38 Attention deficit hyperactivity disorder

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Case scenario

Your first patient of the morning is brought in by his parents for evaluation of school problems. By history, he had always been described as "on the go". When he was 4 years old, a preschool teacher expressed some concern that, at times, his activity level limited play with some of the other children. Now, in the middle of the second grade, he is underachieving and not keeping up with either reading or arithmetic lessons. His teacher reports that he moves constantly, and he cannot keep his hands off the other children. Friendships are limited and not sustained. His teacher suggested that he be evaluated by his primary care physician for attention deficit hyperactivity disorder, so his parents have come to you for this and to discuss treatment options.

Background

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of children and adolescents.[1] The hallmarks of this disorder are hyperactivity, impulsivity, and inattention that are beyond normal developmental expectations for a child's age, occur across multiple settings, begin prior to the age of 7 years, and are associated with clinically significant impairment.[2] The diagnostic criteria for ADHD from the *Diagnostic and statistical manual of mental disorders* (4th edn; DSM-IV) are displayed in the box on p. 342.[2] According to DSM-IV, children should meet diagnostic criteria in order to receive a diagnosis of ADHD.

For those children who don't meet criteria for ADHD, the *Diagnostic and statistical manual for primary care, child and adolescent version* (DSM-PC) was developed to guide clinicians.[3] The DSM-PC provides a description of common behavior problems followed by characteristic symptoms. These symptoms describe a spectrum from normal childhood variations to the disorder level found in DSM-IV. The intent of the DSM-PC is to classify common behavior problems and provide a guide for primary care clinicians in their evaluation of behavior problems in children and adolescents. However, limited empirical work has been performed to confirm the validity of the DSM-PC format.

ADHD is frequently diagnosed in children who present to primary care providers with behavioral problems or academic underachievement.[4] Although the diagnosis of ADHD can be made reliably in children using a standardized approach,[5] concerns regarding the validity of the diagnosis of ADHD often arise. At present there is no biological marker that reliably identifies those with ADHD. Furthermore, it is unclear whether the symptoms of ADHD represent a unique disorder or merely one end of the continuum of age-appropriate behavior.[6,7] Evidence supporting the validity of ADHD as a diagnosis comes from multiple sources:

- cohort studies that consistently show similar long-term outcomes for children identified with ADHD;
- twin studies that demonstrate higher concordance rates of ADHD among monozygotic twins than among dizygotic twins or related siblings;
- genetic studies that show higher rates of gene alterations involving dopamine neurotransmission;
- brain imaging and physiological studies that show a greater proportion of abnormalities among those with ADHD than similar controls.[1,6]

Framing answerable clinical questions

You wonder how likely it is that a school-age boy with academic difficulties and disruptive behaviors has ADHD, what tests will help you diagnose ADHD, whether the teacher's request for stimulant medications is reasonable or whether other treatments might work, and what this child's prognosis is, if he really has ADHD. These questions can be framed in a manner that addresses the target population, the intervention, the event or exposure, and the specific outcome of interest. In addition, each question can be classified according to the type of information that is sought: causation, diagnosis, therapy, risk, or prognosis. You frame five specific questions to address.

Diagnostic criteria for ADHD (DSM-IV)*

A. Either (1) or (2):

1. Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.

Inattention

(a) Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) Often has difficulty sustaining attention in tasks or play activities
(c) Often does not seem to listen when spoken to directly
(d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
(e) Often has difficulty organizing tasks and activities
(f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) Often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, or tools)
(h) Is often easily distracted by extraneous stimuli
(i) Is often forgetful in daily activities

2. Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.

Hyperactivity

(a) Often fidgets with hands or feet or squirms in seat
(b) Often leaves seat in classroom or in other situations in which remaining seated is expected
(c) Often runs about or climbs excessively in situations where it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) Often has difficulty playing or engaging in leisure activities quietly
(e) Is often "on the go" or often acts as if "driven by a motor"
(f) Often talks excessively

Impulsivity

(g) Often blurts out answers before questions have been completed
(h) Often has difficulty awaiting turn
(i) Often interrupts or intrudes on others (e.g. butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g. at school (or work) and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of pervasive developmental disorder, schizophrenia, or other psychotic disorder, and are not better accounted for by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).

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Questions

1. In school-age children (*population*), what is the likelihood of ADHD (*outcome*)? [**baseline risk**]
2. In school-age children (*population*) with ADHD (*exposure*), what is the likelihood of additional psychiatric disorders (*outcome*)? [**baseline risk**]
3. In school-age children suspected of having ADHD (*population*, *exposure*), what is the utility of behavior rating scales and other tests (*intervention*) in the diagnosis of ADHD (*outcome*)? [**diagnostic test**]
4. In school-age children with ADHD (*population*, *exposure*), what is the effectiveness of stimulant medications, other psychotropic medications, and/or behavioral treatments (*interventions*) on ADHD behaviors (*outcome*)? [**therapy**]
5. In school-age children (*population*) with ADHD (*exposure*), what is the long-term risk of persistence of ADHD symptoms, delinquency, school failure, or development of substance abuse disorders (*outcome*)? [**prognosis**]

General approach to searching for evidence

You start by looking for high-quality evidence syntheses in two locations: the Cochrane Database of Systematic Reviews (CDSR)[8] and the Centre for Evidence based Mental Health (CEBMH).[9] You also perform a search of electronic databases to identify high-quality syntheses.

Searching for evidence syntheses

- Cochrane Library: attention deficit disorder with hyperactivity
- Centre for Evidence based Mental Health: scan list of titles
- MedLine (Ovid), CINAHL, HEALTHstar, EMBASE, PsycINFO:
  - Attention deficit disorder with hyperactivity AND child AND diagnosis
  - Attention deficit disorder with hyperactivity AND child AND (drug therapy OR behavior therapy OR cognitive therapy)

Your search nets no completed reviews from the CDSR, eight abstracts from the Database of Abstracts of Reviews

of Effectiveness (DARE), and four references to other sources of information. Three of the abstracts appear relevant, two of which are meta-analyses of stimulant medications in children with ADHD and the third is a systematic review concerning the effectiveness of stimulant medications on errors on continuous performance testing in children with ADHD. You notice that the two meta-analyses were published in the early 1980s, and therefore may not provide up-to-date information. The systematic review addresses an outcome that is tangential to the one you desire. From the other sources of information, you identify two references to recent systematic reviews of treatment of ADHD in children that appear promising. One is published by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) in Ottawa,[10] and the other is published by the Agency for Health Care Policy and Research (AHCPR) in the United States.[11] You obtain copies of these documents and learn of another systematic review on the diagnosis of ADHD commissioned by AHCPR.[12] This latter synthesis addresses your first two questions on the baseline risk of ADHD and your third question on diagnostic tests in ADHD. The other two syntheses address your fourth question on therapy in ADHD.

The Website for the CEBMH contains an on-line journal with evidence based reviews of the published literature concerning mental health disorders in children and adults. The journal is published quarterly and dates back to 1998. It is organized by volume and study type, such as prevalence, treatment, or prognosis. Because there is no search engine, you scan the titles to obtain reviews pertaining to ADHD in children, and find three, including one on therapy and one on prognosis.[13, 14]

In your search of electronic databases, you decide to include only studies that are published in English language between 1980 and 1999, that include school-age children 6–12 years old, and that are either meta-analyses or systematic reviews. You restrict studies to those which base the diagnosis of ADHD on criteria from the *Diagnostic and statistical manual of mental disorders* (3rd edn, DSM-III; 3rd edn revised, DSM-IIIR; 4th edn, DSM-IV), or the *International classification of diseases* (all editions, ICD). Studies published prior to the release of DSM-III in 1980 may contain children without ADHD, since diagnostic criteria changed substantially with the release of DSM-III. You reject studies that do not have appropriate control populations for comparison.

You find three systematic reviews and a meta-analysis that cover diagnosis and/or treatment. The first review[1] may assist in addressing your question on therapy, but the review of diagnostic tests and prognosis is too cursory to be of much help in addressing your questions. You find two other systematic reviews and a meta-analysis, which is actually a synthesis of three previously published meta-analyses from the early 1980s.[15] You are concerned that these data may be dated, so you decide to exclude this study. One of the two systematic reviews is a qualitative synthesis of psychosocial interventions for children with ADHD,[16] while the other is a qualitative synthesis of drug therapy and prognosis in children with ADHD.[17] Two of the reviews refer to a large-scale randomized clinical trial (RCT) that will evaluate the long-term effects of combination therapy in children with ADHD, the Multimodal Treatment Study of Children with ADHD (MTA). You type the name of the study at the search screen using the textword format, and locate the study, which is too recent to have been reviewed by CEBMH or incorporated into any of the systematic reviews of therapy that you previously identified.[18]

Critical review of the evidence

Question
1. In school-age children (*population*), what is the likelihood of ADHD (*outcome*)? [**baseline risk**]

Prevalence estimates of ADHD vary widely, mainly as a result of including different populations (referral-based vs community samples) or using different diagnostic criteria (DSM-III vs DSM-IIIR vs DSM-IV). You decide to examine studies that include populations similar to yours, and exclude studies with referral-based population samples. Ideally, you would like to examine baseline risk among school-aged boys who present with academic difficulties or disruptive behaviors similar to your patient, but you note that there are no studies which provide such data.

The systematic review by Green *et al*. can be used to answer this question, since it examined the prevalence of ADHD among children aged 6–12 years.[12] In the review, a description of the search strategy indicates that the authors undertook a comprehensive search for evidence using multiple electronic databases, hand-searches of the reference lists of articles and a published clinical guideline on ADHD, and requests for additional citations from American Academy of Pediatrics members. The inclusion criteria for the review limited studies to those which used children aged 6–12 from non-referred samples in communities, schools, or clinics. No scoring system was used to grade the quality of the included articles. Since this review appears to be a high-quality synthesis, you decide not to search other sites.

Ten of the 14 articles included in this review were published between 1982 and 1996, and made determinations of prevalence based on either DSM-III or DSM-IIIR criteria. All 10 articles reported data by gender, age, and setting with a range of overall prevalence between 4% and

12%. With the use of a random effects model to pool data due to significant heterogeneity (in measurement methods, populations, and informants), the pooled prevalence estimates were 6.8% (95% CI 5.0%, 9.0%) with DSM-III criteria, and 10.3% (95% CI 7.7%, 13.4%) with DSM-IIIR criteria. A single study using DSM-IV criteria reported a prevalence rate of 6.8%. The prevalence of ADHD was 3-fold higher for males 9.2%, (95% CI 5.8–13.6%) than females 3.0%, (95% CI 1.9–4.5%). The results did not vary by age.

Question

2. In school-age children (*population*) with ADHD (*exposure*), what is the likelihood of additional psychiatric disorders (*outcome*)? [**baseline risk**]

Coexisting psychiatric disorders are more frequently diagnosed in children with ADHD than in children without ADHD.[19] Published prevalence data on these disorders in children with ADHD vary substantially, probably due to differences in study populations, diagnostic criteria, and methodologies. You exclude studies that report prevalence data from referred populations and that base diagnoses on criteria other than those from DSM-III, DSM-IIIR, or DSM-IV.

The systematic review by Green *et al*. includes a section on prevalence of coexisting psychiatric disorders among children aged 6–12 years with ADHD.[12] Prevalence data are reported for oppositional-defiant disorder, conduct disorder, depressive disorder, anxiety disorder, and learning disabilities. The results were collapsed across age and gender, so you will be unable to determine age and gender-specific prevalence rates. No overall combined estimate of the prevalence of all coexisting psychiatric disorders is given. Because this is a high-quality evidence synthesis, you decide not to pursue other sources.

The review cited five studies that met inclusion criteria and reported prevalence rates of various psychiatric disorders with DSM-III or DSM-IIIR criteria. Four of these studies used unscreened populations, while one study used a screened population. In the latter study, the study population completed a screening instrument, and only those who had elevated scores were further evaluated for psychiatric disorders. The authors pooled the rates for each disorder using a random effects model. Results indicated that coexisting psychiatric disorders were relatively common in children with ADHD, with pooled prevalence estimates of 35% for oppositional-defiant disorder (95% CI 27.2, 43.8%), 25% for conduct disorder (95% CI 12.8, 41.3%), 18% for depressive disorders (95% CI 11.1, 26.6%), and 25% for anxiety disorders (95% CI 17.6, 35.3%). The authors were unable to make a pooled estimate for learning disabilities, citing significant heterogeneity in the studies. Over 28% of children had more than one coexisting disorder (95% CI 7.6 to 56.3%). One additional study reported prevalence figures with DSM-IV criteria. The results from this study were consistent with the pooled estimates, except for a lower rate of conduct disorder at 10%.

Question

3. In school-age children suspected of having ADHD (*population*, *exposure*), what is the utility of behavioral rating scales and other tests (*intervention*) in the diagnosis of ADHD (*outcome*)? [**diagnostic test**]

This question concerns the validity and reliability of diagnostic tests in the evaluation of children with ADHD. You seek to address whether these tests can reliably distinguish children with ADHD from those without. Studies that independently and blindly compare each test to a gold standard, in this case the DSM criteria, will be able to answer this question. The systematic review by Green *et al*. contains a section on diagnostic testing for ADHD.[12] This synthesis examines the accuracy of behavioral screening tests and medical screening tests in the diagnosis of ADHD in children aged 6–12 years from any clinical setting. You recall from the first question that this is a high-quality synthesis.

Behavioral rating scales were designed as tools to screen for psychiatric disorders. In general, these scales use a checklist format, which can be quickly scored. Behavioral rating scales fall into two general categories: ADHD-specific, and broad-band checklists. ADHD-specific screens contain items relevant to specific ADHD-associated behaviors, while broad-band screens contain items relevant to a number of common behavioral disorders of which ADHD is one. The systematic review examined 10 ADHD-specific checklists including subscales and seven broad-band checklists. Other published checklists were not included in the review, because data on their sensitivity and specificity could not be found. The results from these studies were reported as effect sizes, which represent a common metric indicating the number of standard deviations separating the ADHD and non-ADHD populations. Effect sizes for each study were calculated as the difference in means between children with and without ADHD divided by the pooled standard deviation. These effect sizes, however, were not weighted (typically by the inverse of the variance) as is done in most meta-analytic studies.[20] Therefore, studies with different sample sizes would receive equal weight in determining the effect sizes.

ADHD-specific checklists adequately discriminate between children with and without ADHD. The combined effect size for all the ADHD-specific checklists including all subscales was 2.9 (i.e. a difference of 2.9 standard deviations on average between children with and without ADHD). This was translated into a sensitivity and

specificity of approximately 94% or a likelihood ratio for a positive test of >15. The Conners DSM-IV Symptoms Scales, both teacher and parent versions, performed best with effect sizes of 3.7 and 3.4 respectively. Barkley's School Situations Questionnaire performed worst with an effect size of only 1.3. The combined effect size for the hyperactivity subscales was 3.4. The DSM-III SNAP Hyperactivity Subscale performed best with an effect size of 5.1, while the ACTeRS-Parent Version Hyperactivity Subscale performed worst with an effect size of 1.5. Effect sizes were not combined for the inattention and impulsivity subscales, but effect sizes ranged from 2.0 for the ACTeRS-Parent Version Attention subscale to 5.5 for the DSM-III SNAP Checklist Impulsivity Subscale. Reliability may be limited, however, because effect sizes for each checklist were calculated from single studies.

Next, you look at the broad-band checklists and find that they do not sufficiently discriminate between children with and without ADHD. The outcome measure for the analysis was ability to discriminate between populations referred and not referred to mental health for ADHD evaluation, rather than ability to discriminate between populations with and without ADHD.

Continuous Performance Tests were developed to provide an objective measure of inattention, impulsivity, and vigilance, and take up to 30 minutes to administer. Green *et al*. evaluated 12 studies of this type of test in children with ADHD. Despite heterogeneity in types of tests and measurement methods, the data from the studies were pooled and reported as an effect size, as described previously. All 12 studies found statistically significant differences in errors of commission or omission in many of the subscale areas measured between children with and without ADHD. When the data were pooled, the combined effect sizes were small, ranging from 0.49 (95% CI 0.03, 0.96) for vigilance to 0.62 (95% CI 0.10, 1.14) for inattention. Effect sizes <1.0 were converted into sensitivities and specificities of <70% or likelihood ratios of <3 for a positive test.

Next, you evaluate the use of imaging studies of the central nervous system (CNS). Green *et al*. evaluated nine imaging studies. In two studies, no differences were found in the CNS between children with and without ADHD by computed tomography. In the other seven studies, several differences in the CNS architecture were noted. These differences involved the size, shape, symmetry, and volume of various CNS structures. However, these differences were not consistent from study to study, and it is not clear whether these differences are unique to ADHD.

Finally, you examine the evidence for electroencephalographic (EEG) studies in the diagnosis of ADHD. Eight studies were abstracted and reviewed by Green *et al*.[12] No significant EEG abnormalities were discovered in children with ADHD in any of the eight studies. Although seven studies found significant EEG differences between children with and without ADHD, these differences were not consistent from study to study.

In summary, you decide that evidence exists for the inclusion of ADHD-specific behavior scales in the assessment of children for ADHD. Overall, data suggest that ADHD-specific rating scales can reliably discriminate between children with and without ADHD, while broad-band checklists and Continuous Performance Tests do not. Neuroimaging and neurophysiological tests are of little assistance in the evaluation of ADHD.

Question

4. In school-age children with ADHD (*population*, *exposure*), how effective are stimulant medications, other psychotropic medications, or behavioral treatments (*intervention*) on ADHD behaviors (*outcome*)? [**therapy**]

Stimulant medications have been the mainstay of treatment for ADHD for the past 60 years.[17] They are the most commonly used medications for ADHD and account for 80–90% of all psychotropic medications prescribed for children with ADHD.[21] Recent estimates have shown a 2.5-fold increase in the use of stimulants in the US from 1990 to 1995.[22] Answers to questions regarding the effectiveness of therapy are best derived from RCTs in which patients and study investigators are blinded to treatment assignments. Systematic reviews or meta-analyses in which the results of randomized trials are pooled together also provide solid evidence.

To address the effectiveness of stimulant medications on ADHD behaviors, you examine the systematic review of treatments for ADHD by Miller *et al*.[10] The authors undertook a comprehensive search of multiple electronic databases, hand searches of the reference lists of key review articles and book chapters, and made requests for data from drug manufacturers to identify potential trials. Criteria for inclusion in the review were that trials be randomized, published after 1981, include children with ADHD, and measure outcomes using behavior rating scales. A quality assessment scale was used to evaluate study quality. You regard this as a high-quality synthesis to address your questions on therapy.

The authors identified 13 RCTs that used the Conners teacher rating scales or another behavioral rating scale as the outcome. The data were then pooled using a random effects model to account for heterogeneity between trials. Methylphenidate (eight trials), dextroamphetamine (four studies), and pemoline (one study) all were effective in improving teachers' and parents' assessments of behavior relative to placebo. Only one trial, which you found on the CEBMH website, reported on the long-term (15 months) effects of stimulant medications vs placebo.[13] This

randomized, placebo-controlled trial involved 62 children aged 6–11 years with DSM-IIIR established ADHD. The study enrolled children from a referral population that included pervasive developmental delay, autism, and mild mental retardation, which may limit generalization of the results to your patient. In addition, you note that a significantly greater number of patients withdrew from the placebo group than the treatment group, which may introduce bias by favoring the treatment group. The results of this trial demonstrated that amphetamines were superior to placebo on ratings of disruptive behavior and on measurements of a scale of intelligence.

The synthesis by Miller does not address the question of relative effectiveness between stimulants. However, the systematic review by Jadad *et al*.[11] examined short-term and long-term effectiveness of different interventions for ADHD. The authors undertook a comprehensive search to identify relevant trials including a systematic search of electronic databases from 1966, a search of the Cochrane Library, hand-searches of the bibliographies of eligible articles, and searches of the personal files of the research team. Trials were included if they were published in peer-reviewed journals in any language, evaluated a treatment for ADHD in children or adults, and were randomized trials. The authors used a quality score based on randomization procedures, blinding, and withdrawals to evaluate for bias. Due to significant heterogeneity among the included trials, the authors did not pool results but rather reported outcomes qualitatively. You regard this as a high-quality synthesis.

Eighteen studies compared stimulant medications head-to-head. Two studies compared different isomers of either methylphenidate or amphetamine, and reported conflicting results: d-methylphenidate was better than l-methylphenidate in improving attention, while d-amphetamine and l-amphetamine were not significantly different. Three studies compared sustained release vs regular methylphenidate and found no differences. Nine studies compared methylphenidate vs dextroamphetamine. Of these nine studies, eight reported no statistically significant difference between the two, while one reported an advantage of methylphenidate over dextroamphetamine. Two studies compared methylphenidate vs pemoline and showed no statistically significant difference between the two. One study of dextroamphetamine vs pemoline found no significant differences between the two. Finally, one study compared all three medications and found them to be generally equivalent.

The systematic review by Jadad *et al*. examined the evidence for the effectiveness of tricyclic antidepressants (TCAs).[11] The synthesis included nine studies that compared the effectiveness of TCAs to placebo: six studies involved desipramine, and three studies involved imipramine. Five of the six studies showed a benefit of desipramine over placebo on parent and teacher ratings of behavior. Only one of the three studies of imipramine reported a beneficial effect over placebo on parent and teacher ratings of behavior.

The review by Jadad *et al*. examined the relative effectiveness of stimulants vs TCAs.[11] Four studies met criteria involving head-to-head comparisons between stimulants and TCAs and were selected. One study found benefits in favor of stimulants, while another study found benefits in favor of imipramine. It appears that more rigorous studies are needed to help resolve this dilemma.

Psychosocial treatments are commonly utilized in the treatment of ADHD, either singly or in combination with medications. Psychosocial treatments used in the treatment of ADHD include cognitive-behavioral therapy, parent and teacher behavior modification therapy, and intensive contingency management therapy.[23] Pelham *et al*. systematically reviewed the evidence for the effectiveness of such treatments.[16] The authors undertook a comprehensive literature search and included articles that met the requirements of the Task Force on the Promotion and Dissemination of Psychological Procedures. However, these requirements are not clearly specified. Few details are given of the search strategy, inclusion/exclusion criteria, or details of the studies identified, so you are left to wonder whether important studies were overlooked or excluded. Fifty-eight articles were selected for inclusion in the review. The data were not pooled, but instead examined qualitatively. The results of this review indicated that there is little evidence that cognitive-behavioral therapies improve the behavior or academic performance of children with ADHD. On the other hand, behavior modification and contingency management therapies consistently demonstrated a beneficial effect on parent and teacher ratings of behavior across studies.

Since you are unsure of the quality of this synthesis, you decide to examine another source of evidence. The systematic review by Miller *et al*. that you previously evaluated for stimulant effectiveness includes a section on the effectiveness of behavioral treatments.[10] This review identified two studies that met criteria and compared cognitive-behavioral treatments with a control group. Teacher rating scales were the outcome of interest. One study showed a significant benefit in favor of cognitive-behavioral treatments, while the other study did not. The pooled effect size for the two studies was not significant.

Combination therapy pairs medications with psychosocial interventions. Intuitively, you think that this intervention may appear better adapted to address the wide array of problems in children with ADHD. The systematic review by Miller *et al*. reviewed the efficacy for combined medical and psychological/behavioral treatments on teacher and parent ratings of behavior[10] and identified three studies that met their criteria. The results indicated that

combination therapy might be more efficacious than placebo or no treatment. The pooled effect size for parent ratings of behavior was significant, but not for teacher ratings of behavior. Furthermore, the effect of combination treatment was not significantly different from medication alone. The pooled effect size was significant for parent rating of behavior but not for teacher ratings of behavior. Finally, combination treatment appeared to be more efficacious than psychological treatment alone. The pooled effect size was significant for parent rating scales but not for teacher rating scales.

Jadad *et al*. also reviewed the published literature on combination treatments for ADHD.[11] The results, although qualitative in nature, are similar to the results of the review by Miller. Five studies compared combination treatments with stimulants alone, and showed little difference between combination treatments and stimulants alone on parent and teacher ratings of behavior in four of the five studies. This suggests that psychosocial treatments add little to the effect of stimulant medications on children's behaviors. Comparison of combination treatments with psychosocial treatments alone showed that combination therapy was not significantly different from psychosocial treatments alone, suggesting little advantage of adding stimulants to a regimen consisting of psychosocial interventions.

You note that the vast majority of studies reporting on the effectiveness of combination treatments for ADHD are of a relatively short duration and involve relatively small numbers of children. The Multimodal Treatment Study of Children with ADHD[18] randomized 579 children aged 7–9 years to one of four treatment arms: monthly medication management with supportive care; intensive behavioral treatment; combination medication management with supportive care and intensive behavioral treatment, and usual community care over a period of 14 months. There was excellent follow-up and results were analyzed on an intention-to-treat basis. However, you are concerned that the strict medication titration regimen may not be feasible in your office setting. Combination and medication-only treatments were superior to behavioral treatments and community care in reducing ADHD and oppositional-aggressive symptoms. There was no statistically significant difference in combination and medication-only treatments for ADHD symptoms. However, combination treatments provided modest benefits over medications alone in non-ADHD symptoms areas, specifically in internalizing symptoms such as anxiety disorders, in social skills, in consumer satisfaction, and possibly in academic achievement.

In summary, stimulant medications are efficacious in improving behaviors associated with ADHD compared to placebo. There appears to be little difference between the types or formulations of stimulants. Of the TCAs, desipramine shows beneficial effects on behaviors, while imipramine has had inconsistent effects. There does not appear to be a benefit of stimulants over TCAs but few studies have examined this comparison. Psychosocial interventions demonstrate positive effects on ADHD behaviors. The addition of psychosocial interventions to medications does not show a benefit over medications alone on ADHD behaviors, but may provide modest benefit over medications alone on non-ADHD symptom areas.

Question

5. In school-age children (*population*) with ADHD (*exposure*), what is the long-term risk of persistence of ADHD symptoms, delinquency, school failure, or substance abuse (*outcome*)? [**prognosis**]

You wonder about the long-term risk of adverse outcomes for a young school-age child with ADHD. Studies of prognosis are best answered by prospective cohort studies that follow children with ADHD and a comparable group of children without ADHD over time until relevant outcomes occur.

The systematic review by Elia *et al*., which included nine studies that prospectively followed cohorts of children with ADHD from school-age until adolescence or early adulthood, may answer your question.[17] The search strategy and inclusion criteria were not stated in the article, and baseline characteristics of the children in each of the studies are not listed. Data from the various studies were reported in a qualitative fashion.

The results from the review indicated that symptoms of ADHD abate over time, but a significant number still meet DSM-IIIR criteria for ADHD as adults. The proportion of older adolescents who continued to meet criteria for ADHD ranged from 22% to 71%, and the proportion of young adults who continued to meet diagnostic criteria ranged from 4% to 50%. In addition, of those who did not meet explicit criteria for ADHD, many still exhibited residual symptoms of ADHD as young adults (up to 66%).

The systematic review found that the prevalence of conduct disorder and substance abuse disorders was significantly greater among adolescents and young adults with ADHD than peers without ADHD. The proportion with conduct disorder diminished over time, while the proportion with substance abuse disorder did not. The proportion with conduct or antisocial personality disorder in late adolescence ranged from 27 to 42%, and in early adulthood from 10 to 18%. In the two studies that looked at the prevalence of substance abuse, the data were conflicting, with one study showing a smaller proportion with substance abuse disorder and the other study showing no change.

To determine the risk of academic failure among children with ADHD, you examine the prospective cohort study by Fergusson *et al*. which you found on the CEBMH

website.[14] This study followed a birth cohort of 1265 children born in an urban region of New Zealand until age 18 years. Children were not formally diagnosed with ADHD, but were divided at age 8 into five groups of increasing attentional difficulties based on a combined behavioral rating scale. You suspect that children in the highest percentiles of attentional difficulties (96–100%) may be most likely to have ADHD. Children in this highest group of attentional difficulties incurred the highest proportion of school failures (59.5%) by age 18. This proportion was statistically significantly higher than the group with the lowest percentiles of attentional difficulties. The authors then adjusted the risk of school failure for conduct problems, demographic factors, school factors, and family factors, and still found a significant association.

The extent to which various treatments may alter these increased risks in children with ADHD is unknown. The MTA study may provide answers to this question in the future, since the authors are planning longitudinal follow-up of enrolled children.[18] A recent cohort of 75 boys with ADHD and 137 controls followed prospectively found that non-medicated boys with ADHD were six times more likely to develop substance abuse than boys without ADHD. Medicated boys with ADHD had this risk reduced by 85%. Although this study involved a referral population, the results suggest that treatment may alter the risk of substance abuse.[24]

In summary, the available evidence suggests that symptoms of ADHD diminish over time. However, up to 50% of adolescents and young adults may still meet criteria

Summary table

Question	Type of evidence	Results	Comment
Prevalence (baseline risk) of ADHD in the general population	Systematic review of population-based surveys (10 studies published between 1982 and 1996)	6.8% (CI, 5.0–9.0) using DSM-III 10.3% (CI, 7.7–13.4) using DMS-IIIR Male rate 3 × higher than female No variability by age	Significant heterogeneity among studies owing to measurement methods, populations, and informants
Risk of co-morbid psychiatric disorders	Systematic review of population-based surveys (5 studies)	Oppositional-defiant disorder: 35% Conduct disorder: 25% Depressive disorders: 18% Anxiety disorders: 25% Multiple disorders: 28%	Unable to pool results for learning disabilities owing to significant heterogeneity between studies
Utility of tests in diagnosis of ADHD	Systematic review of studies using DSM criteria as gold standard	Behavioral rating scales: LR >15 for ADHD-specific scales LR = 4 for broad-band checklists LR <3 for continuous performance tests EEG, CNS imaging not useful in diagnosis	Connors DSM IV Symptom Scales performed best
Effectiveness of stimulant medications	Systematic reviews of RCTs using behavior rating scales as outcome	Methylphenidate, dextroamphetamine, and pemoline all equally effective; tricyclics also appear effective; no clear advantage for any specific drug	Psychosocial interventions do not add to effectiveness for ADHD symptoms
Long-term prognosis for children with ADHD	Systematic review of cohort studies	ADHD symptoms abate but 21–70% still have symptoms as older adolescents, 4–50% meet diagnostic criteria as adults. Risk of conduct disorder decreases to 10–18% in adulthood. Up to 60% may experience academic failure by age 18	Few studies, results vary widely

for ADHD, and a significant number of others may exhibit symptoms compatible with ADHD. While the prevalence of conduct disorder appears greater in children with ADHD, this may diminish over time. The risk of school failure in children with attentional difficulties is significantly greater than in those without attentional difficulties. Currently, there is little evidence that various treatments alter the risk of persistence of ADHD, delinquency, school failure, and substance abuse.

Resolution of the scenario

The baseline prevalence of ADHD in school-age boys is 9%, and likely to be higher for children with academic or behavioral problems, so you decide to evaluate your patient for this disorder. You choose to incorporate ADHD-specific checklists, specifically the Conners Parent and Teacher Rating Scales, since they have likelihood ratios in excess of 15 and utilize current DSM-IV diagnostic criteria in your evaluation. If his rating scales are elevated and he meets diagnostic criteria for ADHD, you estimate his post-test probability of ADHD to be approximately 65%. Owing to insufficient evidence, you decide against the use of Continuous Performance Tests, neuroimaging tests, and neurophysiological tests in the evaluation. Given a diagnosis of ADHD, you estimate that he has a probability of between 18 and 35% of having one or more of the following additional disorders: oppositional-defiant, conduct or anxiety disorders, or depression. Since the evidence for the effectiveness of stimulants is strong and consistent across studies, you recommend these. You inform the parents that psychosocial treatments may be combined with stimulant medications, but the combination treatment may not be any better than stimulant medications alone for improving ADHD-specific behaviors. The combined treatment may be of benefit in non-ADHD symptom areas, such as internalizing symptoms, social skills, parent satisfaction, and learning. Following the evaluation, you inform the parents that ADHD is a chronic disorder and that their child has a 50% risk of persistence of ADHD symptoms into adolescence and young adulthood.

Future research needs

- The baseline risk of ADHD for school-age children who present with academic difficulties or behavior problems to their clinicians is unknown. Knowing this information would help you to adjust your baseline risk estimates more precisely.
- The baseline risk of other psychiatric disorders (e.g. substance abuse or learning disorders) among school-age children with ADHD is unknown. These additional disorders may also exert a substantial impact on ADHD.
- Whether the prognosis among children with ADHD who receive treatment with stimulants or psychosocial treatments is ameliorated to any degree is largely unknown. Decisions to initiate and maintain treatment can be influenced heavily by the potential for improvements in long-term risk.

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