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Current Drug Therapy Recommendations for the Treatment of Attention Deficit Hyperactivity Disorder

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Contents

Abstract

Attention deficit hyperactivity disorder (ADHD) is characterised by symptoms of inattentiveness and/or hyperactivity-impulsivity which are not appropriate to the child's age. This disorder usually manifests by age 3 and affects up to 5% of school-age children. Although the aetiology is unknown, ADHD appears to have a strong genetic component and to involve dysregulation of the CNS dopaminergic system.

Psychostimulants are the mainstay of therapy. The majority of patients will respond to an adequate trial of one of the 3 available stimulants, methylphenidate, dexamphetamine or pemoline. Use of the tricyclic antidepressants as second-line

agents is supported by substantial literature. Third-line agents include amfebutamone (bupropion) and clonidine. Other modalities have been studied, but sufficient research is not available to recommend their use over the abovementioned treatments. Assessment of response is best achieved by objective rating scales which allow for input from various environments.

1. Attention Deficit Hyperactivity Disorder

1.1 Diagnostic Criteria

Attention deficit hyperactivity disorder (ADHD) is defined by the American Psychiatric Association in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), as persistent inattentive and/or hyperactive behaviours that are not age-appropriate.[1] These behaviours are pervasive, as demonstrated by their presence in at least 2 environments (e.g. school and home), and are sufficiently severe so as to interfere with social or academic functioning. To meet DSM-IV criteria, patients must demonstrate symptoms of ADHD before the age of 7 years, and symptoms must have been ongoing for longer than 6 months.

Depending on the number of symptoms present, ADHD is subclassified as either predominantly inattentive, predominantly hyperactive-impulsive, or both. If at least 6 symptoms of inattentiveness have been present during the previous 6 months, with fewer than 6 symptoms of hyperactivity-impulsivity, then the classification of predominantly inattentive type is made. The converse would qualify for the predominantly hyperactive-impulsive type, whereas the combined type requires at least 6 symptoms in each category. Symptoms of inattentiveness and hyperactivity-impulsivity as defined in the DSM-IV are listed in table I.

The World Health Organization's International Classification of Disease (ICD-10) recognises these behaviours as hyperkinetic disorder. The ICD construct denotes onset usually before the age of 5, with major areas of impairment being the inability to complete activities requiring concentration or attention, and excessive and indiscriminate motor behaviours. The ICD-10 construct notes that hyperkinetic disorder is commonly associated with delayed motor and language development.[2]

1.2 Aetiology

Numerous aetiological theories based on response to psychostimulants have pointed to lower noradrenaline (norepinephrine) and dopamine turnover, but such a simplistic neuroreceptor theory is unlikely. A more complex theory proposes dopamine dysregulation in the frontal-neostriatal systems which manifests as widely varying states of arousal.[3]

1.3 Incidence

Estimates in the US suggest that ADHD occurs in 3 to 5% of school-age children, and is 4 to 9 times more common in boys than girls.[1] The incidence varies appreciably by country, which may reflect diagnostic constructs, population sampled, and point of view (e.g. physician versus teacher reports).[4-6] Children with first-degree relatives with ADHD are at increased risk for developing ADHD. At least 55% of cases are thought to be inherited, as supported by the 51% concordance rate between monozygotic twins versus a 33% concordance rate between dizygotic twins.[7] Despite the strong evidence supporting a genetic component of ADHD, no specific gene for the disorder has been identified.

The onset of ADHD usually occurs in toddlerhood (age 2 to 3 years), and its course is not predictable. Symptoms were thought to diminish during late adolescence, but in up to 60% of cases they may persist into adulthood.[8]

1.4 Differential Diagnosis and Comorbidity

A thorough mental status examination, input from teachers and family members, and the exclusion of other diagnoses with similar manifestations

Table I. Symptoms of inattention and hyperactivity-impulsivity (from the American Psychiatric Association,[1] with permission)

Inattention
Not attentive to details or makes careless mistakes in schoolwork, work, or other activities
Difficulty sustaining attention in tasks or play activities
Does not seem to listen when spoken to directly
Does not follow through on instructions and fails to finish schoolwork, chores or duties
Has difficulty organising tasks and activities
Avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort
Loses things necessary for tasks or activities
Forgetful in daily activities
Hyperactivity
Often fidgets with hands or feet or squirms in seat
Often leaves seat in classroom or in other situations in which remaining seated is expected
Runs about or climbs excessively in situations in which it is inappropriate
Has difficulty playing or engaging in leisure activities quietly
Often 'on the go' or often acts as if 'driven by a motor'
Talks excessively
Impulsivity
Often blurts out answers before questions have been completed
Has difficulty awaiting turn
Interrupts or intrudes on others

are crucial to establishing the diagnosis. Visual or auditory impairments, anxiety, depression and learning disabilities may sometimes be mistaken for ADHD. Impulsive and maladaptive behaviours associated with oppositional defiant disorder also can be mistaken for ADHD. The discriminating factor is that children with oppositional defiant disorder wilfully or angrily resist any behaviour asked of them by an authority figure, whereas ADHD behaviours are not wilfully disobedient. It is estimated that about 40% of children with ADHD also meet criteria for oppositional defiant disorder.[1,9,10]

Conduct disorder can also be manifested in a similar manner to ADHD. Behaviours associated with conduct disorder include aggressiveness or destructiveness, deceitfulness and/or serious infractions of socially accepted norms. Conduct disorder is present in at least 21% of children with ADHD.[1,9,10]

Overall, children with ADHD have a 25-fold greater risk of institutionalisation for delinquent behaviours, a 5-fold greater risk of drug abuse and a 10-fold greater risk of developing antisocial personality disorder.[10]

2. Psychosocial Interventions

The role of psychosocial interventions in treating ADHD remains equivocal. The National Institute of Mental Health (NIMH) is currently evaluating the relative efficacy of pharmacological, behavioural and multimodal approaches for treating ADHD. The results from this 4-year, multisite study are not yet available .[11]

2.1 Education

One of the psychosocial interventions considered most important is providing education for the child's family, the child and teachers about the illness, treatment and expected treatment outcomes. Although ADHD and similar terms are commonly used, it should not be assumed that the actual elements of the disorder are known or understood.[10]

2.2 Parent Management Training

Parent management training involves teaching the parents consistent and appropriate disciplinary strategies which employ immediate rewards for achieving targeted behaviours. Such techniques reduce the child's disruptive behaviours, decrease family stress and increase the parents' self-confidence in their parenting abilities.[10]

2.3 School-Focused Interventions

School-focused interventions are aimed at enhancing academic performance, improving classroom behaviour and improving peer relationships. Simple modifications such as seating the child in the front of the classroom to minimise distractions can be beneficial. A structured classroom setting with clearly defined rules and expectations, consistent and immediate reinforcement, and regular feedback creates an encouraging learning atmosphere.[10]

3. Pharmacotherapy

3.1 Psychostimulants

Of the pharmacotherapeutic options for treating ADHD, the psychostimulants are the most effective, most commonly used, and most extensively studied. Over 140 studies conducted in primary school–age children (5 to 12 years old) have demonstrated the benefit of stimulants over placebo; a much smaller number of studies have demonstrated their efficacy in other age groups.[12] The stimulants improve hyperactivity, cognition and social interaction. At least 85% of patients respond to one of the 3 major psychostimulants: methylphenidate, dexamphetamine (dextroamphetamine) or pemoline.[13] A positive response to stimulants should not be used as a means of confirming or establishing the diagnosis of ADHD, as these effects are nonspecific.

The proposed mechanism of action of the stimulants is an increase in catecholamine transmission, particularly dopamine and noradrenaline. Psychostimulants enhance catecholamine transmission via several mechanisms: inhibition of dopamine and noradrenaline reuptake; enhanced presynaptic release of dopamine, noradrenaline and serotonin (5-hydroxytryptamine; 5-HT); and inhibition of monoamine oxidase. The stimulants may have a homeostatic effect which moderates the phasic outbursts of dopaminergic transmission in patients with ADHD.[3,14]

Successful response to the psychostimulants may be affected by comorbid diagnoses. For example, patients with IQ lower than 45 may have a lower response rate, whereas patients with aggression may have a more favourable response.[15,16]

When treating with methylphenidate, attention and concentration are improved at doses of 0.3 mg/kg, and social functioning at doses of 0.6 mg/kg. Peak effects on behaviour occur between 1 and 2 hours postingestion, and diminish within 4 to 6 hours. The dosage should be initiated with 5 to 10mg given after breakfast. Scheduling of the second dose is guided by the time to loss of effect. At that time, a second 5 to 10mg dose can be administered. The dosage can be adjusted weekly according to response, increasing up to the maximum recommended daily dose of 60mg. The short pharmacodynamic effect of methylphenidate requires twice- or thrice-daily administration. A sustained release form requiring only once-daily administration is available, but has lower efficacy than the immediate release formulation.[17,18]

Dexamphetamine is as effective as methylphenidate and is often used in the event of an inadequate response to the latter. Subtleties in mechanisms of action among the stimulants allow for response to one stimulant despite nonresponse to another. Dexamphetamine should be initiated with 5mg daily and titrated upwards in 5mg increments in the same manner as methylphenidate. The maximum recommended daily dose of dexamphetamine is 40mg.

Because of the increased potential for hepatotoxicity, pemoline is usually reserved for patients who do not respond to either stimulants. Pemoline is administered once daily, and traditional dosage regimens have advised gradual upward titration from 18.75mg to achieve effect. On the premise that pemoline had a delayed onset of action, increments of 18.75mg were advised every 3 to 4 weeks. Pelham et al.[19] have studied the time- and dose-response curves of pemoline, and have determined that onset of effect occurs within 2 hours after ingestion and lasts for 7 hours. When administered at a pemoline 6mg : methylphenidate 1mg ratio, pemoline has the same efficacy as methylphenidate.[17,19] Conventional dosage recommendations may be too conservative, and Pelham et al.[19] have suggested that pemoline be started at 37.5 to 56.25 mg/day, with dose increments to be made every 2 to 3 days.

Pemoline requires monitoring of liver function tests (LFTs) every 6 months, as 1 to 2% of patients may develop hepatotoxicity. Elevations in LFTs usually return to baseline within 2 to 9 months of discontinuing pemoline,[20] but 3 fatalities resulting from fulminant liver failure secondary to pemoline use have been reported. The relative risk is calculated to be 45 times greater than that associ-

ated with the other stimulants.[21] As onset of hepatitis may occur during any point in therapy, educating the patient and family as to the manifestations of liver failure such as fatigue, nausea or vomiting can be as important as monitoring LFTs.

All stimulants share the same adverse effect profile, with the most common adverse effects being decreased appetite (41%), headache (10%), irritability (26%), insomnia (28%) and gastrointestinal irritability (23%). These tend to be more pronounced when initiating therapy or increasing the dose and tend to decrease with time. Anorexia may be minimised by administration with or after meals.[22]

An adverse effect of some concern is growth suppression. Treatment of ADHD with stimulants has been associated with small but statistically significant decreases in bodyweight and height which do not appear to be clinically significant. Furthermore, children receiving stimulants have not demonstrated bodyweight or height reduction persisting into adulthood.[23] Attempts to minimise growth suppression by using drug holidays during the summer months may allow for a 'catch-up' period of growth. Drug holidays should not be considered an absolute requirement, as they may not be acceptable for children who have significant functional impairment.[24] Dexamphetamine may be the stimulant most likely to cause growth retardation.[25]

Another adverse effect of concern and controversy while treating with stimulants is the potential for developing tics. It is generally accepted that tic disorders can be a contraindication to the use of stimulants, although the clinical basis for this recommendation is equivocal. Stimulants have been reported to unmask or increase the severity or number of tics in some patients,[26] and to ameliorate them in others.[27,28] Evidence which suggests a genetic relationship between ADHD and Tourette's syndrome[29] further complicates the issue. At the current time, the more prudent approach appears to be to avoid the use of psychostimulants if the tricyclic antidepressants (TCAs) or clonidine can be used successfully in patients with concomitant tic disorders. If alternative therapies are not successful, use of the stimulants with careful monitoring for tic exacerbation appears to be an appropriate strategy.

3.2 Tricyclic Antidepressants

Over 25 studies, mostly of imipramine and desipramine, have been conducted in primary school–age children to establish the efficacy of TCAs in treating ADHD.[12] These agents do not appear to provide as much benefit in treating the cognitive symptoms of ADHD as the stimulants, but are considered second-line agents for patients who do not respond adequately to the latter.[24,30] They may be most beneficial for patients with ADHD and a concomitant anxiety disorder.[31] However, monotherapy with TCAs in treating ADHD in depressed patients may not provide adequate antidepressant coverage. Of the 11 double-blind, controlled trials assessing the antidepressant effects of the TCAs in children and adolescents, 10 have shown no antidepressant effect.[32]

TCAs must be given twice daily in children due to their more rapid metabolism and resultant shorter half-life. Administration of drugs such as imipramine and desipramine should be initiated with 10mg twice daily, and titrated upwards every 5 days to 3 mg/kg. Daily doses of up to 5 mg/kg may be administered. There is no established plasma concentration–response relationship, but routine plasma concentrations should be monitored and maintained within the therapeutic range to minimise the toxic potential.[12,22]

The benefits of TCAs over the stimulants include fewer disruptions in sleep, appetite, and growth patterns; lower abuse potential; and no negative effects on tic disorders. Unlike the stimulants, tolerance to the therapeutic effects may develop over time.

The use of TCAs requires that careful attention be paid to the potential for overdose, lowering of seizure threshold and adverse cardiac effects. Seven cases of sudden death have been reported in children receiving desipramine.[33-36] A baseline electrocardiogram (ECG) should be obtained, and

Table II. Electocardiographic parameters of concern in children receiving tricyclic antidepressants[37]

PR interval > 200 msec
QRS interval > 30% above baseline
QRS interval > 120 msec
QT_c interval > 480 msec
Systolic blood pressre > 120mm Hg
Diastolic blood pressure > 80mm Hg
Heart rate > 130 beats/min at rest

should be repeated after steady-state has been achieved. Guidelines for the discontinuation of tricyclics based on ECG monitoring are presented in table II.[37]

3.3 Monoamine Oxidase Inhibitors

On the basis of the monoamine oxidase inhibition effects of the stimulants, the monoamine oxidase inhibitor (MAOI) antidepressants tranylcypromine, clorgiline (clorgyline), moclobemide and selegiline (deprenyl) have been studied in this patient population.[38-42] Results have show moderate to robust response, but only 1 study was controlled. These agents are not popular options due to the need for maintaining a low-tyramine diet when treating with the nonreversible MAOIs, and their use is not supported by the literature.

3.4 Amfebutamone (Bupropion)

Six double-blind studies[43-48] have been conducted to assess efficacy in children with ADHD. All but one[47] yielded positive results. Amfebutamone seems to be a promising antidepressant alternative for the treatment of ADHD. It is neither associated with cardiac conduction abnormalities,[49] nor does it have potential for abuse.[50] Nonetheless, amfebutamone has been reported to exacerbate tics,[51,52] and may increase the risk of seizures in patients with seizure disorders.[22]

3.5 Selective Serotonin Reuptake Inhibitors

No systematic studies are available to assess the efficacy of selective serotonin reuptake inhibitors (SSRIs) in patients with ADHD. Two open-label studies of fluoxetine have demonstrated moderate success in children,[53,54] and a case-study of sertraline in a 24-year-old woman with ADHD suggests efficacy without exacerbation of her tic disorder.[55] At this time, there is not sufficient support for the use of the SSRIs in the treatment of ADHD.

3.6 Antipsychotics

Antipsychotics have been shown to decrease hyperactivity in children with ADHD, but worsen attention and concentration. Effects on learning and cognitive functioning are often deterrents to the use of antipsychotics in this population. Currently available studies are dated and include confounding diagnoses. Given the potential for developing extrapyramidal symptoms, and the lack of evidence supporting improved cognition, the antipsychotics are not recommended for the treatment of ADHD.[12]

3.7 Clonidine

Clonidine is an α_2 noradrenergic agonist which is most commonly used as an adjunctive agent for patients with inadequate response to stimulants alone. Three controlled studies have been conducted in children with ADHD.[56-58] Behavioural improvements were reported in all studies, with fewer effects on cognition. The maximum dosage is 0.3 μg/kg/day divided into 3 or 4 doses. To minimise adverse effects, administration should be initiated with 0.05mg at bedtime. Slow titration and onset of effect delays maximal effects for several months. The patch formulation may be used to enhance compliance, but it may not adhere well in humid conditions.[10]

Clonidine is associated with sedation and anticholinergic adverse effects which may persist for 3 to 4 weeks. The hypotensive, orthostatic and delayed cardiac conduction effects of clonidine require routine monitoring of these parameters, especially when the dose is increased.

Four cases of sudden death have been reported in children receiving clonidine with either dexamphetamine or methylphenidate. A potential causal relationship is clouded by existing cardiac abnormalities, concurrent medications and anaesthesia.

Adverse cardiac effects not resulting in death have been reported with the use of clonidine and methylphenidate.[59]

4. Behavioural Assessments

Assessment of medication response based on a glimpse of the child's behaviour in the office may not be representative of the true picture. The new environment and individual attention paid to the child may result in more controlled behaviour. In order to objectify the child's behaviour across settings, it is necessary to rely on both family and teacher rating scales. Observations in the school setting offer a more practical assessment of the child's symptoms as the teacher is able to observe the child across a number of situations and can compare his/her behaviour with non-ADHD children.

Several rating scales have been developed to objectify ADHD behaviours.[10,60] The Conners' Teacher Rating Scale (CTRS) is a 28-item assessment with a 48-item parental version, the Conners Parent Questionnaire (CPQ).[61] Both make measurements on a 4-point scale, and each requires about 10 minutes to complete. Achenbach's Child Behaviour Checklist[62] is a commonly used parental rating scale which not only detects changes in hyperactive behaviour, but also recognises depressive, aggressive and somatic complaints which can occur concomitantly. The Child Attention Problems (CAP) instrument,[63] derived from the Teacher Report Form (TRF) of the Child Behaviour Checklist,[64] is a 12-item, teacher-rated scale designed to reflect changes in behaviour in response to medication.

In using these rating scales, it is important to remember that the teacher-rated scales tend to provide a more accurate overview of the child's behaviour than the parent-rated scales. A large disparity between the 2 scales, with the parent-rated scale suggesting worse behaviour, may reflect the child's behavioural reactions to family conflict. A 'halo effect', which may reflect the rater's perception of overall behaviours as opposed to specific ADHD symptoms, may result in the rater rating the child more positively or more negatively on all items, on the basis of behaviours which provide a less discriminating assessment of areas of progress. This may be especially important when comorbidity includes oppositional defiant disorder or conduct disorder.

5. Conclusions and Treatment Recommendations

ADHD affects about 5% of school-age children, impairing their social and academic functioning. Potential long term morbidity includes persistence of symptoms into adulthood, increased risk of antisocial behaviours and increased risk of substance abuse.

Therapy relies on pharmacological methods, as the benefit of psychosocial interventions is not yet clear. The psychostimulants are the agents of choice in most cases. The choice of stimulant is based on potential for adverse effects, rather than efficacy. Pemoline carries the greatest risk of causing liver failure, and is usually relegated to third position. The greater risk of abuse and growth suppression may force dexamphetamine into second place if the child or family members have problems with substance abuse. Whichever stimulant is used, the goal is to enhance academic and social functioning while minimising adverse effects. On the basis of clinical experience, clonidine is often used as an adjunctive agent to the stimulants. Clonidine is not as effective in improving cognitive symptoms of ADHD when used as monotherapy. Four deaths have been reported with the use of clonidine and methylphenidate, and the combination should be used with caution until the causal relationship can be clarified.

The TCAs are often used as second-line agents when there is an inadequate response or relative contraindication to using stimulants (e.g. tic exacerbation, patient or parental stimulant abuse). To minimise cardiotoxicity, ECGs should be obtained before the start of therapy, during the titration phase, once the target dose is achieved and periodically thereafter. Use of imipramine over desipramine may also be a prudent means of minimis-

ing the risk of sudden death. Tolerance to the therapeutic effects of the tricyclics may occur.

Amfebutamone appears to be a viable alternative to the abovementioned modalities, but should be used with caution in patients with tic disorders, seizures or eating disorders. Other antidepressants such as the MAOIs and the SSRIs have not been studied extensively in this population and cannot be recommended at this time.

Antipsychotic agents decrease hyperactivity associated with ADHD, but may negatively effect cognition. Due to their less than optimal therapeutic effects and the potential for extrapyramidal symptoms, antipsychotics should be avoided in this patient population.

To best evaluate the benefits of therapeutic interventions, objective input should be obtained using parent and teacher rating scales.

References

1. American Psychiatric Association. Attention-deficit and disruptive behavior disorders. In: American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994: 78-85
2. World Health Organization. Mental and behavioural disorders. In: International statistical classification of disease and related health problems. Vol. 1. 10th rev. Geneva: World Health Organization, 1992: 378-9
3. Evans RW, Gaultieri CT, Hicks RE. A neuropathic substrate for stimulant drug effects in hyperactive children. Clin Neuropharmacol 1986; 9: 264-81
4. Prendergast M, Taylor E, Rapoport JL, et al. The diagnosis of childhood hyperactivity: a U.S.-U.K. cross-national study of DSM-III and ICD-9. J Child Psychol Psychiatry 1988; 29: 289-300
5. Szatmari P, Offord DR, Boyle MH. Ontario child health study: prevalence of attention deficit disorder with hyperactivity. J Child Psychol Psychiatry 1989; 30: 219-30
6. Baumgaertel A, Wolraich ML, Dietrich M. Comparison of diagnostic criteria for attention deficit disorders in a German elementary school sample. J Am Acad Child Adolesc Psychiatry 1995; 34: 629-38
7. Goodman R, Stevenson J. A twin study of hyperactivity: II. The aetiologic role of genes, family relationships, and perinatal adversity. J Child Psychol Psychiatry 1989; 30: 691-709
8. Cantwell DP. Hyperactive children have grown up: what have we learned about what happens to them? Arch Gen Psychiatry 1985; 42: 1026-8
9. Searight HR, Nahlik JE, Campbell DC. Attention-deficit/hyperactivity disorder: assessment, diagnosis, and management. J Fam Pract 1995; 40: 270-9
10. American Academy of Child and Adolescent Psychiatry. Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1997; 36 (10 Suppl.): 85-121S
11. Richters JW, Arnold LE, Jensen PS, et al. NIMH collaborative multisite multimodal treatment study of children with ADHD: I. Background and rationale. J Am Acad Child Adolesc Psychiatry 1995; 34: 987-1000
12. Spencer T, Biederman J, Wilens T, et al. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. J Am Acad Child Adolesc Psychiatry 1996; 35: 409-32
13. Elia J, Borcherding BG, Rapoport JL, et al. Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? Psychiatry Res 1991; 36: 141-55
14. Jacobvitz D, Sroufe LA, Stewart M, et al. Treatment of attentional and hyperactivity problems in children with sympathomimetic drugs: a comprehensive review. J Am Acad Child Adolesc Psychiatry 1990; 29: 677-88
15. Livingston RL, Dykman RA, Ackerman PT. Psychiatric comorbidity and response to two doses of methylphenidate in children with attention deficit disorder. J Child Adolesc Psychopharmacol 1992; 2: 115-22
16. Aman MF, Marks RE, Turbott SH, et al. Clinical effects of methylphenidate and thioridazine in intellectually subaverage children. J Am Acad Child Adolesc Psychiatry 1992; 30: 246-56
17. Pelham WE, Greenslade KE, Vodde-Hamilton M, et al. Relative efficacy of long-acting stimulants on children with ADHD: a comparison of standard methylphenidate, sustained-release methylphenidate, sustained-release dextroamphetamine, and pemoline. Pediatrics 1990; 86: 226-37
18. Fitzpatrick PA, Klorman R, Brumaghim JT, et al. Effects of sustained-release and standard preparations of methylphenidate on attention deficit disorder. J Am Acad Child Adolesc Psychiatry 1992; 31: 226-34
19. Pelham WE, Swanson JM, Furman MB, et al. Pemoline effects on children with ADHD: a time-response by dose-response analysis on classroom measures. J Am Acad Child Adolesc Psychiatry 1995; 34: 1504-13
20. Stevenson RD, Wolraich ML. Stimulant medication therapy in the treatment of children with attention deficit hyperactivity disorder. Clin Pharmacol 1989; 36: 1183-97
21. Berkovitch M, Pope E, Phillips J, et al. Pemoline-associated fulminant liver failure: testing the evidence for causation. Clin Pharmacol Ther 1995; 57: 696-8
22. Bezchlibnyk-Butler KZ, Jeffries JJ, editors. Clinical handbook of psychotropic drugs. Toronto: Hogrefe & Huber, 1996
23. Klein RG, Mannuzza S. Hyperactive boys almost grown up: methylphenidate effects on ultimate height. 1998; 45: 1127-30
24. Spencer TJ, Biederman J, Harding M, et al. Growth deficits in ADHD children revisited: evidence for disorder-associated growth delays? J Am Acad Child Adolesc Psychiatry 1996; 35: 1460-9
25. Greenhill LL. Stimulant-related growth inhibition in children: a review. In: Gittleman M, editor. Strategic interventions for hyperactive children. New York: ME Sharp, 1981: 39-63
26. Lowe TL, Cohen DJ, Detlor J, et al. Stimulant medications precipitate Tourette's syndrome. JAMA 1982; 247: 1729-31
27. Erenberg G, Cruse RP, Rothner AD. Gilles de la Tourette's syndrome: effects of stimulant drugs. Neurology 195; 35: 1346-8
28. Sverd J, Gadow KD, Paolicelli LM. Methylphenidate treatment of attention-deficit hyperactivity disorder in boys with Tourette's syndrome. J Am Acad Child Adolesc Psychiatr 1989; 28: 574-9

29. Knell ER, Comings DE. Tourette's syndrome and attention-deficit hyperactivity disorder: evidence for a genetic relationship. J Clin Psychiatry 1993; 54: 331-7
30. Pliszka SR. Tricyclic antidepressants in the treatment of children with attention deficit disorder. J Amer Acad Child Adolesc Psychiatry 1987; 26: 127-32
31. Kutcher SP, Reiter S, Gardner DM, et al. The pharmacotherapy of anxiety disorders in children and adolescents. Psychiatr Clin North Am 1992; 15: 41-57
32. Birmaher B, Ryan ND, Williamson DE, et al. Childhood and adolescent depression: a review of the past 10 years. Part II. J Amer Acad Child Adolesc Psychiatry 1996; 35: 1575-83
33. Riddle MA, Nelson JC, Kleinman CS, et al. Sudden death in children receiving Norpramin®: a review of three reported cases and commentary. J Am Acad Child Adolesc Psychiatry 1991; 30: 104-8
34. Riddle MA, Geller B, Ryan N. Another sudden death in a child treated with desipramine. J Am Acad Child Adolesc Psychiatry 1993; 32: 792-7
35. Popper CW, Zimnitzky B. Sudden death putatively related to desipramine treatment in youth: a fifth case and a review of speculative mechanisms. J Child Adolesc Psychopharmacol 1995; 5: 283-300
36. Varley CK, McClellan J. Case study: two additional sudden deaths with tricyclic antidepressants. J Am Acad Child Adolesc Psychiatry 1997; 36: 390-4
37. Wilens TE, Biederman J, Baldessarini RJ, et al. Cardiovascular effects of therapeutic doses of tricyclic antidepressants in children and adolescents. J Am Acad Child Adolesc Psychiatry 1996; 35: 1491-501
38. Priest RG, Gimbrett R, Roberts M, et al. Reversible and selective inhibitors of monoamine oxidase A in mental and other disorders. Acta Psychiatrica Scandinavica 1995; 386: 40-3
39. Trott GE, Friese HJ, Menzel M, et al. Use of moclobemide in children with attention deficit hyperactivity disorder. Jugendpsychiat 1991; 19: 248-53
40. Zametkin A, Rapoport JL, Murphy DL, et al. Treatment of hyperactive children with monoamine oxidase inhibitors: I. Clinical efficacy. Arch Gen Psychiatry 1985; 42; 962-6
41. Wender PH, Wood DR, Reimherr F, et al. An open trial of pargyline in the treatment of attention deficit disorder, residual type. Psychiatry Res 1983; 9: 329-36
42. Wood D, Reimherr F, Wender P. The use of l-deprenyl in the treatment of attention deficit disorder, residual type. Presented at the American College of Neuropsychopharmacology, 1982, San Juan, Puerto Rico
43. Conners CK, Casat CD, Gualtieri CT, et al. Bupropion hydrochloride in attention deficit disorder with hyperactivity. J Am Acad Child Adolesc Psychiatry 1996; 35: 1314-21
44. Clay TH, Gualtieri CT, Evans RW, et al. Clinical and neuropsychological effects of the novel antidepressant bupropion. Psychopharmacol Bull 1988; 24; 143-8
45. Casat CD, Pleasants DZ, Schroeder DH, et al. Bupropion in children with attention deficit disorder. Psychopharmacol Bull 1989; 25: 198-201
46. Casat CD, Pleasants DZ, Van Wyck Fleet J. A double-blind trial of bupropion in children with attention deficit disorder. Psychopharmacol Bull 1987; 23: 120-2
47. Wolfe KD, Weller EB, Weller RA, et al. Treating children with attention-deficit disorder: a double-blind trial. Presented at the 40th Annual Meeting of the American Academy of Child and Adolescent Psychiatry; 1993; San Antonio (TX)
48. Barrickman LL, Perry PJ, Allen AJ, et al. Bupropion versus methylphenidate in the treatment of attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1995; 34: 649-57
49. Roose SP, Glassman AH, Giardina EGV, et al. Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. Am J Psychiatry 1991; 148: 512-6
50. Griffith JD, Griffith C, Carranza J, et al. Bupropion: clinical assay for amphetamine-like abuse potential. J Clin Psychiatry 1983; 44: 206-8
51. Jacobsen LK, Chappell P, Woolston JL. Bupropion and compulsive behavior. J Am Acad Child Adolesc Psychiatry 1994; 33: 143-4
52. Spencer T, Biederman J, Steingard R, et al. Bupropion exacerbates tics in children with attention-deficit hyperactivity disorder and Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 1993; 32: 211-4
53. Barrickman L, Nayes R, Kuperman S, et al. Treatment of ADHD with fluoxetine: a preliminary trial. J Am Acad Child Adolesc Psychiatry 1991; 305: 762-7
54. Campbell NB, Tamburrino MB, Evans CL, et al. Fluoxetine for ADHD in a young child. J Am Acad Child Adolesc Psychiatry 1995; 34: 1259-60
55. Frankenburg FOR, Kando JC. Sertraline treatment of attention deficit hyperactivity disorder and Tourette's syndrome. J Clin Psychopharmacol 1994; 14: 359-60
56. Gunning B. A controlled trial of clonidine in hyperkinetic children [thesis]. Department of Child and Adolescent Psychiatry, Academic Hospital Rotterdam, Sophia Children's Hospital Rotterdam, 1992
57. Hunt RD, Minderaa RB, Cohen DJ. Clonidine benefits children with attention deficit disorder and hyperactivity: report of a double-blind placebo-crossover therapeutic trial. J Am Acad Child Psychiatry 1985; 24: 617-29
58. Hunt Rd, Minderaa RB, Cohen DJ. Therapeutic effect of clonidine in attention deficit disorder with hyperactivity: a comparison with placebo and methylphenidate. Psychopharmacol Bull 1986; 22: 229-36
59. Cantwell DP, Swanson J, Connor DF. Case study: adverse response to clonidine. J Am Acad Child Psychiatry 1997; 36: 539-44
60. Edlebrock CS, Rancurello MD. Childhood hyperactivity: an overview of rating scales and their applications. Clin Psychol Rev 1985; 5: 429-45
61. Conners CK. A teacher rating scale for use in drug studies with children. Am J Psychiatry 1969; 126; 884-8
62. Achenbach TM. Integrative guide for the 1991 CBCL/4-18, YSR, and TRF profiles. Burlington: University of Vermont Department of Psychiatry, 1991
63. Barkley RA. Attention deficit hyperactivity disorder: a handbook for diagnosis and treatment. New York: Guilford, 1990
64. Achenbach TM. Manual for the Teacher's Report Form and 1991 Profile. Burlington: University of Vermont Department of Psychiatry, 1991

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