive behavior was assessed through classroom observation (3 studies employed a blinded observer). All studies reported improved task-related attention and ability to delay activities and decreased disruptive behaviors.

Only three studies conducted follow-up assessment beyond the immediate intervention period, two studies reported maintenance of gains 2 weeks (McGoey and DuPaul 2000) and 22.5 weeks later (Bornstein and Quevillon 1976) and one study reported increase in attending behavior immediately following treatment, but gains were not maintained at follow-up 2 weeks later (Billings and Wasik 1985).

Behavioral approaches applied to the whole classroom affect all children in the classroom and reduce the sense of "unfairness" of ADHD children receiving special treatment. Whole classroom approaches reduce the burden of designing individual programs for multiple children with problem behaviors in the classroom. Finally, this approach may benefit whole class environment, producing a more positive climate (Conduct Problems Prevention Research Group 1999). In the classroom treatment group in the Barkley et al. (2000) study, the kindergarteners meeting dimensional threshold for hyperactive, impulsive, inattentive, and aggressive scores randomized to the special behavior treatment classrooms showed improvements over children randomized to the regular, no treatment classrooms. However, the positive effects did not generalize beyond the classroom setting and were not evident at two-year follow-up (Shelton et al. 2000).

Summary of psychosocial interventions. There is evidence for short-term efficacy of psychosocial interventions, especially parent behavior training, in reducing disruptive behaviors in preschool children; evidence is much more limited for ADHD outcomes. Four randomized studies employed parent behavior training in preschool children formally diagnosed with ADHD and one of these studies reported improvement in ADHD symptoms. Evidence for efficacy of child training is limited to case series/case reports that included a total of 16 preschool children, only one of these studies employed a structured diagnostic procedure and blinded classroom observation, and reported improvement in ADHD symptoms.

Since it has been postulated that long-term behavioral improvements require psychosocial interventions (Ialongo et al. 1993), preschool years are an especially opportune time to promote appropriate inhibitory control by teaching positive and consistent parenting skills as well as training children directly (Diamond et al. 2007; Dowsett and Livesey 2000).

Alternative treatments for attention-deficit/ hyperactivy disorder in preschool children

Here we review four alternative treatment options that may be more practical and/or effective during preschool years than later, may be better justified to try at this age, and may be undertaken in conjunction with standard treatments such as behavioral and pharmacological treatment. As with

Table 6. Published Studies of Psychosocial Treatments in Preschhool Children with Attention-Deficit/Hyperactivity Disorder: Child Training

Authors	*Age in years*	*N*	*Procedure for ADHD Diagnosis & Inclusion Criteria*	*Psychosocial intervention*	*Study Design/ Duration*	*Outcome Assessment (for ADHD and disruptive behaviors)*	*Study Outcome*
Allen et al., 1967	4.5	1	No clinical diagnosis of ADHD, preschool classroom teacher complaint of moving constantly from 1 activity to another confirmed by classroom observation	Teacher administered shaping procedure with contingent social reinforcement	Single-subject, prospective, open-label treatment, four-stage design: baseline, reinforcement, reversal and reinstatement/ Forty-seven 50-minute periods	Classroom observation for number of activity changes	Number of activity changes decreased by 50% compared to baseline and reversal conditions.
Bornstein & Quevillon, 1976	4	3	No clinical diagnosis of ADHD, Head Start teacher complaint of highly disruptive classroom behavior, inability to complete standard preschool classroom tasks, short attention span, not attending to tasks, overactivity	Individual 2-hour massed self-instruction training session with verbal modeling, prompts, reinforcement and fading	Case series, prospective, blind, multiple baseline design across subjects and an observer-expectancy control manipulation/40 observation days over 10 weeks	Classroom observation for on-task behavior	On-task behavior increased from an average of 11.7% at baseline to 77% post-treatment and 70.7% at follow-up 22.5 weeks later. Behavioral gains were transferred to the classroom setting. Gains maintained at follow-up 22.5 weeks later
Bryant & Budd, 1982	4–5	3	No clinical diagnosis of ADHD, remedial classroom teacher complaint of low rates of on-task behavior, high distractibility and non-compliance	Nine or more individually administered 10-minute sessions of self-instructional training over 3–8 days followed by classroom intervention with contingent reinforcement by the teacher	Case series, prospective, open-label treatment, multiple baseline design across subjects and sequential administration of self-instructional training and classroom intervention/ 8 days	Classroom observation for on-task and disruptive behaviors, work completion, and work accuracy	On-task behavior increased from an average of 43.8% at baseline to 53.3% after self-instructional training and 67.7% after introduction of the classroom intervention, work accuracy increased with self-instructional training. Rate of work completion increased after the classroom intervention with contingent reinforcement was instituted.
Billings & Wasik, 1985	4.2–4.8	4	No clinical diagnosis of ADHD, Head Start teacher complaint of off-task, disruptive and inattentive behavior, and at least 25% off-task behavior on observation	Individual 2-hour massed self-instruction training session with verbal modeling, prompts, reinforcement and fading	Case series, prospective, open-label treatment, multiple baseline design across subjects; one child used as control/ 4 weeks	Blinded classroom observation for on-task behavior and teacher interactions. Self-control Rating Scale completed by the teacher	Increase in attending behavior immediately following treatment phase, but gains were not maintained at follow-up 2 weeks later. Observed high levels of teacher attention to negative behaviors may have maintained the inappropriate behaviors in the children.

(*continued*)

Table 6. Published Studies of Psychosocial Treatments in Preschhool Children with Attention-Deficit/Hyperactivity Disorder: Child Training (Cont'd.)

Authors	Age in years	N	Procedure for ADHD Diagnosis & Inclusion Criteria	Psychosocial intervention	Study Design/ Duration	Outcome Assessment (for ADHD and disruptive behaviors)	Study Outcome
McCain & Kelley, 1993[1]	5	1	ADHD diagnosis by the referring pediatrician, teacher complaints of inattentive, impulsive, distractible, and disruptive classroom behavior, Conners' Rating Scale-Teacher (CRS-T) scores >2 SD	Daily school-home notes and home-based positive reinforcement contingency	Single-subject, prospective, open-label treatment. reversal (ABAB) design/ 4 weeks	Blinded classroom observation for on-task, number of activity changes and disruptive behaviors	On-task behaviors increased from an average of 58% in the baseline and reversal conditions to 84.5% in the active treatment conditions. Number of activity changes and disruptive behaviors decreased from an average of 7 and 31% respectively in the baseline and reversal conditions to 2 and 8% in the active treatment conditions.
McGoey & DuPaul, 2000	4.3–5.1	4	ADHD diagnosis on a parent interview using the Diagnostic Interview for Children and Adolescents and parent or teacher rated Early Childhood Inventory; cutoff threshold on the Hyperactivity and the Attention Problems subscales of the Behavioral Assessment System for Children	Teacher administered token reinforcement and response cost	Single-subject, prospective, open-label treatment, reversal design to compare token reinforcement and response cost counterbalanced between participants; a peer comparison child matched for age from each classroom for a measure of expected behavior in the classroom/ 36–40 sessions	Teacher-ratings on the ADHD Rating Scale, Preschool and Kindergarten Behavior Scales, Teacher Acceptability Ratings, blinded classroom observation	Both interventions were associated with reductions in hyperactivity and disruptive behaviors in 3 of the 4 participants to levels commensurate with their matched peers. Reductions in disruptive behaviors observed initially with both interventions for the 4th participant were replicated with reintroduction of response cost but were not replicated with reintroduction of token reinforcement. Gains maintained at 2 week follow up

[1]Parents had previously participated in a group parent training with improvement in the child's behavior at home, but behavioral problems in the preschool had continued.
ADHD = attention-deficit-hyperactivity disorder.

established treatments, information about alternative treatments is mostly available for school age children.

The quality of evidence ranges from randomized controlled trials to anecdote. In evaluating the evidence, or lack thereof, it is important to consider relative risk, difficulty, and expense. An intervention that is safe, easy, cheap, and sensible (SECS) can be accepted pragmatically on less evidence than one that is risky, difficult, or expensive (in terms of either cost or parental effort and time, which is a resource that should not be squandered on unproven intense treatments).

Of the myriad of alternative treatments advocated for ADHD, four seem especially applicable to preschoolers: elimination diets, vitamin/mineral and other dietary supplementation, vestibular stimulation, and massage. For a review of other popular alternatives, such as EEG and biofeedback that may be more appropriate for older children, see (Arnold 1999; Arnold et al. 2002).

Elimination diets. At the time of the 1982 NIH Consensus Development Conference on Defined Diets and Childhood Hyperactivity (1982) most elimination diets (defined diets) were popularly known as Feingold diets. The Feingold (1975) hypothesis had stated that many children are sensitive to dietary salicylates and artificially added colors, flavors, and preservatives, and that eliminating the offending substances from the diet could ameliorate learning and behavior problems including ADHD. Despite a few positive studies (Swanson and Kinsbourne 1980; Williams et al. 1978), most controlled studies were interpreted by the investigators and reviewers as nonsupportive of the hypothesis (Conners 1980; Kavale and Forness 1983; Mattes 1983). The consensus panel called for more controlled research.

Since the 1982 NIH Consensus Development Conference, a literature search revealed 9 peer-reviewed reports on the use of elimination diets (additive free diet [food colors and/or preservatives] and/or few-foods diet) involving preschool children who either had a diagnosis of ADHD or displayed ADHD Symptoms (Table 7). Two studies included preschool children only (Bateman et al. 2004; Kaplan et al. 1989); the other 7 studies included both school age and preschool children with children ranging in age from 1.6–15 years (mean age ranging from 7.3–9.7 years). Only three of these seven studies specified the number of preschoolers participating in the studies (Boris and Mandel 1994; Egger et al. 1985; Rowe and Rowe 1994). A DSM diagnosis of ADHD was the required inclusion criteria in only three of the studies (Carter et al. 1993; Egger et al. 1992; Kaplan et al. 1989); one study was a population-based study (Bateman et al. 2004), and the remaining four studies included children with a DSM diagnosis of ADHD or ADHD symptoms.

Many of the studies did not use rigorous diagnostic procedures. Most studies employed a multi-phase design with open elimination diet (additive free diet and/or few-foods diet), open challenge to identify the incriminated food(s) followed by a randomized, placebo-controlled double-blind challenge with food additives (food colors and/or preservatives) in 5 studies (Bateman et al. 2004; Kaplan et al. 1989; Pollock and Warner 1990; Rowe 1988; Rowe and Rowe 1994) and/or the incriminated food in 4 studies (Boris and Mandel 1994; Carter et al. 1993; 1985; 1992).

In order to maintain the blind, food colors and/or food preservatives were administered in a capsule and/or meals were provided to the study participants. The few-foods or oligoantigenic diet most commonly included two meats (e.g., lamb and chicken), two carbohydrates sources (e.g., potatoes and rice), two fruits (e.g., banana and apple), vegetables (any brassica, e.g., cauliflower, cabbage, broccoli, or Brussels sprouts), cucumber, celery, carrots, parsnip, salt, pepper, water, calcium, and vitamins.

All studies demonstrated either significant improvement compared to a placebo condition or deterioration on placebo-controlled challenge of offending substances. The two studies that included preschoolers only are of particular relevance (Bateman et al. 2004; Kaplan et al. 1989). Both studies investigated additive free diet. Kaplan et al. (1989) conducted a within-subject, placebo-controlled double-blind crossover trial of elimination (additive free) diet and placebo control diet in 24 preschool children (3.56 years of age) with a DSM-III diagnosis of ADHD along with sleep problems and/or other symptoms (e.g., stuffy nose, stomach ache) indicative of food sensitivity. Food was provided for every member of the household. Parent Conners' Abbreviated Symptom Questionnaire ratings were significantly lower during the elimination diet phase compared to the placebo control diet phase ($p < .01$). Bateman et al. (2004) conducted a population-based, randomized, double-blind, placebo-controlled challenge study of elimination diet (additive free) in 277 3-year-old preschoolers (4 groups of preschoolers with hyperactivity crossed with atopy). Preschoolers in all four groups showed a general increase in parent rated hyperactivity symptoms with artificial food colors and benzoate preservatives, with effect size of $d = 0.5$ compared to placebo challenge. There was no effect of prior levels of hyperactivity or by atopy. Table 7 presents a summary of the available studies on elimination diet that included preschool children with ADHD or ADHD symptoms and monitored ADHD outcome.

A related dietary strategy, simple elimination of sugar or candy, has not garnered convincing scientific support from repeated placebo-controlled acute challenge studies (Ferguson et al. 1986; Krummel et al. 1996; Wender and Solanto 1991; Wolraich et al. 1995) despite a few encouraging reports (Goldman et al. 1986). Even a well-controlled 3-week trial of a sugar-restricted diet found no effect (Wolraich et al.1994). However, Wesnes et al. (2003) did demonstrate in a sample of school children not diagnosed for ADHD that a whole-grain cereal and milk breakfast resulted in fewer inattentive symptoms over the course of the morning than the same number of calories in a glucose drink. It does not appear that sugar or candy restriction alone is a widely applicable treatment for ADHD. On the other hand, sugar is not an essential food group, and there does not appear to be any risk from restriction or elimination of candy and other densely sugared foods.

In summary, there is some evidence for efficacy of elimination diet, especially additive free diet, in preschool children with ADHD. The 4 studies showing efficacy of few-foods diet included a mixed age sample and either did not specify the number of preschoolers or did not report outcome separately for preschoolers, thus making it difficult to assess specific response of the preschoolers to the few-foods diet.

Dietary elimination (additive free diet and/or few-foods diet) may be more practical as well as more effective for preschoolers than for older patients because of better care-

Table 7. Published Studies of Alternative Treatments in Preschool Children with Attention-Deficit/Hyperactivity Disorder: Elimination Diets

Authors	*Age Range in years (Mean age ± SD in years)*	*N/n < 6 years*	*Procedure for ADHD Diagnosis; Inclusion Criteria*	*Type of intervention*	*Study Design/ Duration*	*Outcome Assessment (for ADHD and disruptive behaviors)*	*Study Outcome*
Egger et al., 1985	2–15 years (7.3[1])	76/10	Clinical assessment, dimensional cutoff score on short form of the Conners' Rating Scale; Hyperkinetic syndrome or behavioral disturbance with overactivity	Oligoantigenic (few-foods) diet[2]	Elimination diet followed by challenge, 3-phase design: 4-week open elimination diet (oligoantigenic diet), open weekly reintroduction of foods and synthetic colorings, 4-week or longer double-blind, placebo-controlled crossover challenge trial of one incriminated food/ Information about duration of the open reintroduction phase not provided	Conners' Abbreviated Scale, actometer recording	Improvement on parent ratings on the Conners' scale during placebo compared to the active substance in the double-blind crossover phase. 62/76 (82%) improved in the open elimination phase, no treatment effect on actometer readings. IgE levels were in the atopic range for age in 68% of the responders and 20% of the non-responders
Rowe, 1988	3–15 (7.7 ± 2.9)	55/ n < 6 not specified	Clinical assessment; Suspected hyperactivity	Feingold diet (no synthetic food colorings)	Elimination diet followed by challenge, 3-phase design: 6-week open elimination diet (Feingold diet with no synthetic food colorings), open sequential liberalization of the diet, double-blind. placebo-controlled crossover challenge trial with azo dyes (carmoisine and tartrazine)/ 18 weeks	Daily 8-item parent- and teacher-completed checklist of ADHD and behavioral symptoms	40/55 (72%) improved on open Feingold diet; 26/55 (47%) showed placebo effect as they remained improved after discontinuing the Feingold diet; 14/40 (35%) had an adverse reaction to the open-reintroduction of synthetic additive; 2/8 (25%) children completing the double-blind trial reacted adversely to the dye challenge.
Kaplan et al., 1989	3.5–6 (4.48 ± 1.04)	24/24	Clinical interview, Conners' Parent Rating Scale rating > 1 SD; DSM-III criteria for ADDH along with sleep problems and physical complaints	No food dyes, flavors, preservatives, monosodium glutamate, chocolate, caffeine and any suspected food, little sugar	Elimination design: 3-week baseline diet, double-blind, placebo-controlled crossover phase on 3-week placebo control (equivalent) diet and 4-week experimental diet counterbalanced across subjects/ 10 weeks	Conners' Abbreviated Symptom Questionnaire (CASQ), 10-item physical signs and symptoms questionnaire, Visual Attention Span Test	Significantly lower parent scores on the CASQ during experimental diet phase compared to the baseline and placebo diet phases. 14/24 (58%) had behavioral and sleep improvement with negligible placebo effect

Pollock & Warner, 1990	2.8 – 15.3 (8.9[1])	39/ n < 6 not specified	No clinical assessment for a diagnosis of ADHD: History of improvement in ADHD symptoms with a diet free of artificial food colors prior to study entry	Artificial food coloring free elimination diet	Challenge design: Double-blind placebo controlled, crossover challenge with artificial food colors. Maintenance of food additive elimination diet of each child for the duration of the trial/ 7 weeks	Connors' Hyperactivity Index	Mean daily Connors' Hyperactivity Index scores during the 2 active weeks were higher than placebo. However. the changes were small. were not clinically significant and were not detected by parents. Outcome results are reported for 19/39 (48.7%) completers.
Egger et al., 1992	3–15 (9.3[1])	40/ n < 6 not specified	Clinical assessment, cutoff threshold on parent rated short form of Conners' Rating Scale; DSM III-R diagnosis of hyperkinetic syndrome	Oligoantigenic (few-foods diet) water, calcium, magnesium, zinc and vitamins	Desensitization. 4-phase design: Open elimination diet, open sequential reintroduction, double-blind placebo controlled, 2-parallel groups trial of enzyme-potentiated desensitization with 3 intradermal injections of mixed food antigens and food additives (food colors and food preservatives) every 2 months followed by open reintroduction of provoking foods/ 7 or more months	Parent rated short form of Conners' Rating Scale	Conners's scores decreased from a mean of 23 at baseline to 7.5 after open-elimination diet. Significantly more children in the active group (n = 15) were able to continue to eat the previously identified provoking food versus in the placebo group.
Carter et al., 1993	3–12[3]	78/ n < 6 not specified	Standardized psychiatric interview, ratings on the Conners' Rating Scale Parent and Teacher (CRS-P and CRS-T); DSM III criteria for ADHD	Few-foods diet[2] bottled water, sunflower oil. milk-free margarine, and already suspected foods were avoided	Elimination diet followed by challenge, 3-phase design: Open restricted (few foods) diet for 3–4 weeks, open sequential reintroduction of the offending foods, 4-week double-blind, placebo-controlled crossover challenge trial/ 10–12 weeks	CRS-P, global rating of severity of behavior problems by the parent, direct behavior observation for ADHD symptoms	76% (59/78) improved on open restricted diet, 80% (47/59) relapsed with open challenges, 74% (14/19) completers in the double blind trial showed reductions in parent-rated symptoms of hyperactivity and irritability (mean difference between active and placebo CRS-P scores = 5.2), and directly observed ADHD symptoms while on placebo compared to the incriminated food
Rowe and Rowe, 1994	2–14 (7.1 ± 3.5)[4]	200/25	No clinical assessment for a diagnosis of ADHD; Children referred for suspected hyperactivity in association with diet	Synthetic coloring free elimination diet	Elimination diet followed by challenge. 2-stage study: 6-week open trial of a diet free of synthetic colorings, double-blind, placebo-controlled, crossover randomized trial with 6 different doses of tartrazine/ 9 weeks	Conners' Abbreviated Parent-Teacher Questionnaire (CAPTQ), Behavior Rating Inventory (BRI)	150/200 (75%) improved with elimination diet in the open trial. Worsening of CAPTQ and BRI scores reported during the dye challenge with tartrazine. Younger preschool children were described as restless, disruptive, easily distracted and excited. high as a kite, out of control, and displayed constant crying, tantrums, irritability, and severe sleep disturbance.

(*continued*)

Table 7. Published Studies of Alternative Treatments in Preschool Children with Attention-Deficit/Hyperactivity Disorder: Elimination Diets (Cont'd.)

Authors	Age Range in years (Mean age ± SD in years)	N/n < 6 years	Procedure for ADHD Diagnosis; Inclusion Criteria	Type of intervention	Study Design/ Duration	Outcome Assessment (for ADHD and disruptive behaviors)	Study Outcome
Boris and Mandel, 1994	3–11 (7.5 ± 2.2)	16/6	No information provided on the procedure for diagnosing ADHD: DSM-III diagnosis of ADHD, cutoff threshold for Conners' Rating Scale-Parent-48 (CRS-P-48)	Elimination diet (dairy products, wheat, corn, yeast, soy, citrus, egg, chocolate, and peanuts) and artificial colors and preservatives prohibited	Elimination diet followed by challenge: 2-week open elimination diet, 1-month open sequential food challenges, 7-day double-blind placebo controlled food challenge (DBPCFC)/ 7 weeks	CRS-P-48	73% (19/26) improved on open elimination diet, 79% (15/19) responders were atopic. During the DBPCFC mean CRS-P-48 Hyperactivity index score on challenge days was 18 ± 7 compared to 8.4 ± 4.9 on placebo days. Atopic subjects were more likely to respond to the elimination diet.
Bateman et al. 2004	3.2–4 (3.7[1])	277/277	Cutoff threshold on the EAS Activity Scale and Weiss-Werry-Peters Activity Scale (WWPAS); 3–4 year old children living on the Isle of Wight	Artificial food coloring and sodium benzoate free diet	Elimination diet followed by challenge in 4 groups of children with hyperactivity crossed with atopy (Hyperactive [HA]/ Atopic [AT] not-HA/AT, HA/not- AT, and not- HA/ not-AT): 1-week artificial food coloring and sodium benzoate free diet, double-blind, placebo controlled challenge with 1-week of 20 mg of artificial food colorings and 45 mg of sodium benzoate or placebo separated with one week of washout/4 weeks	Parent completed daily WWPAS ratings, weekly in-clinic assessments on structured tasks for inattention, activity and impulsivity	Reduction in parent-rated hyperactivity between baseline and end of the week of elimination diet. Greater increase in parent-rated hyperactivity during the dye challenge period compared to the placebo challenge period. No effect detected with direct behavioral observation. No effect of atopy or severity of hyperactivity symptoms.

[1]SD not provided.
[2]Few-Foods diet included two meats (e.g., lamb and chicken), two carbohydrates sources (e.g., potatoes and rice), two fruits (e.g., banana and apple or pear), vegetables (cabbage, sprouts, cauliflower, broccoli, cucumber, celery, carrots, parsnip), salt, pepper, water, calcium, and vitamins.
[3]Mean age not provided.
[4]Mean age reported for the 34 children participating in the double-blind trial.
ADHD = attention-deficit-hyperactivity scale.

giver control of diet, and can be considered when there is a history of formula intolerance, food sensitivity, or general allergic diathesis. It is important to emphasize that an elimination diet trial should be implemented only under the supervision of the child's primary healthcare provider and a nutritionist to ensure that growing preschoolers do not suffer from nutritional deficiencies with the restricted diet. The restricted diet (additive free diet and/or few-foods diet) can be tried for 2 weeks (Egger et al. 1985). If there is no benefit from the restricted diet, it should be discontinued. A stringent elimination diet should not continue for more than 2 weeks without obvious benefit because of the danger of imbalance, especially of calcium and some vitamins. If there is benefit, start adding back the restricted foods weekly (Egger et al. 1985), one food component at a time to identify the problem foods to be excluded from a less restrictive permanent diet.

Vitamin/mineral supplementation. Unfortunately, there is no research on effects of Recommended Daily Allowance/Recommended Dietary Intake (RDA/RDI) of multivitamins/minerals in diagnosed ADHD children even though some reports suggest mild deficiencies in diet and blood levels that might be addressed. However, in a randomly assigned double-blind placebo-controlled trial of RDA vitamin and mineral supplementation in 47 6-year-old children not selected for ADHD, Benton and Cook (1991) found an 7.6 point IQ advantage ($p < .001$), mainly based on nonverbal ability increases. They also found increased concentration and decreased fidgeting on a frustrating task ($p < .05$), and advantage on a reaction time task reflecting sustained attention (Cohen's $d = 1.3$, $p < .05$). These data warrant a controlled trial in ADHD, although the benefit may be confined to a subgroup with poor diets (Benton 2001).

Regarding a more specific nutrient, Metallinos-Kasaras et al. (2004) found in 3- and 4-year-old children with anemia (and serum lead levels of <50 ppb) not diagnosed with ADHD that iron supplementation (15 mg/day) yielded significant improvements in selective attention compared to placebo. There were no effects of iron supplementation in preschoolers who were not anemic. As seen in Table 8, there is one case report in a 3-year-old child (Konofal et al. 2005) and one double-blind, randomized, placebo-controlled trial in 5- to 8-year-old non-anemic children with low serum ferritin levels, diagnosed with ADHD, reporting improvement in ADHD symptoms with iron supplementation (Konofal et al. 2008).

Another nutritional consideration is essential fatty acids, especially omega-3 long-chain polyunsaturated fatty acids. Omega-three deficiency in infants impairs visual attention e.g., (Neuringer 1998). There have been 7 placebo-controlled trials of essential fatty acids relevant to ADHD, all in school-age children.

Five of the seven studies were in children diagnosed with ADHD showing equivocal or no effect in three (Aman et al. 1987; Arnold et al. 1989; Voight et al. 1998), and promising results in two (Sinn and Bryan 2007; Stevens et al. 2003). The other two were in children with dyslexia and developmental coordination disorder, both of which have large overlap with ADHD.

Preschoolers, with their rapid growth/metabolism and smaller bulk for storage of nutrients, may have a special need for nutritional attention. Adequate nutrition becomes even more of a concern when the child is given an appetite-suppressing stimulant for ADHD. It is important in evaluating a preschool child with ADHD to take a careful diet history. If history reveals a diet poor in iron sources, a blood test for iron may be advisable (Konofal et al. 2008). Similarly, if the diet appears unbalanced in other ways, one might suspect other nutritional deficiency.

Recommendation of RDA/RDI multivitamin/minerals is well within the purview of conservative medical practice, at least until the child's diet can be balanced. Consumption of wild ocean fish a couple of times a week is recommended by the American Heart Association to protect against omega-3 deficiency (Kris-Etherton et al. 2002).

Vestibular stimulation. Mulligan (1996) reported significant impairment of vestibular processing in 309 children with ADHD compared to 309 matched 4- to 8-year-old children without ADHD ($p < 0.01$). As seen in Table 9, improvement in Conners' teacher ratings from vestibular stimulation compared to a sham condition was reported in two randomized studies in a mixed-age sample (school-age and preschool age children) with symptoms of ADHD (Arnold et al. 1985; Bhatara et al. 1981). Bhatara et al (1981) mentioned that the largest effect was found in the younger children.

Vestibular stimulation is not a proven treatment, but the SECS rule may apply here. The vestibular stimulation of rocking, spinning, piggyback and horsie rides, and swings is a natural environment for preschoolers and can be augmented by sit-and-spin toys, swivel chairs, and rotational games.

Massage. The tactile and deep pressure stimulation of massage has been reported to elicit several benefits. Of relevance to ADHD, massage increased on-task behaviors of 3- to 6-year-old autistic children (Escalona et al. 2001), and attentiveness/responsivity and increased vagal activity were associated with increased attention span in 22 preschool children with autism (Field et al. 1997). In adults, it improved math performance (Field et al. 1996), which is sometimes used as an objective outcome measure in pharmacological treatment of ADHD.

The only study in diagnosed ADHD was a randomized, controlled trial in 28 adolescent boys with DSM-III-R ADHD. Massage was reported to reduce teacher-rated Conners' 10-item scale scores from 28 at baseline to 11.3 while the relaxation therapy controls deteriorated from 19.6 to 28.5 (Field et al. 1998). There are no studies on effects of massage in preschool children with ADHD.

Massage of the child by the parent appears to be a safe and cheap intervention that at least should improve parent-child relationship and fits naturally into the cuddling, rough-housing, and other tactile stimulation appropriate for preschoolers. Massage may be especially helpful at bedtime.

Summary of alternative treatments. Of the four alternative interventions described, only the elimination diet has some convincing evidence at this point, and it is probably applicable to only a minority of children with ADHD (although probably a larger percent of preschoolers than of older children (Dulcan and Benson 1997). However, the other three interventions have some controlled evidence (albeit not con-

Table 8. Published Studies of Alternative Treatments in Preschool Children with Attention-Deficity/Hyperactivity Disorder: Nutritional Support

Authors	*Age in years (Mean age ± SD) in years*	*N/n < 6 years*	*Procedure for ADHD Diagnosis; Inclusion Criteria*	*Type of Intervention*	*Study Design/ Duration*	*Outcome Assessment (for ADHD and disruptive behaviors)*	*Study Outcome*
Konofal et al., 2005	3	1/1	Clinical diagnosis, parent and teacher Conners' Rating Scale: DSM-IV diagnosis of ADHD, low serum ferritin level	Iron supplementation (ferrous sulphate 80 mg/day)	Case report/ 8 months	Parent and teacher Conners' Rating Scale	Parent and teacher reports of improvement in impulsivity, hyperactivity and behavior with ferrous sulphate treatment
Konofal et al., 2008	5–8 (6.05 ± 1.05)	23/ n < 6 not specified	Clinical diagnosis; DSM-IV diagnosis of ADHD, normal hemoglobin level, serum ferritin level <30 ng/ml,	Iron supplementation (ferrous sulphate 80 mg/day)	Double-blind, randomized, placebo controlled, parallel groups (ferrous sulphate, placebo)/ 12 weeks	Parent and teacher Conners' Rating Scale, ADHD Rating Scale (RS), Clinical Global Impressions (CGI)	Significant decrease in ADHD-RS and CGI-Severity ratings with ferrous sulphate compared to placebo. Improvement on parent and teacher Conners' Rating Scale with with ferrous sulphate compared to placebo was significant at the trend level ($p = 0.076$)

ADHD = attention-deficit/hyperactivity disorder.

Table 9. Published Studies of Alternative Treatments in Preschool Children with Attention-Deficit/Hyperactivity Disorder: Vestibular Stimulation

Authors	*Age in years*	*N/ n < 6 years*	*Procedure for ADHD Diagnosis; Inclusion Criteria*	*Type of Intervention*	*Study Design/ Duration*	*Outcome Assessment (for ADHD and disruptive behaviors)*	*Study Outcome*
Bhatara et al., 1981	4–14 (mean & median = 8)	18/3	Clinical assessment, cutoff threshold on the Davids hyperkinetic scale: clinical DSM-II diagnosis of hyperkinetic reaction of childhood	Vestibular and visual stimulation	Crossover design with twice weekly vestibular stimulation with eyes open in a lighted room for 4 weeks and 4 weeks of placebo contact in random order/ 8 weeks	Parent- and teacher-completed Shortened Conners' Rating Scale and Davids Hyperkinetic Scale	Teacher Conners' ratings and psychiatrist's assessment showed significant treatment benefit for children younger than 10 years. Parent ratings showed significant placebo effect from the control sitation. Mild side effects, mostly nausea, were noted from the vestibular stimulation, none withdrew from the study because of side effects. Five children took concomitant psychotropic medication.
Arnold et al., 1985	5–9 (mean & median = 7)	30/ n < 6 years not specified	Teacher-completed rating for DSM-III seminal draft criteria for ADDH, cutoff threshold on the Davids Hyperkinetic Scale, Conners' Rating Scale; Nonclinical sample from elementary schools meeting DSM-III seminal draft criteria for ADDH	Vestibular and visual stimulation	Crossover design with children randomized to 1 of the 2 series: 4 weeks each of control condition, combined visual and vestibular stimulation and either vesribular stimulation alone or visual stimulation alone/ 12 weeks with follow-up at 1 year	Parent- and teacher-completed Davids Hyperkinetic Scale, Conners' Rating Scale	Improvement on teacher ratings at the end of treatment and at one-year follow-up with comparatively larger effect size for vestibular stimulation alone than for either visual stimulation alone or the tactile-auditory-vestibular control condition

ADHD = attention-deficit/hyperactivity disorder.

clusive), are safe, easy, cheap, and sensible, seem more widely applicable in preschool children, and can be implemented in conjunction with standard behavioral and/or pharmacological treatment.

Conclusions

Pharmacological intervention studies outnumber nonpsychopharmacological intervention studies. Pharmacological interventions have been studied in comparatively larger samples of preschool children and have tended to use more rigorous methodology than nonpsychopharmacological interventions.

Specifically, MPH demonstrates efficacy compared to placebo in treating ADHD symptoms in preschool children with DSM diagnosis of ADHD in at least five double blind, randomized, controlled, group treatment trials (Barkley 1988; Conners 1975; Greenhill et al. 2006; Musten et al. 1997; Short et al. 2004). Thus for informing clinical practice, adequacy of MPH efficacy data in preschool children is at Level A. In terms of safety data, preschoolers are reported to be sensitive to the adverse effects of MPH with increased rate of irritability, mood changes, withdrawal, and lethargy (Wigal et al. 2006) and a decreased rate of height and weight velocity (Swanson et al. 2006). Additionally, no information about long-term safety and effects of MPH on brain development of preschool children is available. Hence, caution is needed when considering pharmacological treatments in preschool children with ADHD. Information about the efficacy and safety of other stimulants and non-stimulants in preschool children is at Level C.

Among nonpsychopharmacological interventions, there are comparatively more studies for parent behavior training than child training, and evidence is sparse for alternative interventions for treating ADHD in preschool children. Adequacy of parent behavior training (PBT) data is at Level B as shown by improvement in ADHD symptoms with PBT ($n = 30$) compared to a Parent Counseling and Support Group ($n = 28$) and a Waiting List Control Group ($n = 20$) in preschool children meeting DSM-IV diagnostic criteria for ADHD (Sonuga-Barke et al. 2001). Efficacy of child training in preschool children with ADHD was supported in one single case design series that included preschool children with a formal diagnosis of ADHD ($N = 4$) and showed reductions in hyperactivity and disruptive behaviors with both token reinforcement and response cost in a reversal design (McGoey and DuPaul 2000). Hence, adequacy of the child training data is at Level B, the small number of subjects limits the generalizability of the findings.

Adequacy of additive free elimination diet data is at Level B as shown by one double-blind crossover study that included 24 preschool children with a formal diagnosis of ADHD and showed improvement in ADHD symptoms with the elimination diet compared to the placebo diet (Kaplan et al. 1989). The evidence for other alternative treatments is generally at Level C.

In summary, the level of evidence to support short-term treatment of preschool ADHD with MPH is Level A and with parent behavior training, child training and additive-free elimination diet is Level B. It is important to emphasize that the difference between the level of evidence for adequacy of pharmacological and nonpharmacological treatments for preschool ADHD does not necessarily indicate difference in efficacy between these treatments; rather it indicates relative paucity of adequate research with nonpharmacological treatments compared to pharmacological treatments. There is only one study that followed preschoolers, formally diagnosed with ADHD, prospectively for 10 months and reported long-term effectiveness of MPH. There are no studies of comparative and/or combined efficacy or long-term safety of any of the treatment interventions for ADHD in preschoolers.

Clinical Guidelines

Given the short- and long-term safety concerns and lack of information about effect of psychopharmacological interventions on brain development of preschoolers, there is a strong clinical consensus that psychosocial interventions should be tried first in preschoolers with ADHD (Dulcan and Benson 1997; Gleason et al. 2007; Kollins et al. 2006). A psychosocial intervention plan should address child's behavior problems both at home and at school. Parent behavior training should be offered to the caregivers, and parents should be encouraged to work with their child's preschool or daycare teacher to integrate coordinated behavior management strategies at home and at preschool or daycare. Direct child training in the classroom can be implemented as indicated. Comorbid disorders should be identified and appropriate work-up and interventions (e.g., speech, language, and communication assessment and treatment for preschoolers presenting with language delays) should be included in the treatment plan. It is important to assess and support treatment and social support needs of the caregivers. If the caregivers believe that their child's behavioral symptoms become worse with food additives and/or certain foods, a careful trial of additive free and/or the restricted diet can be implemented under the supervision of a nutritionist and the child's pediatrician, as described previously.

Pharmacological intervention can be considered when psychosocial intervention has been unsuccessful (Dulcan and Benson 1997) or only partially successful. Care and caution should be exercised in selecting medication dosage for preschool children. Practitioners need to consider the unique sensitivity of preschool children to adverse events and should follow the rule of "start low, go slow" allowing sufficient time on a particular dose to estimate adverse effects and efficacy. At the same time care should be taken to avoid undertreatment with lower doses. Preschoolers should be followed closely for monitoring of possible emergence of adverse effects and dosage adjustment with weekly or biweekly (every other week) visits for the first 1–2 months and then monthly for maintenance visits once the preschooler is on an optimal dose.

Parent and teacher rating scales (e.g., CRS, SNAP, CBCL-$1\frac{1}{2}$, ADHD-RS) should be collected for baseline behaviors and repeated regularly for ongoing monitoring of treatment response during follow-up visits.

As mentioned previously, MPH has the best evidence (Greenhill et al. 2006) and is most frequently started at 2.5 mg BID and increased to 7.5 mg BID or TID over the course of 2–4 weeks depending on the child's response and any side effects. It is important to note that there are a minority of preschoolers who may benefit from 1.25 mg TID of MPH; 15% of the preschoolers in the PATS were reported to be best responding to 1.25 mg TID, and teachers reported improved

ADHD symptoms with 1.25 mg TID compared to placebo (Greenhill et al. 2006).

Decision for a BID or TID dose may be based on the child's and family's needs. For example, some parents want their preschooler to take medication only when the child attends school and hence may prefer BID dose instead of the TID dose used in the PATS (Greenhill et al. 2006).

There are no controlled efficacy data for long acting MPH or other psychostimulants or non-stimulants in preschoolers with ADHD. If a preschooler does not respond to MPH, clinicians are left to extrapolate data from older school-age children. Based on school-age ADHD treatment data, if a child does not respond to a trial of one class of stimulants (e.g., MPH), switching to the other class (e.g., amphetamines) is recommended before using another drug class (Arnold et al. 1978; Dulcan and Benson 1997; Elia et al. 1991). There are no empirical data to guide dosing schedules for amphetamines in preschoolers with ADHD; it has been suggested that amphetamines are twice as potent as MPH (Pelham et al. 1999). If a preschooler does not respond to stimulants and/or has unacceptable side effects, a trial of atomoxetine or alpha-agonists is recommended (Gleason et al. 2007). As mentioned previously, there are no controlled efficacy or dose response data for atomoxetine or alpha-agonists in preschoolers with ADHD. Improvement in ADHD symptoms in 22, 5- and 6-year-old children (mean age 6.1 $\pm$ 0.58 years) was reported in a prospective open-label trial with 10–40 mg/day or 0.47–1.88 mg/kg/day of atomoxetine (mean dose = 1.25 mg/kg/day $\pm$ 0.35 mg/kg/day) administered as a single morning dose or BID (morning and afternoon) (Kratochvil et al. 2007). Adverse effects included mood lability in 54.5% and decreased appetite in 50% of the children. Regarding alpha-agonists, there are only 2 case reports of open-label treatment with clonidine (0.025 mg TID) and guanfacine (0.25 mg BID to 0.5 mg BID) both reporting improvement in ADHD symptoms and side effect of sedation early in treatment.

The limited evidence for efficacious treatment options relative to the frequency with which preschool children are referred for treatment of ADHD is striking. Additionally, it is noteworthy that as noted earlier, nonpharmacological treatment investigations lag behind pharmacological treatment studies in preschoolers formally diagnosed with ADHD. This is especially salient since there are short- and long-term safety concerns and there is little information regarding the effect of pharmacological agents on the brain development of preschool children with ADHD. Because of the fewer safety concerns compared to pharmacological treatments, clinicians, caregivers of preschoolers with ADHD, professional organizations making treatment recommendations, and the community at large prefer psychosocial interventions as a first line of treatment for preschool ADHD. This calls for more research to find the best possible treatments matched with parent preferences in order to expand the limited intervention options that are currently available for treating ADHD in preschoolers. There is an urgent need for well-designed, blind, randomized, controlled, between-group treatment trials to study comparative and combined efficacy and safety of psychopharmacological, psychosocial and alternative treatments in well characterized samples of preschool children with ADHD. It is important to study the long-term outcome and safety of treatment interventions and their impact on the developing brain of preschool children with ADHD.

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