

emphasis remains on parental involvement.

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What is the most effective treatment for ADHD in children?

■ EVIDENCE-BASED ANSWER

Stimulant medication therapy is the most effective treatment for attention deficit/hyperactivity disorder (ADHD) in children, producing significant improvements in symptoms and modest improvements in academic achievement (strength of recommendation [SOR]: **A**, based on multiple randomized controlled trials [RCTs]). Nonpharmacologic therapies, such as behavior therapy, school-based interventions, and family therapy, are not as effective as stimulants but may add modest benefit to the effects of medication (SOR: **B**, based on 1 RCT).

While atomoxetine (Strattera) improves the symptoms of ADHD (SOR: **A**, based on multiple RCTs), stimulant medications other than methylphenidate offer no distinct short-term advantages (SOR: **A**, based on meta-analyses of multiple RCTs). Combination drug therapies offer no significant advantage to stimulants alone unless a comorbid condition is present (SOR: **A**, based on a meta-analysis of 20 RCTs).

The combination of methylphenidate and clonidine (Catapres) improves symptoms in children with both ADHD and tics (SOR: **B**, based on 1 RCT). Clonidine is less effective alone and has significant side effects (SOR: **B**, based on a meta-analysis of nonrandomized trials).

■ EVIDENCE SUMMARY

In numerous systematic reviews, RCTs, and meta-analyses, 70% of children responded to stimulant medications with short-term improvements in ADHD symptoms (inattention and hyperactivity/

impulsivity) and academic achievement. A forty-year review looked at 135 trials and 413 RCTs of methylphenidate in over 19,000 children with an average age of 8.8 years (range, 8.3–9.4 years) for an average duration of 6 weeks (range, 3.3–8.0 weeks).^{1–3}

Study groups included mostly elementary school-aged male children, with few minorities represented. Comorbid conditions, present in 65% of children with ADHD, were often poorly controlled. Outcome measures varied among studies.³

The effect size from stimulant medication in these studies averaged 0.8 for symptom relief and between 0.4 and 0.5 for academic achievement. (Effect size is the difference between the means of the experimental and control groups expressed in standard deviations. An effect size of 0.2 is considered small, 0.5 is medium, and 0.8 is considered moderate to large.)

A large randomized trial of 579 children with ADHD (20% girls) aged 7 to 9.9 years compared outcomes of 4 treatment strategies: stimulant medication, intensive behavioral treatment, combined stimulant medication and behavioral interventions, and standard community care.⁴ All children met the *DSM-IV* criteria for ADHD Combined Type (the most common type of ADHD in this age group). The stimulant medication strategy included an initial dose titration period followed by monthly 30-minute visits. Intensive behavioral treatment involved child, parent, and school personnel components of therapy. Combination therapy added the regimens for medication and behavioral treatment together. Standard community care consisted of usual (nonsystematic) care, evaluated at 6 different sites.

After 14 months of treatment, children in the medication group and the combined treatment groups showed more improvement in ADHD symptoms than children given intensive behavioral treatment or those who received standard community care. When combined with medication, those treated with behavioral therapy

TABLE

Commonly used medications for ADHD

Medication	Starting dose	Maximum dose	Monthly cost (generic)
Methylphenidate	5–10 mg 2–3 times daily	45 mg/d	\$20
Dextroamphetamine	5 mg 1–2 times daily	40 mg/d	\$18
Amphetamine/ Dextroamphetamine	5 mg 1–2 times daily	60 mg/d	\$50
Atomoxetine	40 mg once daily	100 mg/d	\$86

Common adverse drug reactions for all ADHD medications: Nervousness, insomnia, dry mouth, anorexia, abdominal pain, nausea, constipation, palpitations, tachycardia.

showed slight improvement in social skills, anxiety, aggression, oppositional behavior, and academic achievement over medication alone. At the conclusion of the study, 74% of the 212 children on medication were successfully maintained on methylphenidate alone, 10% required dextroamphetamine, and no children required more than one medication. This study found that higher doses of medication with more frequent office follow-up and regular school contact were important features of successful treatment. Only 40% of families were able to complete the intensive behavioral therapy.

Several short-term reviews and meta-analyses show that side effects from stimulant medications are mild and have short duration.⁵ More long-term studies are required to evaluate effects on growth. RCTs have limited power to detect rare adverse events that may be better detected by large observational studies.⁶

Atomoxetine, a specific norepinephrine reuptake inhibitor, is an FDA-approved alternative to stimulants for ADHD treatment in children and adolescents. Based on 3 RCTs⁷ of 588 children between the ages of 7 and 18 years, atomoxetine showed dose-related improvement in ADHD rating scales. Side

effects of atomoxetine are similar to stimulants and include mild but significant increases in blood pressure and pulse.⁷

A meta-analysis of 11 non-randomized trials using clonidine for ADHD showed a smaller effect size compared with stimulants.⁸ One RCT of 136 children with ADHD and tics showed improvement of both problems with the use of methylphenidate and clonidine, particularly in combination.⁹ Second-line medications such as clonidine, pemoline (Cylert), and tricyclic antidepressants have more potential serious side effects and are not well studied.¹⁰

■ RECOMMENDATIONS FROM OTHERS

The American Academy of Pediatrics recommends that clinicians: 1) manage ADHD as a chronic illness, 2) collaborate with parents, the child, and school personnel to define specific desired outcomes, 3) use stimulant or behavioral therapy to improve these outcomes; if one stimulant is not effective at the highest feasible dose, try another, 4) reevaluate the diagnosis, treatment options, adherence, and possible coexisting conditions if treatment is not achieving the desired outcomes, and 5) follow-up

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Education and behavioral therapy often improves patient satisfaction and compliance with medication

regularly with parents, child, and teachers to monitor for progress and adverse effects.¹¹

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■ CLINICAL COMMENTARY

When patients, parents, and teachers are educated, we achieve better outcomes

Stimulants and atomoxetine improve symptoms of ADHD quite effectively, making office treatment of ADHD a gratifying experience. Like many other diagnoses, there are numerous medications available to treat ADHD. Becoming familiar with a few and regularly prescribing them makes the treatment of ADHD more comfortable for the physician.

Sometimes patients and parents are hesitant to take medication for ADHD. Education about ADHD, along with trials of behavioral therapy, often improves patient satisfaction and compliance with medication. Likewise, children and adolescents may resist medication because of stigma or feeling unfairly labeled with a disease. Because of this, it is helpful to choose a medication with a long duration, so school dosing can be avoided. Artful negotiation with the patient and parent is beneficial.

In my experience, when patients, parents, and teachers are well-educated about ADHD and use behavioral therapy along with medication, we achieve better outcomes. Useful information for physicians and parents regarding medication use and behavioral therapy are described in the American Academy of Pediatrics ADHD Toolkit available at www.nichq.org/resources/toolkit.

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What is the interval for monitoring warfarin therapy once therapeutic levels are achieved?

■ EVIDENCE-BASED ANSWER

The international normalized ratio (INR) should be measured monthly once therapeutic levels are achieved and are stable for at least 8 weeks, although treatment should be individualized and an increased frequency may be required by some patients (**Table**) (strength of recommendation [SOR]: **C**, consensus statements). For highly compliant patients with stable levels and a clear understanding of factors that influence anticoagulation (changes in health, diet, medications), routine monitoring may be extended to 6 weeks (SOR: **B**, single randomized controlled trial [RCT]) or longer (SOR: **C**, case series). Patient-managed warfarin therapy, using biweekly self-measurements, results in more time in therapeutic range than routine physician-managed care (SOR: **A**, RCTs).

■ EVIDENCE SUMMARY

Under- or over-treatment with warfarin can result in life-threatening complications. Limited research exists to guide the selection of an interval for monitoring anticoagulation in stabilized patients. One RCT compared INR monitoring in an anticoagulation clinic at 6 weeks and 4 weeks among 124 patients with a prosthetic heart valve on stable oral anticoagulant treatment and found no difference in thromboembolic or hemorrhagic events.¹ A study in the United Kingdom used a 14-week interval for selected patients, but it used no comparison group.² Kent et al developed a computer-based model to compute

the optimum interval for monitoring anticoagulation that considers the variability of the patient's previous levels and costs associated with testing and potential complications. This model achieved a maximum interval of 11 weeks for very stable patients.³

More frequent testing results in higher time in therapeutic range, particularly when patients self-monitor. A German study of 200 patients with prosthetic heart valves found that they tested within a therapeutic range 48% of the time when monitored by their physician "as usual" (average interval 24 days), and 64% of the time when the interval was increased to 2 weeks.⁴ When the same patients then went to self-monitoring every 8, 4, and 2 days, they achieved therapeutic levels 76%, 89%, and 90% of the time, respectively. Bleeding and thromboembolic complications were not reported, but have been demonstrated elsewhere to be lower among patients who self-test frequently (eg, twice weekly) when compared with usual care (average interval 19 days) (4.49% and 0.9% vs 10.9% and 3.6%; number needed to treat [NNT]=15.6 for bleeding, NNT=37 for thromboembolism).⁵

■ RECOMMENDATIONS FROM OTHERS

The American College of Chest Physicians (ACCP) recommends individualizing management as the optimal frequency of INR monitoring varies according to patient compliance, dosing decisions, duration of therapy and changes in health, diet, or medications.⁶ The ACCP, the American Heart Association,⁷ Micromedex DrugPoints System,⁸ Goodman and Gilman's *Pharmacological Basis of Therapeutics*,⁹ and Cecil's *Textbook of Medicine*¹⁰ all recommend monthly monitoring once stable. The Institute for Clinical Systems Improvement's *Anticoagulation Therapy Supplement Management*¹¹ and *Managing Oral Anticoagulation Therapy Clinical and Operational Guidelines*¹² also recommend monthly monitoring for stable patients, but suggest that the interval can be increased to 6 weeks for selected stable patients.

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