Once-daily treatment of ADHD with guanfacine: patient implications

Brandon C Strange

Department of Psychiatry at The Ohio State University, Columbus, OH, USA

Abstract: The standard of care for treating ADHD is to use a psychostimulant as the first line agent. Recent medical literature reports that approximately 70%–90% of patients with ADHD received some benefit from a stimulant medication. Even though psychostimulants have a high rate of efficacy, an estimated 30%–50% of children and adults may discontinue psychostimulants secondary to adverse effects or inadequate response. Guanfacine has been used for a number of years as an off label alternative to psychostimulants. This article reviews the current literature on the effectiveness of guanfacine in treating ADHD. It also introduces the preliminary data for guanfacine extended release and its effectiveness in decreasing the symptoms of ADHD.

Keywords: guanfacine, alpha adrenergic agonist, attention deficit/hyperactivity disorder, impulsivity, attention

Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed psychiatric disorders in school aged children. The National Institute of Mental Health (NIMH) estimates that its prevalence is between 3% and 10%, with ADHD affecting approximately 2 million children in the United States (Biederman et al 2006; Lopez 2006). ADHD is diagnosed 2–3 times more often in boys than girls, and is commonly "co-morbid" with other mental disorders such as depressive and anxiety disorders, substance abuse, conduct disorder, and antisocial behaviors (NIMH). ADHD is associated with significant psychiatric morbidity and functional impairment, including disruptive behaviors and a loss in educational productivity. Children with untreated ADHD have higher than normal rates of accidents and injury (NIMH). According to the Center for Disease Control Center (CDC), the estimated cost attributable to ADHD is about US$3.5–4.0 billion annually due to its impact on education, health care, and the juvenile justice system. The annual medical cost of families who have a child diagnosed with ADHD is 2–3 times that of comparison families (Jenson et al 2005).

The short-term efficacy of psychostimulants in the treatment of ADHD has been well demonstrated, but an estimated 30%–50% of treated children and adults nevertheless discontinue psychostimulants due to adverse effects or inadequate response. (Biederman et al 2006). Warnings by the Food and Drugs Administration (FDA) that psychostimulants may be associated with sudden death and serious cardiovascular adverse events and the suspension of Adderall® (Shire) distribution by Canadian authorities because of these same concerns have generated unease among both consumers and professionals (www.fda.gov). Atomoxetine, the first non-stimulant approved by the FDA for the treatment of ADHD, has received a "black box warning" from the FDA due to reports of increased suicidal thoughts and behaviors. Consequently, clinicians may explore alternative medications and approaches toward the treatment of ADHD.

Correspondence: Brandon Strange
899 East Broad Street, 3rd Floor,
Columbus, OH 43206, USA
Tel +1 614 355 8000 ext 38099
Fax +1 614 355 8030
Email strangeb@chi.osu.edu

This article reviews of the safety and efficacy of guanfacine for the management of youth with ADHD, including available but as yet unpublished data regarding guanfacine extended release (GXR) (Tenex ER®; Shire)

Methods

A review of the literature was done using PubMed. The search terms initially used were: guanfacine, attention, hyperactivity, alpha agonist, children, and ADHD. Limiting articles only to studies on children ages 0–18 years old was initially used, but this caused the results to be too narrow and specific. The final search terms that yielded the most articles with pertinence to guanfacine and ADHD were "guanfacine and attention." There were 74 articles and 44 of them were reviewed. Articles that were excluded were mostly animal models which met the search criteria because of key words, but were not relevant to the topic of this article. Also there were a few articles related to ADHD and other medications which were included in the search result, but were not suitable. The final articles which were reviewed consisted of relevant human and animal trials of guanfacine, open label studies, chart reviews, and placebo controlled trials. Also, some information about Tenex ER® was received from Shire in the form of poster presentations.

Mechanism of action

Guanfacine, like clonidine, is an alpha 2-agonist (α). α_2-agonists stimulate the α_2 adrenergic receptor (AR) in the brain (Scahill et al 1999). There are 5 general classes of adrenergic receptors, α_1, α_2, β_1, β_2, and β_3 (MacDonald et al 1997). Within these general classes there are subtypes of receptors; the α_2 receptor has 3 subtypes: the α_{2A}, the α_{2B}, and the α_{2C} (MacDonald et al 1997). Clonidine stimulates all 3 subtypes, as well as the imidazoline I1 receptor (Coupry et al 1989; Uhlen et al 1994), whereas guanfacine more selectively interacts with the α_{2A} subtype (Uhlen et al 1994). The α_{2A} subtype can be found both presynaptically on NE neurons, and postsynaptically on nonNE neurons (Aoki et al 1998; Wang et al 2007). Indeed, the majority of α_{2A} receptors are actually postsynaptic to NE neurons (U'Prichard et al 1979). Stimulation of the presynaptic α_2 receptors reduces NE release from terminals and decreases the firing of NE cell bodies in the locus coeruleus (LC). Clonidine is 10 times more potent than guanfacine at these presynaptic actions (Engberg and Eriksson 1991), while guanfacine appears to be more potent at postsynaptic receptors (Arnsten et al 1988).

The therapeutic properties of guanfacine in ADHD arise from actions in the prefrontal cortex (PFC). The PFC has a significant role in executive functions, which includes regulation of attention, planning, impulse control, and processing (Arnsten and Li 2005). Dysfunction with these areas causes forgetfulness, distractibility, impulsivity, impairment in working memory, and mental flexibility (Arnsten and Li 2005). Disruption in the PFC, and its projections to the striatum and cerebellum, are also associated with ADHD symptoms (Castellanos et al 2002; Seidman et al 2006). Inattention, impulsivity, and distractibility are all core features of ADHD.

Guanfacine enhances prefrontal cortical regulation of attention and impulse control by strengthening PFC functions. In animal studies, infusion of guanfacine directly into the PFC improves performance of PFC tasks (Mao et al 1999; Ramos et al 2006). This improvement can be observed at the cellular level as well, where electrophysiological recordings show that guanfacine strengthens the connections between PFC networks, increasing network firing (Wang et al 2007). PFC neuronal networks interconnect via glutamate synapses on dendritic spines. Guanfacine appears to strengthen PFC network connections by stimulating postsynaptic α_{2A} receptors on the dendritic spines of PFC pyramidal cells, the sites of PFC network connections (Wang et al 2007). Stimulation of these α_{2A} receptors with NE or guanfacine inhibits local cAMP production, which in turn closes nearby ion channels that make the membrane "leaky". Closing of these channels strengthens glutamatergic synaptic inputs onto the spine, increasing network firing and allowing greater control over attention and behavior (Wang et al 2007). This strengthening of PFC neuronal firing is reflected in greater cerebral blood flow to the PFC in monkeys and humans (Avery et al 2000; Swartz et al 2000).

Conversely, blocking α_2 receptors in PFC with yohimbine weakens PFC functions and induces a profile similar to ADHD. Yohimbine causes a collapse in PFC network firing, silencing PFC neurons (Wang et al 2007). Infusions of yohimbine into the monkey PFC weaken working memory and impulse control, and induce locomotor hyperactivity, similar to the symptoms of ADHD (Ma et al 2003, 2005). Impaired PFC function is also observed in ADHD patients with inadequate NE due to genetic alterations in dopamine beta hydroxylase, the synthetic enzyme for NE (Bellgrove et al 2006; Kieling et al 2008).

The PFC is one of the few intelligent inputs to the LC, and thus guanfacine strengthening of PFC function may also enhance regulation of LC noradrenergic release throughout the brain (Sara and Herve-Minvielle 1995; Arnsten

et al 1996). With optimal PFC regulation, the LC fires to relevant but not irrelevant stimuli (Aston-Jones et al 2000). In contrast, without this informed regulation, the LC appears to fire to distractors (Aston-Jones et al 2000). The PFC also regulates attention and behavior through massive projections to the sensory and motor cortices, the basal ganglia, and cerebellum (Goldman-Rakic 1987). Thus, strengthening PFC networks optimizes orchestration of brain function.

Pharmacokinetics

Guanfacine hydrochloride (Tenex®; Shire) was approved by the FDA for use in adult hypertensive patients in 1986. It is N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride. It also has off label use for ADHD and tics. Guanfacine is absorbed in the gastrointestinal track with almost 100% bio-availability (Cornish 1988). Its half-life is 17 hours (range 10–30 hours) in adults and 13–14 hours in children and adolescents. Its peak time in the serum is 1–4 hours. The area under the concentration-time curve (AUC) increases linearly with dosage. Approximately 30%–50% of guanfacine is eliminated in the urine unchanged and the remainder is metabolized by the liver CYP2C9; CYP2C19. Phenytoin and phenobarbital can induce the metabolism of guanfacine (Sorkin and Heel 1986; Cornish 1988; Fuller and Sajatovic 2002).

Elimination half-life is not significantly changed with renal impairment. Serum drug levels of guanfacine are only slightly increased in patients with renal dysfunction compared to patients with normal renal function (Cornish 1998). This is thought to be caused by increased non-renal elimination, most likely performed by the liver (Cornish 1988; Sorkin and Heel 1986). The guanfacine-to-creatinine clearance ratio is greater than 1, which would suggest that tubular secretion of the drug occurs. The drug is approximately 59%–100% bound to plasma proteins and not influenced by plasma concentration (Cornish 1988; Mosqueda-Garcia 1990). The volume of distribution in the body is 6 L/kg (Cornish 1988), which suggests a high distribution of drug to the tissues.

The pharmaceutical company Shire has been developing a guanfacine extended release formulation (GXR) to help with compliance by providing once-daily dosing. An initial phase 1 randomized, open-labeled, single-dose, crossover pharmacokinetic study was done in 52 healthy adults, ages 18–55. GXR half-life is 16.6–17.5 hours. The pharmacokinetics of GXR is generally linear for dosage from 2 to 4 mg, but there is a less than 2-fold increase between the 1–2 mg doses. This seems contrary to what would be expected. A pharmacokinetic study on GXR showed that the plasma concentration was higher in children than in adolescents. GXR has a linear pharmacokinetics with multiple daily doses (Boellner et al 2007).

Clinical studies guanfacine immediate release (GIR)

One of the first open trials of GIR by Hunt in 1995, as a treatment alternative for ADHD, showed promising results. The studies had 13 subjects, ages 4–20 years old, who received guanfacine for 4 weeks (Hunt et al 1995). There was a significant decrease in the post-medication Conner Parental Ratings Scale (CPRS) score of the subjects. The results of the study may be flawed because subjects were receiving other non-study medication which could greatly impact the final results of the study. This was not clearly discussed in the study (Cohn and Caliendo 1997).

In a follow up open label trial for ADHD and tics, by Chappell, with 10 subjects, ages 8–16 years old, 6 subjects (60%) were medication naïve and 4 (40%) had a prior history of failing or not tolerating a trial of clonidine. The study had mixed results. Even though the overall decrease in CPRS was statically insignificant, 4 (40%) subjects, had moderate-to-marked improvement in CPRS. The Continuous Performance Test (CPT) showed significant improvement in both errors of omission and commission in all the subjects (Chappell et al 1995). Two (20%) subjects dropped out because of persistent headaches and sedation. Two (20%) patients were on other non-study medications and 1 (10%) had comorbid OCD. The methodology of the study was weak because of the variability of follow up between subject and length of time in the clinical trial (Cohn and Caliendo 1997).

An open label trial of guanfacine to treat ADHD was later done using a population within the placebo control trial from the Tics Disorder Clinic of Yale Child Study Center. There were 25 subjects in all, 4 who did not meet the severity for a different placebo-controlled trial, 8 declined to participate in this same trial, and 13 were placebo non-responders for this trial. Their ages ranged from 7 from 16 years. CPRS, Conner's Teacher's Rating Scale (CTRS) and the Yale Global Severity Scale (YGTSS) were used to rate the severity of the patients' ADHD and tics pre and post medication. Seven (28%) participants dropped out due to lack of efficacy. The rating score from their last evaluation was carried forward. On the parent rating scales there was a 27% decrease in the hyperactivity rating and a 36% decrease in the teacher hyperactivity/impulsivity score. The overall tic score decreased by 39. These results were consistent with the open label trials and the one placebo-controlled trial (Boon-yasidhi et al 2005).

A recent 8-week study with guanfacine for children with pervasive development disorder (PDD) and hyperactivity was conducted by the RUPP Autism Network (Scahill et al 2006). There were 25 subjects, all who had failed a larger placebo-controlled trial with methylphenidate. Their ages were 5–14 years. On the Clinical Global Impression (CGI) Severity scale their scores for ADHD were at least moderate. There was a 40% decrease in the hyperactivity subscale of the Aberrant Behavior Checklist per parent rating and a 27% decrease for the teachers as well. The Swanson, Nolan, and Pelham checklist (SNAP-IV) parental rating showed a 41% decrease while the teacher scale was 20%. Of the 25 subjects, 12 were "Much improved" or "Very Much" Improved on the SNAP-IV. Five (20%) subjects withdrew from the study; 2 because of lack of efficacy and 3 because of irritability. This study shows that guanfacine has some efficiency in symptoms reduction of ADHD. Since these subjects have already failed a trial with methylphenidate, their ADHD symptoms may be more resistant to treatment in general. Children with the diagnosis of PDD are typically more sensitive to the side effects of medications and often are more refractory to pharmacotherapy. If the subjects who were accepted had not already failed a trial with a stimulant, there potentially could have had a more robust response to the guanfacine (Scahill et al 2006).

In 2001, Scahill was the first placebo controlled trial for guanfacine treating children with ADHD and tic disorders. There were 34 participants who were randomized into a placebo or medication group, 17 and 17. The CGI, CPRS and CTRS, the Yale Global Tic Severity Scales (YGTSS), and the CPT were used prior to initiation of medication and at the end of the clinical trial. After 8 weeks there was a 37% decrease in ADHD symptoms in the guanfacine group versus 8% for the placebo group. CGI scores rated 9 (53%) of the guanfacine group were very much improved or much improved. Tics decreased by 31%, compared to a 0% change by the placebo group. The CPT had a 22% and 17% decrease in the commission and omission errors in the guanfacine group vs 29% and 31% increase in the placebo group. Parent rates did not show significant difference between the placebo and treatment group. The effect size (ES) was 0.65, which is statistically significant. The ES is calculated by mean change in score for the guanfacine group minus the change for the placebo, divided by the mean standard deviation for endpoint of the study (see Table 1). The mean improvement of guanfacine is 36%, which is significantly less than that of stimulants, which is usually 50%–60%. The power of the study was small as well (Scahill et al 2001).

The single comparative study for adults with ADHD showed that guanfacine was comparable to dextroamphetamine (DAMP). There were 17 subjects, ranging from 21 to 57 years old. They were all diagnosed by meeting DSV-IV criteria for ADHD from 7 years old on. They all were above the 93rd percentile for ADHD symptoms. All subjects had a 2-week trial of placebo, guanfacine and DAMP with a 4-day wash out period between each trial. They were administered the DSM-IV ADHD Behavior Checklist for Adults, the Copeland Symptom Checklist for Adult Attention Deficit, the Beck Depression Inventory (BDI), the Hamilton Rating Scale for Anxiety (HRSA), the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Stroop Color-Word Interference Test, and the Control Oral Word Association Test at baseline and at the end of each 2-week trial. Both DAMP and guanfacine showed a significant improvement on the ADHD Behavioral Checklist for Adults, but were not statistically different from one another. On the Copeland scale both drugs showed some improvement from placebo, but it was statistically insignificant. Even though both guanfacine and DAMP showed improvement from placebo attention and impulsivity, all subjects stated that DAMP was the only medication that improved motivation (Taylor and Russo 2001).

Clinical studies of GXR

Shire funded a multi-site phase 3 placebo-controlled double blind trial of GXR involving 345 children and adolescents ranging in age from 6 to 12 years. Patients were randomized into 4 groups: placebo, 2 mg, 3 mg, and 4 mg. Each group was titrated up to their maximum dose, starting at 2 mg, over 3 weeks. The ADHD-RS-IV was the primary measure and the secondary measures were the CGI-I, CPRS, and CTRS. After 8 weeks the change in subjects' hyperactivity/impulsivity scores on the ADHD-RS-IV adjusted for placebo were –3.68 (2 mg), –3.58 (3 mg), and –5.62 (4 mg) ($p < 0.001$ for all comparisons) and for the inattentiveness subscale were –3.74 (2 mg), –3.94 (3 mg), and –4.26 (4 mg) ($p < 0.01$ for GXR 2 mg and 3 mg; $p < 0.001$ for GXR 4 mg). On the CGI the subjects improved at the endpoint 25.6% (placebo), 56.0% (2 mg), 50.0% (3 mg), and 55.6% (4 mg). The most common treatment emergent adverse events were somnolence (GXR 32% vs placebo 4%), headache, fatigue, and upper abdominal pain. Forty subjects withdrew from the GXR group versus one from placebo. While the GXR subjects had decreased diastolic and systolic blood pressures, the drug was well tolerated. Although the advantage over placebo was significant, the size of the effect could not be calculated due to insufficient data. The standard deviations are

Table 1 Effect size of placebo-controlled trials of ADHD medications

Placebo-controlled trial	Medication	Number of subjects given medication	Effect size	Assessment tools
Scahill et al 2001	GIR	34	0.88	ADHD RS-IV$^{(pm)}$, CGIS, CPRS, and CTRS
Melmed et al 2006	GXR	345	0.79 (0.13–0.17 mg/kg)	ADHD RS-IV$^{(pm)}$, CGIS, CPRS, and CTRS
Wolraich et al 2001	OROS MPH	94	1.05	IOWA Conners Ratings Scale$^{(pm)}$, SNAP-IV, (Teacher and Parent for both)
Wolraich et al 2001	IR MPH	94	1.02	IOWA Conners Ratings Scale$^{(pm)}$, SNAP-IV (Teacher and Parent for both)
Michelson et al 2002	ATX	85	0.71	ADHD RS-IV$^{(pm)}$, CGIS, CPRS, and CTRS
Weiss et al 2005	ATX	101	0.63	ADHD RS-IV$^{(pm)}$, Academic Performance Rating Scale, Academic Performance Rating Scale, The Social Skills Rating System-Teacher, The Conners Global Index-Teacher, CGI, CPRS
Conners et al 1996	Buproprion	61	0.16 (parent scale) 0.27 (teacher's scale)	CPRS$^{(pm)}$, CTRS$^{(pm)}$, CGIS, Continuous Peformance Test

Abbreviations: ATX, atomoxetine; G, guanfacine; IR, immediate release; XR, extended release; MPH, methylphenidate; OROS®, MPH (Concerta); $^{(pm)}$, primary outcome measure.
Note: ADHD Rating Scale-IV (ADHD RS-IV), Clinical Global Impression Scale (CGIS), Conners Parental Rating Scales (CPRS), Conners Teacher Rating Scales (CTRS), Swanson, Nolan, and Pelham Checklist, Version IV (SNAP IV).

not given, nor are the data from the pre or post measurement given (Melmed et al 2006) (see Table 1).

Adverse reaction

Similar to clonidine, an α-agonist, the major side effects of GIR and GXR are sedation and fatigue. The rate of sedation for the studies ranged from 16% to 35% and fatigue from 12% to 60%. Dry mouth, headaches, stomachaches, sleep disturbance, and irritability were prominent as well (Cornish 1988; Chappell et al 1995; Hunt et al 1995; Scahill et al 1999, 2001; Boon-yashidhi et al 2005). In general the medication was fairly well tolerated. Even though GIR is often used as a blood pressure medication, there were not significant events of orthostatic hypotension or bradycardia. The subjects' headaches and dizziness were not directly associated with any changes in blood pressure. With each dose increase of GXR, there is greater sustained decrease in both systolic and diastolic blood pressure and pulse. No subject had a QRS interval $>$120 msec and/or a QT interval $>$ 480 msec increase from baseline ECG assessment (Melmed et al 2006).

Hypomania, possibly with hallucinations (Boreman and Arnold 2003) is a rare, but possible side effect. If a patient has bipolar or mood disorder, they should be monitored carefully (Horrigan and Barnhill 1998).

Administration

Dosing for GIR and GXR is 1–4 mg per day. GIR is divided bid or tid, while GXR is a single dose per day. Because of the possibility of sedation with GIR, it is best to start at 0.25–0.5 mg at bedtime for 3–4 days and then increase to 0.5 mg in the morning and night. Dosage can be increased by 0.5 mg every 3–4 days (Chappell et al 1995; Hunt et al 1995; Scahill et al 2001, 2006; Taylor and Russo 2001; Posey et al 2004; Boon-yasidhi et al 2005). Most children are usually prescribed 0.5–2 mg bid-tid (Arnold 2002). For GXR, All subjects were started on 1 mg and titrated up by 1 mg per week, to a maximum of 4 mg. This study does not specify whether 4 mg will be the recommended maximum daily dosage for children (Melmed et al 2006).

Screening for any cardiac problems or family history of cardiac complications is essential (Newcorn et al 1998; Pliszka 2007). Blood pressure and pulse rate were monitored regularly in all studies for ADHD, with the exception of the Chappell and Hunt primary studies in 1995. There were no significant sustained changes in systolic or diastolic blood pressure or pulse with GIR, but it was significant in the GXR study. It is unclear whether this difference is due to the lack of an adequate number of subjects for the GIR studies. Since hypotension and bradycardia can be an adverse effect of the medication, regularly monitoring blood pressure and pulse is important (Pliszka 2007).

In an article about α_2 adrenergic agonist, Newcorn et al recommends an electrocardiogram (ECG) at baseline and with increased dosage of Clonidine (Newcorn et al 1998). In the most recent studies, ECGs were taken at baseline

(Scahill et al 2001; Swearingen et al 2007). In the 2007 practice parameter for ADHD published by the American Academy of Child and Adolescent Psychiatry, an ECG is not recommended for clonidine nor for guanfacine (Pliszka 2007). The guidelines recommend a baseline EKG for patients who have preexisting heart disease or symptoms suggesting significant cardiovascular disease. The symptoms include dizziness, chest pain, fainting, palpations, and exercise intolerance. Caution is still warranted with the use of α_2 adrenergic agonist (Pliszka 2007).

GIR, like clonidine, can have a withdrawal syndrome with abrupt cessation. Symptoms include increased blood pressure, headache, tremor, restlessness, and nausea. This is rare, approximately 3% compared to 50%–80% with clonidine. The difference in the withdrawal rates may be explained by guanfacine's longer half-life. Most subjects have mild sympathetic hyperactivity (Sorkin and Heel 1986; Cornish 1988). Standing blood pressures may increase 33 mmHg, systolic, and 16 mmHg, diastolic, over pretreatment baseline (Sorkin and Heel 1986). A placebo-controlled study using GXR on 45 healthy adults, age 19–24 years, showed no clinically significant vital sign or ECG changes in subjects who abruptly stopped GXR versus being tapered off (Kisicki et al 2007).

Discussion

To date there is still only one placebo controlled trial for GIR. The reduction in ADHD symptoms for this guanfacine trial is clinically significant, but it is not as robust as with stimulants. Two-thirds of the patients in Scahill's study had prior treatment failure with psychostimulants. A number of these patients had co-morbid diagnoses as well. These patients may have been more refractory to treatment which could account for the lower response rate and reduction in symptoms (Scahill et al 2001).

The 37% improvement in ADHD symptoms from Scahill's placebo-control study is consistent with percentage improvement in the open label trials for GIR. The percentage change from teacher and parents baseline ratings for hyperactivity ranges from 20%–36.1% and 26%–41% (Boon-yasidhi et al 2005; Scahill et al 2006). Within all the trials, GIR seems to work best on inattentive, impulsive and hyperactive symptoms (Posey et al 2004; Biederman et al 2006). For children with co-morbid tics, guanfacine significantly decreased the prevalence of tics (Chappell et al 1995; Boon-yasidhi et al 2005).

The phase 3 trials by Shire for GXR represent the first placebo-controlled trial for guanfacine in which there is a statistically significant number of subjects. None of the subjects in the study have any other co-morbid psychiatric diagnosis with the exception of oppositional defiant disorder. There is a statistical difference in the reduction in symptoms between the placebo and the GXR group (Melmed et al 2006). This study suggests the efficacy of guanfacine in treating ADHD symptoms with adequate power and study design.

Guanfacine has a longer half-life than clonidine and appears to have fewer problems with sedation, changes in blood pressure and pulse (Newcorn et al 1998; Lopez 2006). GXR can be given once per day which may help with compliance. Dry mouth, sedation, fatigue, and headache are still significant side effects which may adversely impact the patient.

Even though psychostimulants are still the first line treatment for ADHD and atomoxetine is the only non-stimulant approved for ADHD, guanfacine may be a good alternative for children with comorbid ADHD and tic (Chappell et al 1995; Scahill et al 2001). For children who may not be receiving enough of a benefit from psychostimulants and may have trouble with insomnia, there is a possibility of using guanfacine in conjunction with a psychostimulant to help treat their ADHD symptoms and sleep disturbances aggravated by the psychostimulant (Scahill et al 2001). Decreased appetite and gastrointestinal events are a common side effect for atomoxetine (Weiss et al 2005). For children with predominantly impulsivity and hyperactivity, or for children who are unable to tolerate the side effects from either atomoxetine or psychostimulants, guanfacine may be a possible alternative (Posey et al 2004; Biederman et al 2006).

Disclosures

The author has no affiliation with drug companies and has not participated in a study sponsored by one.

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