Does stimulant therapy help adult ADHD?

EVIDENCE-BASED ANSWER

Central nervous system stimulants improve symptoms of attention deficit–hyperactivity disorder (ADHD) in adults (strength of recommendation: B, based on an older, inconclusive systematic review, a lesser-quality systematic review, and several newer small randomized controlled trials).

Although not the focus of this question, nonstimulant medications (including buproprion, modafinil, and guanfacine) have also been studied in the treatment of ADHD in adults. Recently, atomoxetine became the only nonstimulant medication to receive approval by the US Food and Drug Administration for the treatment of ADHD.

EVIDENCE SUMMARY

A well-done systematic review of 12 trials assessing the efficacy of stimulant therapy in the treatment of adult ADHD did not find sufficient evidence that stimulants were effective.[1] Significant heterogeneity and poor reporting of methodology was seen among the studies.

The 1 study rated as high-quality was a 7-week randomized controlled trial using a crossover comparison of methylphenidate and placebo.[2] There was a favorable response in 78% (18/23) of subjects while takin methylphenidate, in contrast to 4% (1/23) while taking placebo (number needed to treat [NNT]=1.4; $P<.0001$). A favorable response was assessed by the Clinical Global Impression Scale, a measure of illness severity and improvement, and a >30% reduction in symptoms as measured by the ADHD Rating Scale. A more recent, but less rigorous, systematic review identified 15 studies of stimulant efficacy in adults.[3] Researchers concluded that under controlled conditions, stimulants are efficacious in the treatment of ADHD in adults. The rate of response among the studies ranged from 25% to 78%.

One of the better studies in this review was a randomized, double-blind, 3-phase crossover study of dextroamphetamine, modafinil (a drug used to treat narcolepsy), and placebo.[4] Each phase was 2 weeks long, with a 4-day washout in between. A favorable response was defined as a reduction of ADHD symptoms by at least 30% on the *DSM-IV* ADHD Behavior Checklist for Adults. Dextroamphetamine and modafinil showed the same response rate in 10 of 21 patients. Both treatments had a significant improvement over placebo ($P<.001$). It was unclear from the study what percentage of subjects responded to placebo.

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What are Clinical Inquiries?

Clinical Inquiries answer real questions that family physicians submit to the Family Practice Inquiries Network (FPIN), a national, not-for-profit consortium of family practice departments, residency programs, academic health sciences libraries, primary care practice-based research networks, and other specialists.

Questions chosen are those family physicians vote as most important through a web-based voting system.

Answers are developed by a specific method:

- FPIN medical librarians conduct systematic and standardized literature searches in collaboration with an FPIN clinician or clinicians.
- FPIN clinician authors select the research articles to include, critically appraise the research evidence, review the authoritative sources, and write the answers.
- Each Clinical Inquiry is reviewed by 4 or more peers and editors before publication in JFP.
- FPIN medical librarians co-author each of the Clinical Inquiries that have required a systematic search.
- Finally, a practicing family physician writes an accompanying commentary.

TABLE

Stimulants used to treat ADHD in adults

Drug	Starting dose	Maximum daily dose
Methylphenidate		
Ritalin, Methylin	5 mg twice daily	65 mg*
Ritalin-SR, Methylin ER, Metadate ER, Metadate CR	20 mg every morning	65 mg*
Concerta	18 mg every morning	54 mg
Dextroamphetamine sulfate		
Dexedrine	2.5 mg twice daily	45 mg*
Dexedrine spansules	5 mg every morning	45 mg*
Mixed amphetamine salts		
Adderall	5 mg	40 mg
Adderall XR	10 mg every morning	30 mg

*American Academy of Child and Adolescent Psychiatry Practice Parameter

A similar study compared dextroamphetamine, guanfacine (an antihypertensive agent), and placebo in 17 patients.[5] On the *DSM-IV* ADHD Behavior Checklist for Adults, subjects taking dextroamphetamine or guanfacine reported similar decreases in mean ADHD scores compared with placebo (24 vs 22 vs 30; $P<.05$). They did not report the number of subjects who had a 30% reduction in symptoms. Of note: at the end of the study but prior to unblinding, subjects were asked which medication they preferred. Twelve subjects chose dextroamphetamine, 4 chose guanfacine, and 1 chose placebo. Subjects' stated reason for choosing dextroamphetamine was the positive effect it had on their motivation.

Another study included in this review was a randomized controlled trial of mixed amphetamine salts. Of the 27 adults who completed the study, 19 (70%) responded favorably to mixed amphetamine salts compared with 2 (7.4%) receiving placebo (NNT=1.6; $P<.001$).[6] Favorable response was defined as more than a 30% reduction of symptoms on the ADHD Rating Scale. Not included in either review was a 7-week randomized controlled trial comparing methylphenidate with sustained-release buproprion.[7] Thirty out of 37 subjects completed at least 1 week of the study. The primary indicator of a favorable response was the Clinical Global Impression Scale. The rate of response was 50% for methylphenidate, 64% for sustained-release buproprion, and 27% for placebo ($P<.14$).

RECOMMENDATIONS FROM OTHERS

The American Academy of Child and Adolescent Psychiatry[8] concluded that stimulant medication can be used to treat adults who have been carefully evaluated. They recommend starting methylphenidate, dextroamphetamine, or mixed amphetamine salts according to patient and clinician preference (**Table**). They do not recommend the use of pemoline due to the potential for hepatic failure.

Michelle E. Lutton, PsyD, *Moses Cone Family Medicine Residency Program, Greensboro, NC;* ***Laura Leach, MLIS,*** *Carolinas Healthcare System, Charlotte, NC*

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CLINICAL COMMENTARY

Medication can help even well-adapted adults with ADHD

Stimulant therapy benefits many adult patients with ADHD. While some adults need scheduled dosing, others do well with as-needed dosing.

Adults with ADHD often have made behavioral adaptations that allow success without medication. Drugs help these patients when focused attention is critical for specific tasks. A salesman doing a month-end report may find the improvement in attention helpful, but not needed for most daily tasks. A college student may need medication only for a specific class or project. Physicians can help patients with ADHD through anticipatory guidance in choosing a program of study or career goal and then collaborating in choosing appropriate behavioral and medication therapies.

Daniel Triezenberg, MD, *Family Practice Residency, Saint Joseph Regional Medical Center, South Bend, Ind*

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Does a high-fiber diet prevent colon cancer in at-risk patients?

EVIDENCE-BASED ANSWER

There is no direct evidence of an effect of dietary fiber on colon cancer incidence. A diet high in fiber has not been shown to be effective in the short-term (2- to 4-year) prevention of recurrent colon polyps (strength of recommendation [SOR]=**A**, based on consistent randomized clinical trials). Furthermore, epidemiological evidence is inconsistent in demonstrating an association between dietary fiber consumption and the occurrence of colon cancer (SOR=**C**).

EVIDENCE SUMMARY

The term "dietary fiber" refers to a heterogeneous group of substances that may vary in their biologic effects. Fiber is thought to reduce the risk of colon cancer through the following proposed mechanisms—decreased gastrointestinal transit time, increased stool bulk, and fermentation of volatile fatty acids. Other aspects of diet such as fat content, red meat, and micronutrients may also play a role in the development of colon cancer.

Additional proposed risk factors include sedentary lifestyle, obesity, tobacco use, and alcohol consumption[1]; while the commonly accepted high-risk groups for colon cancer are those aged >60 years, those with a positive family history of colorectal cancer, and those with familial polyposis syndrome. In summary, it appears that the cause of colon cancer is complex and multifactorial.

No randomized controlled trials of interventions test whether increase dietary fiber affects the development of colon cancer. Recent randomized controlled trials of interventions have used colon polyps as a surrogate endpoint, since it is believed that polyps are precursors to cancer. A Cochrane meta-analysis[2] of 5 trials

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(including 4349 subjects) of increased dietary fiber to prevent recurrence of colon adenomas found no difference between intervention and control groups for development of at least 1 adenoma (relative risk [RR]=1.04; 95% confidence interval [CI], 0.95–1.13). In a trial[3] of ispaghula husk fiber, the intervention group actually had significantly more recurrent adenomas after 3 years (29.3% vs 20.2%; RR=1.67; 95% CI, 1.01–2.76; *P*=.04).

Other evidence comes from epidemiological studies, which have limited ability to demonstrate causation. Immigrants to Westernized countries from ethnic groups with lower risk of colon cancer develop colon cancer rates similar to the host country over time. Such data support environmental factors in the risk for colon cancer.

Dietary fiber is 1 of several possible factors, yet epidemiological evidence has not been consistent. A systematic review[4] of dietary fiber and colorectal neoplasia (which included case-control and cohort studies as well as randomized controlled trials) showed that 13 of 24 case-control studies found an association with high dietary fiber as a possible protective factor, while only 3 of 13 longitudinal studies found such an association.

RECOMMENDATIONS FROM OTHERS

The American Gastroenterological Association states that "currently available evidence from epidemiological, animal, and intervention studies does not unequivocally support the protective role of fiber against development of colorectal cancer."[5] They recommend dietary fiber consumption of at least 30–35 g/d from a variety of sources. The intake level of most studies that demonstrate protective effects are in that range, and it is not certain what the best source(s) may be. They state that a high-fiber diet should begin before age 30, because the impact of dietary change may require decades; they also note that a high-fiber diet has other established health benefits.

The American Dietetic Association recommends a diet rich in dietary fiber through consumption of a variety of fruits, vegetables, whole and high-fiber grain products, and legumes for a daily intake of 20–35 g/d for healthy adults and, for children, a daily intake of 5 plus the child's age in grams.[6] They cite the epidemiological association of a high-fiber diet and lower colorectal cancer risk as well as many other health benefits.

Linda French, MD, and Susan Kendall, PhD, *MLIS, Michigan State University, East Lansing, Mich*

CLINICAL COMMENTARY

Dietary fiber has benefits, but is no panacea

Given colorectal cancer's multifactorial nature, it comes as no surprise that dietary fiber is not the panacea for primary or secondary prevention in high-risk patients. These data are specific only to high-risk patients, however, and should not be misinterpreted as reason to abandon recommendations for patients to consume an adequate bulk of fiber on a daily basis. Routine preventive counseling for reducing rates of colorectal cancer should also emphasize the benefits of adequate physical activity and a low-fat diet.

Mark B. Stephens, MD, MS, *Uniformed Services University of the Health Sciences, Bethesda, MD*

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Is screening urinalysis in children worthwhile?

EVIDENCE-BASED ANSWER

Screening urinalysis in asymptomatic children has not been shown to be beneficial (strength of recommendation: **B**; based on extrapolation from 1 meta-analysis). It is unlikely to be cost-effective and should be discontinued. While random urinalyses can be used for case finding of glucosuria, hematuria, pyuria, bacteriuria, and proteinuria, the routine use of screening urinalysis in asymptomatic patients is not likely to be an effective strategy.

EVIDENCE SUMMARY

The prevalence of urinary tract infection in childhood has been estimated to be roughly 1%.[1] For those children with asymptomatic bacteriuria, fewer than 10% progress to symptomatic urinary tract infections.[2] The prevalence of other glomelonephropathies is <0.05%.[3,4] Currently available screening urinalyses using chemical dipstick testing have reported sensitivities ranging from 53% to 93% and specificities of 72% to 98% for detecting significant bacteriuria.[5] All positive screening tests for bacteriuria require confirmation by standard urine culture.

No prospective randomized trials of screening urinalysis in childhood have been published to date. Expert opinion varies as to the necessity of screening urinalysis. No prospective randomized trials demonstrate improved outcomes, and limited evidence suggests that detection and treatment of asymptomatic bacteriuria improves long-term outcomes such as renal scarring, hypertension, or pyelone phritis.[6]

RECOMMENDATIONS FROM OTHERS

The American Academy of Pediatrics recommends 1 screening dipstick urinalysis at age 5.[7] The American Academy of Family Physicians,[8] Bright Futures,[9] Canadian Task Force on the Periodic Health Examination,[10] and the United States Preventive Services Task Force[11] do not recommend screening for asymptomatic bacteriuria in children. The Institute for Clinical Systems Improvement recommends that consideration be given to eliminating routine urinalyses in asymptomatic children.[12]

Mark B. Stephens, MD, MS, *Uniformed Services University of the Health Sciences, Bethesda, MD;*
Laura Wilder, MLS, *University of Texas Southwestern Medical Center Library, Dallas*

CLINICAL COMMENTARY

Numerous false-positives may lead to harmful interventions

In my practice, I have rarely found screening urinalysis to be useful. As mentioned above, it is not cost-effective and currently no available data demonstrate that outcomes are improved. What is not mentioned is the likely high rate of false-positive findings that would need further investigation—eg, hematuria and proteinuria. These investigations could be invasive and potentially harmful and would increase costs further, not to mention add unnecessary worry to concerned parents. Some parents still request a urinalysis, largely due to habits from a previous physician. I have found that a brief discussion of the risks and benefits of a screening urinalysis is enough to reassure parents.

Julian T. Hsu, MD, *A. F. Williams Family Medicine Center, University of Colorado Health Sciences Center, Denver*

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Should jaundiced infants be breastfed?

EVIDENCE-BASED ANSWER

No studies have demonstrated that cessation of breastfeeding in jaundiced infants improves clinical outcomes, although this has only been studied in term infants. Temporarily disrupting or supplementing breastfeeding in jaundiced infants is associated with premature cessation of breastfeeding (strength of recommendation [SOR]: **B**, based on a nonrandomized, nonblinded trial). Jaundiced breastfed term infants have no significant difference in length of phototherapy, and no increased rate of exchange transfusion or kernicterus compared with jaundiced bottle-fed term infants (SOR: **B**, based on a low-quality randomized controlled trial and a prospective cohort study). In light of the association of breastfeeding with improved health outcomes,[1] mothers of jaundiced term infants should be encouraged to continue breastfeed.

EVIDENCE SUMMARY

Although breastfeeding jaundice is a benign entity, other risk factors for bilirubin toxicity can coexist. These include jaundice in the first day of life, previously jaundiced sibling, early gestational age, significant bruising or cephalohematoma, Rh and ABO incompatibility, G6PD deficiency, and elevated hour-specific serum or transcutaneous bilirubin levels.[2,3]

Late initiation of breastfeeding and temporary cessation or supplementation of breastfeeding increase the likelihood of premature breastfeeding termination.[4] In a prospective cohort study of 138 breastfed term infants, more than twice as many mothers of jaundiced infants had stopped breastfeeding compared with mothers of nonjaundiced infants, at the end of 1 month (42% vs 19%; number needed to harm [NNH]=4; $P<.01$). In addition, 64% of the jaundiced infants whose nursing had been interrupted in the hospital had stopped breastfeeding by 1 month, compared with only 36% of those who had no interruption (relative risk [RR]=1.8; $P<.05$; NNH=4).[5]

Whether they require phototherapy or not, continuing breastfeeding in jaundiced infants is not associated with adverse outcomes. In a prospective cohort study of 163 healthy, jaundiced newborn infants undergoing phototherapy (total serum bilirubin ≥17 mg/dL), exclusively breastfed infants had slower response to phototherapy in the first 24 hours than formula-fed or formula-supplemented infants (bilirubin decreases of 17.1% vs 18% and 22.9%, respectively; $P=.03$). However, there were no significant differences in total length of phototherapy among the 3 groups (phototherapy time of 64.5 hours vs 54.1 hours and 54.9 hours, respectively; $P=.06$).[6]

In a randomized, nonblinded clinical trial, 125 jaundiced breastfed newborns (total serum bilirubin level of ≥17mg/dL) were assigned to 4 treatment groups: (1) continue breastfeeding and observe; (2) discontinue breastfeeding, substitute with formula; (3) discontinue breastfeeding, substitute with formula, and administer

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phototherapy; and (4) continue breastfeeding, administer phototherapy. The study did not find a clinically significant difference in serum bilirubin reduction to normal levels at 48 hours between breastfed and bottle-fed groups undergoing phototherapy (RR=1.07; 95% confidence interval [CI], 0.6–1.92; *P*=.818), or between breastfed and bottle-fed groups who did not have phototherapy (RR not calculated; *P*=.051). No patient required exchange transfusion, and in no case did total serum bilirubin exceed 23 mg/dL.[7]

RECOMMENDATIONS FROM OTHERS

The American Academy of Pediatrics (AAP) has reported numerous positive health outcomes in infants who are breastfed, including reduced incidence and less-severe diarrhea; lower incidence of otitis media, fewer respiratory infections; and lower incidence of bacteremia, bacterial meningitis, botulism, urinary tract infections and necrotizing enterocolitis.

In addition, they reported association between breastfeeding and enhanced cognitive development; and decreased incidence in sudden infant death syndrome, insulin-dependent diabetes mellitus, atopy, and inflammatory bowel diseases. They noted maternal benefits including less postpartum bleeding and lactational amenorrhea; more rapid postpartum weight loss and improved bone remineralization; and reduced risk of ovarian cancer and premenopausal breast cancer.[1]

The AAP discourages the termination of breastfeeding in jaundiced healthy term newborns and encourages continued and frequent breastfeeding (at least 8 to 10 times every 24 hours), encouraging physician's judgment and patient's preferences to determine final treatment options for breastfeeding jaundiced newborns.[2]

Michael D. Shoemaker, MD, *Cox Family Practice Residency, Springfield, Mo;* ***Mark R. Ellis, MD, MSPH,*** *Cox Family Medicine Department, Springfield;* ***Susan Meadows, MLS,*** *Department of Family and Community Medicine, University of Missouri–Columbia*

CLINICAL COMMENTARY

Reassure mothers to prevent cessation of breastfeeding

Breast milk jaundice occurs with such frequency that careful anticipatory guidance provided during later pregnancy is a physician's time well spent. Education of both prospective parents and other potentially influential family members in attendance during a prenatal visit is wise.

In practice, I have found the greatest challenge is providing enough support and encouragement for the nursing mother to counterbalance the suggestions of well-meaning friends and family that she stop breastfeeding altogether. The only treatment generally required is an increase in the frequency of feedings and up to 12 weeks time for all to resolve.

Russell W. Roberts, MD, *Louisiana State University Health Sciences Center, Shreveport*

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What is the best initial treatment of Parkinson's disease?

EVIDENCE-BASED ANSWER

No studies clearly demonstrate the best initial treatment for Parkinson's disease. Levodopa improves motor function in Parkinson's disease; however, long-term use is associated with irreversible dyskinesias and motor fluctuations. Compared with placebo, selegiline improves the motor symptoms of Parkinson's disease and allows a physician to delay the introduction of levodopa by 9 to 12 months (strength of recommendation [SOR]: **A**, based on randomized controlled trials).

Dopamine agonists—alone or combined with levodopa—have fewer associated dyskinesias and other motor complications but produce lower scores on activities of daily living and Unified Parkinson's Disease Rating Scale (UPDRS) when compared with levodopa alone (SOR: **A**, based on systematic reviews of randomized controlled trials). Drug choices should be based on each patient's individual symptoms and response to medication (**Table**).

EVIDENCE SUMMARY

Five randomized controlled trials[1–5] have shown improved motor function and activities of daily living with selegiline vs placebo in early Parkinson's disease. Two of these trials[1,2] found that selegiline delayed the need for levodopa for 9 to 12 months.

One large randomized controlled trial showed no difference in disability scores and an increase in mortality at 5.6 years when comparing selegiline combined with levodopa to levodopa alone.[6] A re-analysis of this study, as well as subsequent studies, have not supported this conclusion and found no increase in mortality in patients with a history of selegiline use.[7–10]

Two Cochrane reviews found that patients who tolerated the dopamine agonist bromocriptine—when administered alone or with levodopa—had delayed dyskinesias and motor complications compared with levodopa alone.[11,12] There was no change in off-time with the combination.[12] A large randomized controlled trial comparing bromocriptine with levodopa demonstrated that at 3 years, disability scores were lower in the patients initially assigned to bromocriptine, but the difference was no longer significant at 9 years.[13]

The bromocriptine group in this trial showed a lower incidence of dyskinesias when data from all patient groups were combined. However, when moderate to severe cases were analyzed separately, there was no significant difference.[13] There was no difference in mortality between patients initially treated with bromocriptine vs levodopa.[13,14]

Studies of other dopamine agonists show results comparable with bromocriptine. Lisuride (not available in the US) with rescue levodopa vs levodopa alone had fewer motor complications at 4 years but lower UPDRS and activities of daily living scores.[15] Another study comparing lisuride (with or without levodopa) vs levodopa alone found no difference in motor complications at 5 years.[16] Studies with cabergoline, pramipexole, and pergolide—alone or combined with levodopa—vs levodopa alone showed a decrease in motor complications with the dopamine agonist but lower activities of daily living and UPDRS scores.[17–19]

RECOMMENDATIONS FROM OTHERS

In 2002, the American Academy of Neurology published practice parameters for the initiation of treatment for Parkinson's disease based on literature from 1966 to 1999. The authors concluded:

- selegiline has mild symptomatic benefit and may be tried as initial therapy, but confers no neuroprotective effect
- either levodopa or a dopamine agonist can be used for the initial treatment of symptomatic Parkinson's disease

TABLE

Medications for Parkinson's disease

Medication	Starting dose	Usual daily dose	Approx cost/mo
Selegiline	5 mg every morning	5 mg every morning and at noon	$29 for 10 mg/d
Carbidopa/levodopa	25/100 mg tab 3 times daily	25/100 mg 3 times daily	$76 for 75/300 mg/d
Pergolide	0.05 mg/d	2–3 mg/d divided 3 times daily	$223 for 2 mg/d
Pramipexole	0.375 mg/d divided 3 times daily	1.5–4.5 mg/d divided 3 times daily	$177 for 3 mg/d
Ropinirole	0.25 mg 3 times daily	3 mg divided 3 times daily	$185 for 3 mg/d

• levodopa has a higher risk of dyskinesias than a dopamine agonist but superior motor benefits,[20] and is less likely to have other side effects (nausea, hallucinations, somnolence, and edema).

Jennifer Schreck, MD, Gary Kelsberg, MD, *Valley Medical Center Family Practice Residency, Renton, Wash;*
Joanne Rich, BSc (Pharm), MLIS, *University of Washington Health Sciences Libraries, Seattle*

■ CLINICAL COMMENTARY

Family physicians play a key role in monitoring Parkinson's

Parkinson's disease has a profound impact on a patient's physical and psychological well-being. Difficulties with movement, autonomic nervous system abnormalities, neuropsychiatric symptoms, and problems with medication effectiveness and side effects all occur throughout its course. Consultation with a neurologist skilled in this disorder can be quite helpful, particularly in younger patients or when the diagnosis is unclear. The family physician plays a key role in monitoring of the patient's condition. Active management of symptoms (and comorbidities as they arise) is crucial in helping patients maintain their functional status and quality of life.

Randy Ward, MD, *Medical College of Wisconsin, Milwaukee*

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