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TECHNICAL REPORT

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Treatment of Attention-Deficit/Hyperactivity Disorder: Overview of the Evidence

ABSTRACT. The American Academy of Pediatrics' Committee on Quality Improvement, Subcommittee on Attention-Deficit/Hyperactivity Disorder, reviewed and analyzed the current literature for the purpose of developing an evidence-based clinical practice guideline for the treatment of the school-aged child with attention-deficit/hyperactivity disorder (ADHD). This review included several key reports, including an evidence review from the McMaster Evidence-Based Practice Center (supported by the Agency for Healthcare Research and Quality), a report from the Canadian Coordinating Office for Health Technology Assessment, the Multimodal Treatment for ADHD comparative clinical trial (supported by the National Institute of Mental Health), and supplemental reviews conducted by the subcommittee. These reviews provided substantial information about different treatments for ADHD and their efficacy in improving certain characteristics or outcomes for children with ADHD as well as adverse effects and benefits of multiple modes of treatment compared with single modes (eg, medication or behavior therapies alone). The reviews also compared the effects of different medications.

Other evidence documents the long-term nature of ADHD in children and its classification as a chronic condition, meriting the application of general concepts of chronic-condition management, including an individual treatment plan with a focus on ongoing parent and child education, management, and monitoring. The evidence strongly supports the use of stimulant medications for treating the core symptoms of children with ADHD and, to a lesser degree, for improving functioning. Behavior therapy alone has only limited effect on symptoms or functioning of children with ADHD, although combining behavior therapy with medication seems to improve functioning and may decrease the amount of (stimulant) medication needed. Comparison among stimulants (mainly methylphenidate and amphetamines) did not indicate that 1 class outperformed the other. *Pediatrics* 2005;115:e749–e757. URL: www.pediatrics.org/cgi/doi/10.1542/peds.; *attention-deficit hyperactivity disorder, stimulant medication, multimodal treatment, behavior management, co-occurring.*

ABBREVIATIONS. AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; MTA, Multimodal Treatment Study for Children With ADHD; MPH, methylphenidate; DEX, dexedrine; PEM, pemoline; RCT, randomized, controlled trial.

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INTRODUCTION

The American Academy of Pediatrics' (AAP) Committee on Quality Improvement, Subcommittee on Attention-Deficit/Hyperactivity Disorder, developed a clinical practice guideline pertaining to the treatment of school-aged children with attention-deficit/hyperactivity disorder (ADHD).[1,2] The review here covers the additional evidence gathered for and by the subcommittee regarding specific treatments for ADHD. It does not include more recent studies published since the publication of the guideline in 2001. Other evidence supports the notion that ADHD is a chronic health condition meriting the application of general principles of management of childhood chronic conditions by primary care clinicians. Longitudinal studies of Barkley et al[3] and Biederman et al[4] document the persistence of the condition over time. Previous policy statements by the AAP describe the elements of chronic-condition care, including educating parents and children about illness, developing individual treatment plans, helping to coordinate multiple services, and encouraging parents to have contact with other parents of children with chronic conditions. Because ADHD has pervasive effects on the child's daily life, including school performance, a partnership of clinicians and school personnel will help ensure the child's best progress and proper assessment of progress.

This report summarizes the empirical literature on which the practice guideline's recommendation for pharmacologic and/or behavioral intervention was based. Certain other aspects of clinical care have not been the focus of careful clinical trials or randomized, controlled studies to determine accurately optimal practices. Thus, many of these recommendations reflect consensus of best practices. The specific areas included in these consensus recommendations include (1) the best specific ways of titrating a child's medications, (2) the frequency of monitoring visits during titration phases and after stabilization, or (3) the specific content of monitoring. Again, these recommendations reflect assessment of best practices in long-term care.

Four main sources of data were examined in developing these treatment recommendations. The McMaster University Evidence-Based Practice Center (under contract with the Agency for Healthcare Re-

search and Quality and in partnership with the AAP and other organizations) reviewed the short- and long-term efficacy and safety of pharmacologic and nonpharmacologic interventions for ADHD and the comparative efficacy of single versus combined treatments. For a full account of the evidence, see the technical report compiled by the former Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality).[5] The second source was a review of interventions for ADHD conducted by the Center for Community Health Research, British Columbia Research Institute for Children's and Women's Health, and the University of British Columbia[6] for the Canadian Coordinating Office of Health Technology Assessment. The third source included the findings from the multisite treatment study conducted by the Multimodal Treatment Study for Children With ADHD (the MTA Cooperative Group),[7,8] which is supported by the National Institute of Mental Health.

After reviewing the findings and conclusions of the 3 sources listed above, the subcommittee conducted an additional search of the available literature to assess further the effectiveness of behavioral interventions both as stand-alone regimens and in combination with pharmacologic treatments. This search selected published reports of trials of behavior therapies in groups of school-aged children with ADHD. Individual case reports were excluded. The evidence from this search was compiled and evaluated by the subcommittee.

McMASTER UNIVERSITY EVIDENCE-BASED PRACTICE CENTER REVIEW

The goals of the evidence-based review conducted by the McMaster University Evidence-Based Practice Center Group[5] were to examine the efficacy of nonstimulant medications and nonpharmacologic interventions for ADHD in children and adults and to examine the comparative efficacy of combined versus individual interventions. The technical review examined (1) drug-to-drug comparisons of specific stimulant medications, (2) stimulants versus antidepressant medications, and (3) comparisons of different forms of the same medication. The stimulant drugs examined were methylphenidate (MPH), dexedrine (DEX), and pemoline (PEM). The review also compared tricyclic antidepressants versus placebo and pharmacologic versus nonpharmacologic interventions. The report also examined long-term studies with a duration of 12 or more weeks. Final categories reviewed were studies examining the treatment of ADHD in adults, treatment combinations, and the adverse effects of pharmacologic interventions. This article reviews only findings pertaining to treatment of ADHD among school-aged children.

The McMaster review selected a total of 92 empirical articles reflecting 78 investigations from a pool of 2405 citations compiled from traditional databases (Medline, Cinahl, HealthStar, PsychINFO, Embase), *The Cochrane Library* (1997, issue 4), reference lists of articles identified in the previous sources, and additional citations suggested by members of the McMaster research team and partnering organizations. Two reviewers independently rated each article to determine the quality of the methodology used in the study. Studies were included in the evidence-based review if they were randomized, controlled trial (RCTs), involved human subjects, and were published as a full report in a peer-reviewed journal. Studies that included participants with diagnoses other than ADHD (eg, oppositional defiant disorder, conduct disorder) were included in the review only if the study provided a separate analysis for the study participants with ADHD.

A problem identified by the review team and associated organizations was the diversity of outcomes used in these many studies. Some studies used indicators or core symptoms of ADHD; others examined aspects of school or social behavior or behaviors at home. This diversity makes clear comparisons among treatment regimens difficult. The McMaster review noted important methodologic limitations in the numerous studies examining interventions for ADHD spanning a period of more than 25 years. Major limitations included small sample sizes and the use of heterogeneous outcome measures. The review found few studies in most of the study areas.

Drug-to-Drug Comparisons

Twenty-three studies on specific drug-to-drug comparisons were included in the review. These included studies comparing different stimulant medications: 8 studies compared MPH and DEX,[9–17] 2 compared MPH and PEM,[18,19] and 1 compared DEX and PEM.[20] Three studies compared a stimulant drug and a tricyclic antidepressant. One study compared MPH and desipramine,[21] and 2 compared MPH and imipramine.[22,23] Also included were studies comparing different formulations of the same drug. Three studies compared regular and sustained-release formulations of MPH,[24–26] and 1 study compared different isomers of MPH (L-MPH versus D-MPH).[27] Finally, 1 study compared DEX and levoamphetamine.[9]

The stimulant-stimulant comparisons documented few, if any, differences among MPH, DEX, and PEM. Findings from the 3 reviewed studies comparing a stimulant medication with a tricyclic antidepressant medication were inconclusive. The study comparing MPH and desipramine[21] included children with symptoms of both ADHD and depression. MPH outperformed desipramine in improving children's vigilance and ability-to-learn paired associations. Of the 2 studies comparing MPH and imipramine, 1 found no significant differences, and the other provided data favoring imipramine compared with MPH.[22,23] Finally, the studies comparing different formulations of the same drug revealed no significant formulation effects.

Tricyclic Antidepressants Versus Placebo

Nine reviewed studies compared the efficacy of tricyclic antidepressant medication and placebo in managing symptoms of ADHD. Six studies (described in a total of 8 reports) examined the effects of desipramine,[21,28–34] and all of the studies revealed

improvements for children taking desipramine when compared with placebo. Three studies examined the efficacy of imipramine[23,35,36] and reported inconsistent findings, with improved performance on some tasks and behavior measures but not others.

The studies showed that desipramine is more effective than placebo despite the small sample sizes and heterogenous designs. Results were inconsistent for studies comparing imipramine with placebo. The McMaster report suggests the need for more research to determine the role of these drugs for the treatment of ADHD.

Pharmacologic Versus Nonpharmacologic Interventions

Six reviewed studies compared pharmacologic versus nonpharmacologic interventions. Five studies compared some form of psychological or behavioral intervention versus medication,[6,7,37–40] and 1 study compared DEX and the dietary supplement Efamol (Efamol Ltd, North Yorkshire, United Kingdom).[41] The evidence review noted that these studies, with the exception of the study by the MTA Cooperative Group, provided insufficient detail regarding the interventions and methodology and much heterogeneity in the type of nondrug intervention and outcomes assessed. The MTA Cooperative Group provided much more detail regarding its clinical interventions and outcome measures. Because this study was well designed, had a large sample, and provided a rich source of information, findings from the MTA Cooperative Group study are reviewed in a separate section of this article.

Combined Interventions

The McMaster team found 20 studies satisfactory to review to determine the benefits of combined interventions over and above the effects of single interventions. Five studies compared drug combinations (ie, MPH combined with either amphetamine, caffeine, desipramine, or haloperidol) and a single stimulant medication.[42,43] Fourteen studies involved comparisons of either behavior or cognitive therapy along with combined nonpharmacologic intervention and stimulant medication.[7,8,37–39,44–54] None of these studies, with the exception of that by Carlson et al,[47] provided evidence to suggest that nonpharmacologic intervention alone performed as well as the nonpharmacologic intervention plus stimulant medication.

Long-Term Intervention for ADHD

The McMaster report reviewed available studies that examined the effects of long-term intervention for ADHD. Even with a definition of "long-term intervention" as a treatment administered for 12 or more weeks, only 14 studies were found for review.* The review concluded that, regardless of treatment, there was an overall trend for improvement over time as long as the treatment is continued, indicating the importance of treatment adherence.

*Refs 7, 8, 15, 22, 37–39, 45, 46, and 55–60.

Adverse Effects of Pharmacotherapy for ADHD

The McMaster group also reviewed 33 reports based on 28 RCTs and 1 nonrandomized study to evaluate the adverse effects of pharmacotherapy. Nearly two thirds of the reports evaluated adverse effects for less than 12 weeks, and in many of the studies, sample sizes were small (ie, 30 or fewer participants). Most ($n = 15$) studies focused on MPH. Nine examined amphetamines (DEX or L-amphetamine); 2 examined PEM; and 2 examined antidepressants. Across studies, the most frequently examined adverse effects were appetite suppression, sleep disturbances, headaches, motor tics, abdominal pain, irritability, nausea, and fatigue. The report concluded that, overall, many of the adverse effects associated with the use of stimulant medications in the management of ADHD symptoms seem to be mild, of short duration, and responsive to dosing or timing adjustments. However, it should be noted that RCTs are not a sufficient source for the determination of rare adverse effects such as liver failure in PEM use.

The McMaster review found few, if any, differences across different stimulants (MPH, DEX, PEM). However, it made no conclusions regarding the relative effectiveness of stimulants versus tricyclic antidepressant medications in managing ADHD symptoms. The review concluded that stimulant medication outperforms nonpharmacologic interventions in controlling the core symptoms of ADHD but provided insufficient information to conclude whether drug combinations outperform stimulant medications alone or that nonpharmacologic intervention adds to pharmacologic intervention. They noted a need for more definitive studies examining the value of combination treatments, studies that will require significant resources and collaboration and more complex study designs. One such study, the MTA Cooperative Group study, is reviewed later in this technical report.

A report of the Canadian Coordinating Office for Health Technology Assessment[6] reviewed empirical evidence addressing several issues pertaining to the treatment of ADHD. The report addressed the efficacy of MPH, the efficacy of psychological/behavioral treatments for ADHD, comparisons between MPH and other stimulant medications, comparisons between MPH and psychological/behavioral treatments, and comparisons between combined drug and psychological/behavioral treatments for ADHD.

This review considered 195 treatment studies from a pool of more than 1000 citations from articles published after 1980 compiled from traditional databases (Medline, Current Contents, HealthStar, PsychINFO, First Search, CUE, Embase), selected reference lists, and published and unpublished studies made available by pharmaceutical manufacturers. Studies were included in the review if they were RCTs involving either parallel group designs or within-subjects crossover designs with participants randomly assigned to treatment order, involved children 18 years or younger, and involved children with ADHD who were unselected for the presence of specific coexisting disorders (ie, the presence of coexisting disorders

were acceptable if the study did not focus on the effects of intervention on a specific ADHD subpopulation as defined by a particular coexisting condition). These strict criteria allowed inclusion of only 26 of the 195 articles for full review, including 21 drug studies, 2 psychological/behavioral studies,[55,61] and 3 studies of combined drug and psychological/behavioral treatment.[37,45,62] Among the drug studies, posttreatment assessments generally were conducted between 7 and 25 days after the onset of pharmacologic intervention and at a time when the child was still receiving medication. The 5 studies examining either psychological/behavioral interventions or psychological/behavioral interventions combined with pharmacotherapy included both posttreatment assessments 70 to 120 days after the initiation of treatment and follow-up assessments ranging from 112 to 365 days after initiation of treatment.

For comparisons across trials, the report used the hyperactivity index of the Conners' Teacher Rating Scale and Conners' Parent Rating Scale[63,64] to avoid interpretational difficulties that occur as a result of examination of heterogeneous outcome measures across studies. This point is discussed further in the section ("Multi-Modal Treatment Study of Children with ADHD") describing findings from the MTA Cooperative Group study.

Stimulant Medication

A body of evidence attested to the efficacy of MPH in treating the symptoms of ADHD.[6] Of the 34 studies reviewed involving MPH, 15 focused on the elementary school–aged population, with few studies among preschoolers ($n = 6$) and adolescents ($n = 13$). Only the findings pertaining to school-aged children are discussed in this technical report.

MPH improved functioning in a number of other domains, at least in the short term. However, the effect sizes varied among symptom domains, with the strongest effects of stimulant medication on measures of attention, distractibility, and impulsivity (effect sizes: 0.75–0.84; mean: 0.78) and observable social and classroom behavior (effect sizes: 0.63–0.85; mean: 0.81). Only modest effects were reported for academic achievement (effect sizes: 0.19–0.47; mean: 0.34).

Direct comparisons of different stimulant medications revealed no clear differences among MPH, DEX, and PEM. Two studies examining the efficacy of psychological/behavioral treatments compared with a control group revealed inconsistent findings. One study showed significant treatment effects when considering parent reports of ADHD symptoms on the Revised Behavioral Problems Checklist,[65] although this checklist was not identified as one of the acceptable outcome measures as determined by the Centre for Health Evaluation Research.[55] The other study used the Conners' Teacher Rating Scale and showed no treatment effects.[61]

Combined Interventions

Three studies addressed combined medical and psychological/behavioral therapy with inconclusive results.[37,62]

Overall, this review concluded that evidence consistently supports the efficacy of drug therapy in managing the core symptoms of ADHD, with no clear differences among MPH, DEX, and PEM. However, the ability to make comparisons among these drug treatments was limited by the few data available for medications other than MPH at the time of the review. Psychological/behavioral therapies without medication treatment were not efficacious in managing the core symptoms of ADHD. Combined therapy did not outperform medication alone, at least when examining core ADHD symptoms. Finally, Miller et al[6] reported that findings were inconsistent with regard to the benefit of combining psychological/behavioral therapies with medication versus psychological/drug therapy alone, with combined therapies seeming more efficacious when considering the ratings of the parent, but not of the teacher, for ADHD symptoms. Again, conclusions are limited by the paucity of well-controlled studies, the small number of participants in those studies, and the assessment of treatment effects focusing on the core symptoms of ADHD as captured by a narrow selection of behavior ratings scales.

MULTIMODAL TREATMENT STUDY OF CHILDREN WITH ADHD

The National Institute of Mental Health Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder[7,8,66] included 579 children with ADHD (combined subtype) who were assigned randomly to 1 of 4 treatment groups: state-of-the-art medication management, intensive behavioral intervention, a combination of the 2 interventions, and a community treatment control group who received "usual care" (most commonly medication). Outcomes were assessed in multiple domains and included measures reflecting the core symptoms of ADHD as well as measures of co-occurring problems in social skills, parent-child relations, oppositional defiant behavior, internalizing behavior problems (eg, anxiety), and academic achievement. Outcome data reflected assessments conducted while children in groups involving pharmacotherapy were still receiving medication, although the behavioral interventions in the behavioral and combined treatment groups had been completed.

In terms of treatment outcome, all 4 treatment groups showed improvements over time, with medication management and the combined intervention associated with greater improvement than the intensive behavioral intervention alone and the community treatment control group, when considering the core symptoms of ADHD.[7,8,66] However, only families assigned to the combined treatment group showed consistently greater benefits than the families in the community treatment group across other outcomes domains (eg, disruptive behavior, parent-

child relations, social skills).[7,8,66] Children with ADHD who had coexisting anxiety disorders responded well in both of the treatment groups that included the intensive behavioral interventions.[67,68]

Treatment outcome was also examined against a broad composite outcome measure that aggregated treatment responses across a broad array of symptom and functional domains including internalizing (ie, anxiety, depression) and externalizing (opposition, aggression) symptomatology and social skills.[69] The investigators added this analysis to address the concern that measures that assess primarily core symptoms of ADHD may be less sensitive to the effects of behavioral intervention. Using this composite measure as an outcome variable, analyses revealed that children who received the combined intervention exhibited the best treatment response.[69]

Wells et al[70] examined the effect of treatment on parent and family stress measures. Data revealed no differences among the 3 study treatment groups and the community treatment control group on measures of family distress (eg, parenting stress, depressive symptoms among parents, marital adjustment). However, compared with the community treatment control group, parents in the medication management, intensive behavioral intervention, and combined treatment groups reported greater reductions in their use of negative or ineffective discipline.[70] Data were also examined to determine if such parent-reported changes in parenting behavior were associated with teachers' reports of child behavior at the end of treatment.[71] Findings revealed that, at the end of treatment, teachers' ratings of disruptive child behavior fell within the normal range for families that participated in the combined treatment group, and this group reported the greatest reductions in negative and ineffective discipline. This effect was not found for families who participated in behavioral intervention alone.

One component of the intensive behavioral intervention arm of the MTA Cooperative Group study was a summer treatment program. Pelham et al[72] evaluated 117 children participating in a summer program at 3 of the MTA Cooperative Group sites. Approximately half of these children were assigned to the behavior intervention alone group and half were assigned to the combined treatment group. Children in the behavioral summer program who were also medicated showed a better response to treatment on 5 measures (following rules, good sportsmanship, peer negative nominations, and summer program teacher ratings of ADHD symptoms). However, children responded similarly to treatment regardless of medication status on 30 other measures. For 6 of the 35 measures of child behavior, children in the combined treatment group were more likely than those in the behavioral treatment alone group to fall within the normative range.[72]

ADDITIONAL SUBCOMMITTEE SEARCH AND REVIEW

The goal of the additional literature search was to identify additional investigational evidence to quantify the effectiveness of behavioral treatment in combination with drug treatment. This review originally provided ~200 potentially relevant articles, most of which were already included in other sources of information. After excluding case reports and general review articles, the subcommittee formally reviewed 28 articles and included 12 articles of relevance that had not been cited previously in other reviews.[45,47,51,72–79] Table 1 summarizes the evidence of these reviews. The subcommittee assessed the additional evidence obtained from this review and noted an imbalance in the quality of evidence available for drugs versus behavioral interventions. Although drug regimens were highly specific as to type of drug, dose, and duration of treatment, behavioral interventions lacked this specificity and were less quantified. Investigators did not use identical behavioral interventions and used varying degrees of detail to describe the interventions.† The subcommittee found diversity in the type, intensity, and duration of interventions; for example, some focused on the family setting, and others focused on the school setting. No data directly compared the benefits of these different modalities, such as comparing daily report cards and summer training programs. The costs of these programs varied widely. Subcommittee members noted that these factors made it unlikely that a strong evidence-based recommendation for behavioral intervention per se would be possible.

The subcommittee concluded, on the basis of data from this additional literature review, that drug treatment alone showed a consistent dose-sensitive effect in improving the core symptoms of ADHD. Behavioral interventions alone did not demonstrate statistically significant results. Medication treatment in combination with behavioral interventions was shown to be as beneficial as drug treatment alone. In addition, some studies found that combined modalities yielded 2 additional desirable outcomes: (1) they enhanced teacher and parent acceptance, and (2) they lowered the drug doses needed to achieve the same therapeutic benefits as with drug treatment alone.[47]

CONCLUSIONS

ADHD is a chronic condition that requires ongoing management and monitoring. A robust evidence base attests to the efficacy of stimulant medications in helping to manage the symptoms of ADHD among school-aged children. The stimulant drugs tested seemed equally effective. Tricyclic antidepressants may be effective also but are recommended only when children have been refractory to 2 or more stimulant drugs or have intolerable adverse effects. When considering evidence from RCTs, the data in support of behavioral intervention are less compelling. None of the nonpharmacologic interventions

† Typically, medication trials provide an easier task for researchers, insofar as the intervention can be highly and tightly specified. Most other interventions (eg, physical therapy for arthritis, cognitive therapies for mental health conditions, rehabilitation for stroke, behavior therapies for ADHD) all have difficulty with much less specificity and exactness in specifying the intervention. This problem in specificity means that for most conditions, medications will have a stronger evidence base.

TABLE 1. Review of Interventions for ADHD

Author, Year	Study Type	No. of Subjects Randomized	Diagnosis Model	Interventions	Duration	Quality Assessment Score (of 5)	Outcomes of Interest Measured	Outcome Results
Anderson et al,[85] 1981	Crossover	12 boys (IQ low-average)	Clinical	MPH, self-control, placebo	2 wk	2	Sustained attention, Conners, CCT	MPH > placebo; MPH > no medication; MPH > self-control; self-control = NS
Klassen et al,[73] 1998	Meta-analysis	999 (26 trials)	DSM-III: ADD, ADD-H, ADHD	MPH, BT	Variable	Meta	CTRS*, CPRS*, CAP, HSQ, Iowa	MPH > BT; BT = NS; MPH = combined
Pfiffner and McBurnett,[74] 1997	Parallel	27	DSM-III-R	SS with and without parent generalization	8 wk	2	SSRS, UCI-SSS, CLAM, SNAP-R, TRF	Both groups > null
Horn et al,[75] 1991	Parallel	117 (96 evaluated, 78 completed; referrals)	DSM-III-R	MPH high dose, MPH low dose, placebo (each group with and without [PT + SC])	12 wk	4	CBCL, SNAP, Conners, CTRS, SOAPS	MPH high or low dose > placebo; MPH alone = MPH + PT + SC, except teacher ratings (for which MPH low dose + PT + SC = MPH high dose); parent ratings improved in all study groups including placebo alone
Carlson et al,[47] 1992	Crossover	24 boys (summer medication program)	DSM-III-R	MPH high dose, MPH low dose, BM versus none, placebo	8 wk	3	Class observation, self-rating, academics	MPH high dose > MPH low dose > placebo. For on-task and disruptive behavior: MPH high dose > BM + placebo; MPH low dose > BM + placebo. For classroom points: BM > none
Abikoff and Gittelman,[51] 1985	Parallel	50 (44 MPH, 3 DEX, and 3 PEM)	Conners: CTRS ≥ 1.8/3.0	Med, Med + CT, Med + control	16 wk + 4-wk placebo follow-up	4	CTRS Hillside, Hahneman, parent reports, achievement, cognitive	CT = NS; Med > Med + control; achievement = NS. For classroom behavior: CT > control. Placebo follow-up: CT = NS
Hall and Kataria,[76] 1992	Parallel + Crossover	21 (referrals)	Gordon: Children's Intervention Rating Profile	CT, BM, control (all groups with and without MPH)	6–8 wk	2	Gordon, BDS	For impulsivity: MPH + CT > MPH alone; MPH + CT > CT alone. For vigilance: CT = NS; BM = NS
Brown,[45] 1986 AHRQ Dl-row 3	Parallel	40 (33 complete; referral)	DSM-III	MPH + CT, MPH + AC, placebo + CT, placebo + AC	3 mo	4	Cognitive, achievement (parent and teacher rating)	MPH > placebo; CT = NS
Pelham et al,[53] 1993	Parallel	32 (30 evaluated)	DSM-III, CTRS*, CPRS*	MPH + SS/BT, MPH + BT, placebo + SS/BT, placebo + BT, SS alone	9 mo	11	CTRS*, CPRS*, achievement (classroom observation)	MPH + BT > placebo + BT; BT > control; BT + MPH = BT; BT + SS = BT
Kolko et al,[77] 1999	Crossover	16 boys (all with comorbidity + partially hospitalized)	DSM-III-R	BM + MPH (alternating) (all with STEP intensive medication)	9 wk	3	CTRS, peer conflict, positive mood/behavior	MPH > placebo; BM > placebo; MPH + BM = MPH = BM
Klein and Abikoff,[78] 1997 AHRQ C1-row 5†	Parallel	89	Other	MPH MPH + CT placebo + CT	8 wk	1	CTRS, CPRS, Hillside, NIMH, classroom observation	MPH + CT, MPH > placebo + CT; MPH vs MPH + CT = NS; core/global = NS except MPH + CT > CT; depression = NS
Ialongo et al,[79] 1993 (see row 4, "Horn et al,[75] 1991"	Parallel	71 (from original 78 studied by Horn et al[75]; referrals)	DSM-III-R	MPH high dose, MPH low dose, placebo (each group with and without [PT + child training])	9-mo follow-up	4	CBCL, SNAP, Conners, CTRS, SOAPS	Combined treatment did not offer long-term improvement; parent ratings improved
Greene, 1997		Study not relevant						
Hoagwood		Study not relevant						
Horn, 1983		Study not relevant						

AC indicates attention control; ADD, attention-deficit disorder; ADD-H, attention-deficit disorder with hyperactivity; BM, behavioral modification; BT, behavioral therapy or training; CBCL Child Behavior Checklist; CCT, Children's Checking Test; CPRS, Conners' Parent Rating Scale; CPT, Continuous Performance Test; CT, cognitive testing; CTRS, Conners' Teacher Rating Scale; DSM-III, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*; Med, stimulant medication (DEX, PMH, or PEM); NIMH, National Institute of Mental Health Children's Psychiatric Rating Scale; NS, not significant; PT, parent training; SOAPS, Structured Observation of Academic and Play Settings; SC, self-control training.

* Abbreviated version of test

tested were more effective than medication in treating the symptoms of ADHD. Long-standing clinical experience dictates that education and counseling of the patient, family, and school personnel are valuable and necessary adjuncts to drug therapy, as with most long-term treatments for chronic conditions.

ADDENDUM

Atomoxetine is a nonstimulant licensed by the Food and Drug Administration in November 2002 for the treatment of ADHD in children and adolescents.[80] It is a selective inhibitor of the presynaptic norepinephrine transporter in the central nervous system. Atomoxetine increases both norepinephrine and dopamine levels, especially in the prefrontal cortex. In a randomized, placebo-controlled trial in children and adolescents 8 to 18 years of age over an 8-week period, atomoxetine demonstrated a statistically significant reduction in core ADHD symptoms and improvement in social and family functioning compared with the placebo group.[81] Atomoxetine was compared with MPH in a randomized, open-label trial in children with ADHD during a 10-week study period. Significant improvements in inattentive and hyperactive/impulsive symptom domains were similar with both medications when assessed by parents and clinicians. Adverse effects were also similar (appetite suppression, initial weight loss), with the exception that atomoxetine does not cause or worsen insomnia but in the early phase can cause drowsiness.[82] Atomoxetine treatment was associated with small but statistically significant increases in mean systolic pressure in adults and diastolic pressure in children and adolescents.[83] Blood pressure and pulse tended to increase early in therapy, then stabilized, and returned toward baseline after drug discontinuation. There was no significant difference as revealed by electrocardiogram between atomoxetine and placebo groups in change in QT interval for all study populations. Discontinuations because of cardiovascular-related events did not occur in the child/adolescent group.

Atomoxetine has a slower onset to action than do stimulants; thus, effects may not be seen until the end of the first week of treatment, but atomoxetine seems to have a longer duration of action after a once-a-day dose with suggestions of symptom relief during the evening and early-morning hours. The treatment effect size (0.71) for core ADHD symptoms is similar when once-daily dosing is compared with twice-daily dosing, and parent ratings document a sustained effect late in the day.[84] Motor and verbal tics associated with atomoxetine have not been reported.

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