Nonstimulant Treatments for ADHD

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KEYWORDS

• Nonstimulants • ADHD treatment • Psychopharmacology

KEY POINTS

- We discuss monotherapy and combined treatment of ADHD, with review of mechanism of action, pharmacokinetics, efficacy, tolerability, and safety of approved, off-label, and pipeline nonstimulants.
- Nonstimulants have an important role when response or tolerability to psychostimulants is poor, when comorbid disorders are present, or if patients prefer to use nonstimulants. There also may be advantages relative to the duration of activity.
- Four nonstimulant medications have FDA approval for ADHD–the norepinephrine reuptake inhibitors, atomoxetine and viloxazine extended release, and the α-2 long acting adrenergic agonists, clonidine extended release and guanfacine estended release.
- Characteristics of clinical response vary across drug classes, including nature of response, approach to titration, time to onset of improvement, and temporal characteristics of treatment.
- Identification of nonabusable treatments with comparable efficacy to stimulants, favorable tolerability profile and consistent effects throughout the day remains a high priority for the field.

INTRODUCTION/HISTORY/DEFINITIONS/BACKGROUND

Overview, The use of nonstimulants in ADHD has a long history; the first publication of a randomized, controlled clinical trial with imipramine was published almost 50 years ago.[1]Since then, a variety of publications have attested to the utility of nonstimulants in ADHD. Initially these medications were used "off-label" (ie, outside of FDA approval),

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and some continue to be used that way. However, there are now 4 nonstimulant medications that have FDA approval for ADHD—the norepinephrine (NE) reuptake inhibitors, atomoxetine (approved in 2002) and viloxazine extended release (ER; approved in 2021), and the long acting α-2 adrenergic agonists, extended release clonidine (CLON-XR; approved in 2010) and extended release guanfacine (approved in 2009).

Rationale for the development and use of nonstimulant medications in ADHD, Despite the high degree of efficacy of stimulant medications, their limitations attenuate applicability to a subgroup of individuals with ADHD—more for some individuals than others.[2] Some patients treated with stimulants do not achieve optimal symptom reduction/response, or they do not tolerate psychostimulant treatment well[3]; these are not infrequently related.[4] Time-action properties of stimulants are also problematic. Stimulants are inherently short-acting medications, and even the long-acting formulations developed during the last 20 years may not cover the entire day adequately. In addition, stimulants are controlled substances (eg, in the United States: Class II), have documented potential for abuse, and there is a substantial amount of misuse and diversion, particularly among college students and young adults.[5] Therefore, identification of nonabusable treatments for ADHD that have comparable or near comparable efficacy to stimulants, a favorable tolerability profile and consistent effects throughout the entire day is a high priority for the field.

Neurobiological basis of nonstimulant medications for ADHD, The executive control network—including the prefrontal cortex (PFC), anterior cingulate gyrus, striatum, and cerebellum—has long been implicated in the pathophysiology of ADHD.[6] The brain regions within this network are characterized by high levels of dopaminergic and/or noradrenergic neurotransmission, leading to the conceptualization of ADHD as a disorder of catecholamine function. This is attributable, in part, to an elegant series of studies illustrating that methylphenidate (MPH) binds to the dopamine (DA) transporter (see the study by Nora Volkow[7]), thereby enhancing synaptic DA. However, NE also plays an important role in the regulation of attention,[8] stimulants bind to the NE transporter and enhance synaptic NE, and NE is a potent agonist of the DA D4 receptor. Consequently, recent conceptualizations of catecholamine mechanisms in ADHD have focused on interactive properties of DA and NE neurotransmission, as well as on the modulating roles of other neurotransmitter systems. This research provides a neurobiological rationale for the use of nonstimulant agents—all of which (thus far) target NE in one way or another—in the treatment of ADHD.

Objectives, To review each of the FDA-approved nonstimulant medications in detail, provide information on medications approved for other conditions that are used off-label in ADHD and introduce several investigational medications in the ADHD pipeline. We will present information regarding mechanism of action, pharmacokinetics, efficacy, and tolerability/safety profile. In addition to reviewing the evidence-base regarding nonstimulant medications, we will offer expert opinion that may inform clinical use, including both monotherapy and combined treatment.

DISCUSSION

Nonstimulant Medications Used in ADHD

The 4 FDA-approved nonstimulant medications are described in detail below. In addition, information regarding dosing and issues related to clinical use are provided in **Table 1**.

ATOMOXETINE

Atomoxetine (ATX) was the first US Food and Drug Administration (FDA)-approved nonstimulant medication for ADHD (in 2002), and it is labeled for use in both children

Table 1
FDA-approved Nonstimulant

Drug	Class	FDA Approvals	Dose	Common Adverse Effects	Comments
ATX[a]	NRI[e]	Children <70 kg Adults >70 kg	0.5–1.4 mg/kg 40–100 mg	Sedation, nausea/vomiting, increased heart rate, and BP. Irritability. Decrease in appetite and/or growth (less than with stimulants)	Approved for once or twice daily administration. First medication specifically approved for adult ADHD. Metabolized by CYP2D6; poor metabolizers have greatly increased half-life and plasma levels. Warnings for suicidal ideation and hepatic toxicity. Best to take with food. Twice daily administration during titration may aid in reducing sedation and GI side effects. Can be administered in AM or PM/evening—effect is less robust if administered in the evening. Time to onset can be seen within weeks in excellent responders but the full effect may not be seen for up to 3 mo
VER[b]	NRI [e]	Children 6–11 Children 12–17	100–200 mg 200–400 mg	Sedation, difficulty sleeping, and decreased appetite Nausea/vomiting, irritability, and increased heart rate	Approved in children; adult data are currently under FDA review. Response (at the group level) is similar across low and higher doses but some potential for improved response with titration. Improvement often seen by 2 wk. Previously approved as an antidepressant in adults. Potential differences

(*continued on next page*)

Table 1
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Drug	Class	FDA Approvals	Dose	Common Adverse Effects	Comments
					from atomoxetine: not metabolized by CYP2D6; half-life is ~7 h; impacts several postsynaptic 5-HT receptors. Strong inhibitor of CYP1A2; may increase levels of drugs metabolized via this enzyme (eg, duloxetine, caffeine, clozapine). Also, viloxazine levels could be increased by drugs impacting CYP1A2 (eg, acetaminophen). Weak inhibitor of CYP 3A4; could increase levels of drugs metabolized via this mechanism (eg, dextromethorphan; guanfacine).
GXR[c]	α-2 agonist[f]	Children 6–17	1–4 mg (up to 7 mg in adolescents)	Sedation, decreased HR and BP, hypotension, light-headedness, dizziness, irritability, and dry mouth and/or eyes	Approved for monotherapy or combined therapy with stimulants. Sedation can be prominent when initiating therapy or raising the dose. Sequential up-titration of 1 mg/wk to minimize side effects. Discontinuation should be gradual to avoid rebound hypertension—1 mg/wk. CYP3A4 metabolized—so watch

					for drug interactions. Half-life is 14–17 h; drug levels peak at ~6 h. Post hoc analyses support a weight-based dosing approach; target of ~.08–.10 mg/kg
CXR[d]	α-2 agonist[f]	Children 6–17	0 .1–0.4 mg (bid dosing)	Sedation, decreased HR and BP, hypotension, light-headedness, dizziness, irritability, dry mouth and/or eyes	Approved for monotherapy or combined therapy with stimulants. Sedation can be prominent when initiating therapy or raising the dose. Sequential up-titration of 0.1 mg/wk to minimize side effects. Discontinuation should be gradual to avoid rebound hypertension—0.1 mg/wk. Partially metabolized via CYP2D6. Half-life is 12–16 h; drug levels peak at ~3–5 h

[a] Atomoxetine
[b] Viloxazine extended release.
[c] Guanfacine extended release.
[d] Clonidine extended release.
[e] Norepinephrine-reuptake inhibitor.
[f] Alpha-2 adrenergic agonists.

and adults. ATX is a relatively selective NE reuptake inhibitor, which also has weak effects at the serotonin transporter, although the latter is not thought to contribute to therapeutic efficacy. ATX increases synaptic NE in multiple brain regions and DA levels in PFC.[9] However, ATX has a low potential for abuse because it does not bind to receptors associated with abuse potential and does not increase DA in the striatum or nucleus accumbens. There is also no evidence of tolerance over time.

A multitude of research has demonstrated that ATX is effective in treating core ADHD symptoms, with apparently equivalent response in inattentive and hyperactive–impulsive domains, with effect sizes that are very solid (in the moderate range overall), but somewhat lower than for stimulants.[10] Treatment is associated with a reduction in impairment across several domains of function, including child self-esteem (as reported by parents), and social and family function.[11] Review of all premarketing studies of ATX in children and adolescents[10] found that response to ATX was bimodal, with most children falling into categories of "much improved" or "nonresponders," rather than "minimally improved." This means that the effect size (ES) of 0.7 in children, which includes both responders and nonresponders, is not a very good way to portray response for this medication; it may do very well for responders, with effects near if not quite the equal of stimulants. The problem is that there is not really a good way to identify excellent responders a priori. Only onset of response by 4 weeks predicts excellent response[10]

The drug is metabolized via the cytochrome P (CYP) 2D6 system; 5% to 7% of individuals have a genetic polymorphism, which makes them poor metabolizers, and a small number of individuals are ultrarapid metabolizers. In poor metabolizers, the half-life of ATX is 19 to 21 hours (vs 4.5 hours in extensive metabolizers), and plasma medication levels are much higher for any given dose.[12] Although it is not necessary to determine CYP2D6 genotype before treatment (studies using blind titration in slow and extensive metabolizers found that end of titration doses were nearly equivalent[12]), there is some suggestion that poor metabolizers have slightly better efficacy and slightly higher adverse event (AE) rates.[12,13] ATX administration does not affect the pharmacokinetic properties of concomitant medications metabolized via CYP2D6 substrates. However, medications that alter CYP2D6 function, such as fluoxetine and paroxetine, can affect the metabolism of ATX by inducing poor metabolizer status.[14] For selected individuals, this strategy could potentially be used to extend the duration of the medication effect, and possibly enhance response.

ATX is dosed on a weight-based schedule; the target dose is 1.2 mg/kg, with a range of 1.0 to 1.4 mg/kg. The medication is effective whether administered once or twice daily. Atomoxetine maintains its effect over an extended period. Time to duration of onset of atomoxetine has been a matter of some debate. Newcorn and colleagues (2009)[10] examined predictors of response in acute trials of atomoxetine in youth, finding that early response to atomoxetine (2–4 weeks) predicted response at trial endpoint. However, De Brukyere and colleagues (2016),[11] using pooled data from short-term (10 weeks) and long-term (24 weeks) clinical trials in adults, found that although symptom reductions and global improvement scores at weeks 4 and 10 were statistically significant predictors of response at later time points, they did not fully account for improvement over time. The authors therefore recommend that the only way to determine whether a given individual will respond to atomoxetine is to treat for up to 3 months. Of course, the latter approach would be challenging for patients who are not achieving a good enough response.

The most commonly occurring AEs include sedation, nausea and vomiting, decreased appetite, weight loss, and increase in heart rate and BP (comparable to stimulants). Irritability and increased aggression can also be seen, most often in

individuals with comorbid mood disorders or disruptive behavior disorders.[15] There are warnings for hepatotoxicity and suicidal ideation. In 2004, postmarketing surveillance identified 2 cases of acute hepatotoxicity (out of ~2 million exposures). Both patients had abdominal pain, jaundice, and substantially elevated liver function tests, which resolved with medication discontinuation. Recurrence of the liver function abnormalities on rechallenge in one case suggests a causal relationship.[16] Obtaining routine liver function tests before initiating ATX treatment is not recommended, owing to the very-low frequency of liver toxicity, and the fact that liver toxicity cannot be predicted from baseline laboratory indices. Atomoxetine also has a "black box" warning for suicidal ideation, due to its common mechanism of action (ie, NE reuptake inhibition) with known antidepressants, and data from premarketing clinical trials. Approximately 4 per 1000 patients treated in 12 short-term clinical trials had suicidal behavior, mainly ingestions, although intent was uncertain in almost all of these cases.[16] It should be noted that a comprehensive review did not find that ATX was more highly associated with suicidal behavior than stimulants.[15] It is nonetheless good clinical practice to obtain a careful history of mood problems and/or suicidal behavior before starting medication, to educate patients and families regarding the importance of reporting changes in mental status, and to maintain close contact with patients early in the treatment. Particular attention should be given to changes in emotional state, including sadness, tearfulness, irritability, anger, or euphoria.

Atomoxetine is not labeled for combined treatment with stimulants, and there are no controlled data that systematically evaluate this drug combination but the 2 medication classes can be used together, and ATX is sometimes used that way in practice. Potential advantages might include relatively longer duration of action, potential for lowering stimulant dose, obviating the need for an afternoon stimulant booster dose, and improving sleep (because ATX can be sedating). Potential disadvantages include sedation (if it occurs) and increased heart rate (HR) and blood pressure (BP) (because both ATX and stimulants increase HR and BP).

Alpha-2 Adrenergic Agonists

The α-2 adrenergic agonists have been used to treat ADHD for more than 3 decades, particularly in youth with comorbid tics and/or aggression. Initially, these medications were used off-label in immediate-release (IR) formulations (the only formulations available at the time) as a nonstimulant alternative in individuals with tic disorders or Tourette syndrome, based on the recognition (accepted at that time) that stimulants might precipitate or worsen tics.[17] However, the immediate release formulations have relatively short duration of action despite half-lives that are reasonably long (~12 hours for immediate release (IR) clonidine and ~ 16 hours for IR guanfacine). The need for multiple daily dosing as well as tolerability issues with the IR formulations (mainly sedation) led to the development of extended-release (XR) formulations. Each of the long-acting formulations is FDA-approved for both monotherapy and combined treatment with stimulants. There is also a clonidine patch (not approved for ADHD), which offers activity for approximately 5 to 7 days; however, this is rarely used. Although clinical trials indicate improvement in both inattention and hyperactive–impulsive symptoms, there seems to be a slightly better response to hyperactive/impulsive symptoms. Consequently, these medications are relegated to second line by National Institute for Healthcare Excellence and European Union (EU) regulatory.[18] Behavioral overarousal, aggression, and oppositional defiant behavior—mainly but not exclusively in association with ADHD—are frequent targets of treatment. Other frequent targets include motor or vocal tics, which may occur comorbidly or be exacerbated by stimulant treatment, and insomnia (either independent of or in association with stimulant

treatment) because the α2-agonists can be fairly sedating, especially on initiating treatment. As with atomoxetine, the a2-agonists offer additional nonstimulant alternatives in cases where diversion or abuse of stimulants is suspected, or in individuals with heightened risk for substance use disorders (SUDs). Although none of the formulations of clonidine or guanfacine are FDA-approved for ADHD in adults in the United States, they may be used off-label in adults to augment ADHD treatment (mainly for overarousal, restlessness and impulsivity, or to minimize sleep disturbance) due to their well-established safety profile in the treatment of cardiovascular disease.

Initial research and the clinical use of the α2-agonists were with the IR form of clonidine, which has effects at multiple α2 subreceptors, as well as other neurotransmitter receptors. A large seminal trial of clonidine and MPH in youth with ADHD, tic disorders, or their combination indicated that the combination of MPH and clonidine was more effective than either drug alone in treating both ADHD symptoms and tics.[19] A subsequent trial, which compared the effects of immediate-release clonidine (CLON-IR), MPH, and their combination in youth with ADHD,[20] found that MPH performed better than CLON-IR but CLON-IR yielded improvement in both symptom ratings and global assessment of function. The average total daily dose of CLON-IR was roughly 0.25 mg, with administration spread over 3 daily doses, because the behavioral effects of CLON-IR last only 3 to 6 hours.

CLON-XR was developed to address limitations related to duration of effects. CLON-XR is labeled for twice daily dosing; the total daily dose ranges from 0.1 to 0.4 mg per day, with recommended dose increases limited to 0.1 mg per day weekly. In a large multisite placebo-controlled trial,[21] CLON-XR significantly improved ADHD symptoms, with the initial improvement as early as the second week of treatment with both the 0.2 mg (ie, 0.1 mg BID) and 0.4 mg (ie, 0.2 mg BID) doses. The most common AE was mild–moderate somnolence. Other AEs included changes in HR and BP (typically lower), and mild alterations of the QTc interval (corrected QT interval; with variable direction of effects, or no effects across studies). Sedation and vital sign changes tended to occur early and resolve during the course of the treatment. No significant adverse events (AEs) occurred related to changes in these parameters, and the QTc change from baseline was small. Because there is potential for rebound hypertension with clonidine, abrupt discontinuation should be avoided.

The potential utility of guanfacine for youth with ADHD has similarly been systematically evaluated, initially in youth with ADHD + tic disorders, and subsequently in youth with ADHD alone. Guanfacine is more selective for $a2_A$-receptors than clonidine; it has a somewhat longer half-life and duration of action, and may be less sedating (although sedation is still the most common side effect). As with clonidine, initial clinical use and research were with the IR formulation but most systematic research has been with the now FDA-approved XR formulation. Guanfacine XR (GXR; doses of 1–4 mg) was found to decrease ADHD symptoms significantly in children aged 6 to 12 years, with increasing effects associated with higher weight-adjusted doses.[22,23] Adolescents aged 13 to 17 years showed less adequate response in the initial trials, due to lower weight-adjusted dosing in this group. Subsequent research using doses up to 7 mg in adolescents found the medication to be effective.[24] Adverse effects included sedation, decreased BP, and QTc changes. Sedation and BP changes generally resolved after 2 weeks and were not associated with medication discontinuation. QTc changes were minimal and did not result in adverse outcomes. Guanfacine is primarily metabolized by CYP3A4, so the dose of guanfacine may need to be increased in the presence of CYP 3A4 inducers (eg, phenobarbital, phenytoin, glucocorticoids) and reduced in the presence of CYP 3A4 inhibitors[25] (eg, erythromycin, clarithromycin, verapamil, grapefruit). Retrospective data suggest that using a weight-based

approach may be helpful, with clinical improvement observed from 0.05 up to 0.12 mg/kg. This approach can be helpful in providing a target for titration. Of note, a relatively large controlled trial of guanfacine extended release conducted in adults in Japan found this medication to be effective, with an ES of ~0.5, comparable to what has been found for other nonstimulants in adult ADHD.[26]

Similar to other ADHD treatments, GXR was shown to maintain its therapeutic effect during the long-term.[27] Children/adolescents with ADHD who responded to GXR after 13 weeks of titration were randomized to continued treatment with active drug or placebo for 26 weeks. Treatment failure occurred in fewer of the children randomized to GXR than placebo, and time to treatment failure was significantly longer in GXR treated youth versus placebo.

In some countries (eg, United States and Australia), guanfacine XR is approved both as monotherapy and adjunctive to stimulant treatment. One large clinical trial (n = 461) in children/adolescents, showed improved core ADHD symptom control with combined guanfacine XR and stimulants over stimulants alone.[28] Another small study did not find combined guanfacine IR with D-MPH ER to perform better than D-MPH ER alone in reducing the severity of ADHD core symptoms' (n = 207) or improving working memory (n = 182).[29] Of note, discontinuation due to AEs was comparable between guanfacine IR and D-MPH (1.5% each) and was greater for combined treatment (2.9%). As expected, during acute titration, guanfacine IR decreased HR and BP, whereas D-MPH ER increased both parameters. More surprising was that combined treatment increased diastolic blood pressure but had no effects on HR or systolic blood pressure. Also of note, during the maintenance treatment, decreases in HR associated with guanfacine IR and increases in systolic blood pressure associated with D-MPH ER returned to baseline, suggesting that these effects may attenuate over time.

Similarly, a large study (n = 198) conducted in children/adolescents with CLON ER + stimulants found that the combined treatment was superior to stimulant monotherapy (ie, stimulant + placebo) in decreasing the severity of ADHD core symptoms. Another smaller trial (n = 67) of CLON IR added to stimulants in children/adolescents found no incremental benefit on ADHD core symptoms but significant effects on conduct symptoms. However, in this study, CLON was added to twice daily (i.e., bid) stimulant treatment in the combined treatment arm, whereas the stimulant monotherapy arm did not offer a third dose; perhaps, the impact of clonidine would not have been significant had a third dose of stimulant been added in the stimulant monotherapy arm. Of note, all of these trials showed good tolerability of the combination of stimulants + clonidine, with no major issues in terms of safety. This is noteworthy, because questions had initially been raised about the safety of this drug combination.

Viloxazine extended release

Viloxazine extended release (ER) is an extended release formulation of a medication previously approved in the United Kingdom and several other European countries for the treatment of depression. Viloxazine IR was never available in the United States; it was taken off the market in Europe in the early 2000s for commercial reasons but not safety concerns.[30]Viloxazine ER has documented activity at the NE transporter and several postsynaptic serotonin receptors[31]; its effects as a NE reuptake inhibitor provide a neurobiological rationale for its use in ADHD, although it is possible that serotonergic mechanisms also contribute to response. Viloxazine ER was approved by the US FDA in April, 2021, making it the first nonstimulant drug approved in over a decade (since the α-2 adrenergic agonists).

Viloxazine ER is administered once daily; the labeled dose range is 100 to 400 mg, although studies have examined doses up to 600 mg and found adequate safety in higher doses. The starting dose is 100 mg in children and 200 mg in adolescents, with target doses of 200 and 400 mg, respectively. The half-life of ~7 hours supports the once daily label. The time to peak levels is ~5 hours with a range of 3 to 9 hours after a single 200 mg dose. A high-fat meal modestly decreases levels of viloxazine and delays the time to peak by about 2 hours.

A multitude of publications have demonstrated efficacy in children and adolescents. A phase 2 study in children 6 to 12 years old tested 4 doses of viloxazine versus placebo; findings indicated comparable efficacy for each of the doses, with effect sizes ranging from 0.55 to 0.62, comparable to other nonstimulants for ADHD in children.[32] These findings were replicated in subsequent phase 3 studies, which examined the 100 and 200 mg doses in children and the 200 and 400 doses in adolescents.[33–35] Separation from placebo was seen by 2 weeks, and response seen at 2 weeks was found to predict the end of treatment outcome at 6 weeks.[36] Treatment-related AEs reported in 5% or greater of subjects included somnolence, decreased appetite, and headache; however, there was no impact on QTc.[33,34]

There are not yet sufficient data on combined treatment with stimulants to comment on whether this could yield possible augmentation of stimulant response; however, relatively small n studies examining the pharmacokinetic (pK) profiles of viloxazine XR coadministered with either MPH[37] or lisdexamfetamine[38] found relatively little alternation in the pK profiles of any of the drugs.[38] Of note, viloxazine is only partially metabolized by CYP 2D6 and drug levels are only modestly impacted by CYP 2D6 inducers. This, together with its effects at several postsynaptic serotonin receptors, and its longer half-life than ATX in CYP 2D6 extensive metabolizers, illustrate potential distinctiveness from ATX. Moreover, viloxazine ER is a beaded formulation and can be sprinkled on applesauce or pudding without altering the pK profile; this is the only nonstimulant that offers an alternative delivery option other than swallowing pills.[39] Similar to other stimulant and nonstimulant drugs for ADHD, treatment with viloxazine ER is associated with improved functional status,[35,40] with notable improvement in executive function[41] and learning and school problems.[42] In addition, because it has documented antidepressant activity, it may have a role in treating ADHD + depression and/or anxiety; however, this has not yet been studied. Note that viloxazine is a strong inhibitor of CYP 1A2 and may increase drug levels of medications metabolized via this enzyme (eg, duloxetine, caffeine, clozapine). Similarly, viloxazine levels could be increased by drugs impacting CYP 1A2, such as acetaminophen. Viloxazine is also a weak inhibitor of CYP 3A4 and could increase levels of drugs metabolized via this mechanism (eg, dextromethorphan, guanfacine).

Off-Label and Investigational Drugs

Antidepressants

Several antidepressants with noradrenergic activity have either documented or reported efficacy for ADHD—including the noradrenergic tricyclic antidepressants (TCAs; especially well-documented efficacy for desipramine[43]), the serotonin-norepinephrine reuptake inhibitors (SNRIs) (reported but not well studied),[44] bupropion[45] (fairly well studied), and even the monoamine oxidase (MAO) inhibitors (limited controlled data[46]) — although none are labeled for ADHD. Of these, bupropion is the most relevant for clinical practice.

Bupropian. Bupropion is a mixed noradrenergic–dopaminergic agent that is chemically unrelated to other known antidepressants. It is available in IR, sustained-release (SR; bid administration), and long-acting (XL; once daily administration) formulations.

Bupropion is a relatively weak inhibitor of NE and DA reuptake, and does not inhibit monoamine oxidase. Because it is metabolized by CYP2B6, there is potential for interactions with several psychotropic drugs. Multicenter studies in both children[47] and adults[48] with ADHD found that bupropion was effective, although with a lower ES than is typically seen for stimulants. Results from 5 randomized controlled studies of bupropion were evaluated in a meta-analysis (outcome: CGI-Improvement) with a pooled odds ratio of 2.42 favoring bupropion.[49] However, a recent meta-analysis examining the comparative efficacy of buproprion relative to other drugs for pediatric ADHD reported an ES of 0.32 versus placebo,[50]which is a fair bit lower than for the approved nonstimulants. Similarly, a recent Cochrane review[51] found a significant but low quality level of efficacy.

Bupropion may be particularly useful in the treatment of comorbid ADHD + mood disorders because it is an approved antidepressant in adults. In addition, similar to other nonstimulants, it may be a useful alternative to stimulants in comorbid ADHD + SUD. Bupropion has been found to reduce ADHD symptoms in trials of adolescents and adults with ADHD and comorbid SUD, often in the context of other comorbid disorders (eg, conduct disorder (CD), depression[52]). In addition, it has been shown to decrease craving and/or abuse in some of these studies. Also of note, bupropion is FDA-approved for smoking cessation treatment (under a different trade name[53]); this may be relevant to adults with ADHD, given the high association of nicotine addiction and ADHD.

The most commonly reported AEs include agitation, anxiety, decreased appetite, and insomnia. There is a slightly increased risk for drug-induced seizures at doses greater than 450 mg/d, and a black box warning regarding the risk for suicidal thoughts and behaviors. As with the stimulants, exacerbation of tic disorders has been reported.

SNRIs. Because of their partial noradrenergic mechanisms of action, the mixed SNRI medications have received limited study for ADHD. There are a variety of SNRIs, including venlafaxine, desvenlafaxine, duloxetine, milnacepran, and levomilnacepran. Note that the relative proportion of monoamine reuptake activity differs by drug.[54] Venlafaxine is the most serotonergic; desvenlafaxine and duloxetine are more balanced but strongly favoring serotonin, whereas milnacepran and levomilnacepran actually favor NE reuptake. Venlafaxine, desvenlafaxine and duloxetine exhibit very weak effects on DA reuptake, and only at higher doses. Most research to date has been with venlafaxine, including several low n controlled studies but there are also studies in children and adults with duloxetine.[55] Improvement in ADHD symptoms with venlafaxine has been seen in both parent and teacher ratings, with a generally agreeable AE profile. Open or small n controlled studies, including one comparing venlafaxine to MPH, have shown a modest degree of efficacy but are not totally convincing. Recent reviews suggested that venlafaxine may have short-term utility in treating ADHD and may be considered as an alternative agent (used off-label) in patients not tolerating or failing psychostimulants. However, it seems unlikely that doses less than 150 mg, which do not produce much effect on catecholamine neurotransmission, are likely to be effective. Moreover, given the wealth of effective medications for ADHD, it would seem the most likely use of these medications would be in patients with mood and anxiety disorders who also have ADHD symptoms.

TCAs. The TCAs have been largely replaced in clinical practice by newer antidepressants, which typically have more favorable side effect profiles. However, there is a fairly large literature supporting the efficacy of the noradrenergic TCAs, principally desipramine, in ADHD, which is important to reference. The noradrenergic TCAs

basically act as SNRIs by blocking the serotonin and NE transporters, which supports their role in ADHD. In several double-blind, placebo-controlled studies, desipramine was found to be effective in the management of children with ADHD, including patients who failed to respond to psychostimulants.[56] But, there was an increased risk for elevated diastolic blood pressure and heart rate, and evidence of intraventricular conduction defects on ECG.[56] Thus, alternative noradrenergic nonstimulant options were sought, ultimately leading to the testing and approval of atomoxetine for ADHD.

Buspirone

Buspirone is an anxiolytic agent, which binds to the serotonin 5-HT1A and 5-HT2 receptors (104); it also has agonist activity at D2 autoreceptors. Because of its modest dopaminergic effects, and the role of 5-HT1A receptors in the regulation of impulse control, clinical studies have been conducted in both youth and adults with ADHD.[57] Samples were small and the effects on ADHD symptoms modest; however, this medication may have a role in the treatment of patients with ADHD and comorbid anxiety.

Glutamatergic Agents

There are limited data on the potential utility of the N-methyl-D-aspartate (NMDA) receptor antagonists amantadine[58] and memantine in youth[59] and adults[60] with ADHD. These medications have been studied in open-label studies, one comparison trial versus MPH,[61] and one augmentation trial with MPH.[62] Open studies reported positive results of treatment and acceptable tolerability. In the comparator trial, amantadine was associated with clinical improvement comparable to MPH; however, the sample was small and there was no placebo contrast. A small open-label trial in adults found improvements in both ADHD symptoms and neuropsychological test performance.[60,62] Finally, a small placebo-controlled trial using memantine adjunctive to MPH in adults with ADHD found selected improvements in executive function.[62]

Atypical Stimulants: Wakefulness and Alertness Promoting Agents

Modafinil and its R-stereoisomer, armodafinil, are novel cognitive-enhancing and wake-promoting agents, which are structurally and pharmacologically different from other agents used to treat ADHD. Modafinil and armodafinil are atypical stimulants (DEA Schedule IV in the United States) that selectively activate the cortex and modulate several different neurotransmitters, including hypocretin, histamine, NE, γ-aminobutyric acid (GABA), and glutamate. Modafinil and armodafinil are FDA approved for the treatment of narcolepsy and shift-work sleep disorder and also for adjunctive treatment of obstructive sleep apnea/hypopnea syndrome. Several years ago, a clinical development program examined the efficacy and tolerability of an investigational, extended duration formulation of modafinil.[63] Significant improvement was found for children in ratings of ADHD symptoms both at home and at school; however, adult trials with modafinil have not separated from placebo.[64] This new formulation was not approved by the FDA owing to concerns regarding possible elevated risk for Stevens–Johnson syndrome. Although further investigation is necessary to determine whether modafinil can be used safely and effectively for the treatment of ADHD, the available data[65] suggest that it may represent a viable option for some individuals who do not respond to or cannot tolerate approved stimulant and nonstimulant formulations. Of note, armodafinil has a more extended pharmacokinetic profile than modafinil and may therefore have a better effect on alertness and arousal throughout the day.

INVESTIGATIONAL COMPOUNDS

Several existing (eg, vortioxetine) and novel nonstimulant compounds (eg, dasotraline; metadoxine; fasoracetam) have been studied in clinical trials during the last several years.[66] Unfortunately, many recently studied drugs, particularly those targeting neurotransmitter systems with indirect activity on DA and NE, have failed in phase 3. Two potentially promising investigational nonstimulants for ADHD are described below.

Centanafadine. Centanafidine is a serotonin–norepinephrine–dopamine reuptake inhibitor (ratio of 14:6:1, respectively) which is currently in phase 3 trials in the United States. A recently published placebo-controlled phase 2 study in adults with ADHD evaluated the efficacy and tolerability of 400 mg (divided into 2 doses daily) centanafadine.[67] The ES versus placebo of 0.62 after 3 weeks of treatment indicates that this medication may have efficacy, which is comparable to or slightly greater than other nonstimulants (because ES of existing treatments are typically lower in adults). Observed side effects were generally mild, including decreased appetite, headaches, nausea, and diarrhea. Several cases of rash were observed in early phase trials, so ongoing research will need to document the frequency with which this may occur, and the potential clinical significance.

Mazindol XR. Mazindol is an anorexic substance, not related to amphetamines or metabolized to an amphetamine-like compound, which was approved for the treatment of obesity and also used off-label in narcolepsy. Mazindol was approved in an IR formulation as a schedule IV drug in the United States, which was withdrawn in the early 2000s for commercial reasons and not safety concerns. Mazindol binds to DA, NE, and 5-HT transporters (ie, triple reuptake inhibitor) and is also a partial agonist of orexin.[68] A small open-label pilot study of the immediate release formulation (1 mg/d) in children with ADHD reported greater than 8 hours of activity and greater than 90% improvement in ADHD symptoms after 1 week. Appetite suppression and upper abdominal pain were the most common AEs. A more extensive phase 2 study in adults with ADHD using an investigational extended release formulation[69] found robust effects on both symptom ratings (i.e., ADHD Rating Scale (ADHD-RS) scores) and functional impairment, with an ES for ADHD symptoms comparable to amphetamine. Currently, this medication is being investigated for narcolepsy but it is presumed that further study in ADHD may be undertaken.

CLINICAL USE OF NONSTIMULANTS

Because nonstimulants have a lower ES than psychostimulants (with the actual figure varying by drug and age group), most professional guidelines and treatment algorithms indicate that psychostimulants should be the first-choice medication option for youth and adults with ADHD. However, nonstimulants can have an important role if there is poor response or tolerability to psychostimulants, when certain comorbid disorders are present, or if there is patient or family preference to use a nonstimulant. Therefore, a more inclusive approach to treatment sequencing might be to simply recommend that an FDA-approved medication (stimulant or nonstimulant) be used, with the choice of which agent is selected to be directed by results of clinical trials and a variety of other clinically relevant factors. The presence of comorbid anxiety disorders or autistic spectrum disorders might represent good indications for atomoxetine. Alpha-2 agonists would potentially be a good choice for a patient with ADHD + comorbid tic disorders and/or oppositional or disruptive behavior. Bupropion or viloxazine might be reasonable drugs to recommend for someone with ADHD + comorbid depression and/or anxiety (though neither has formally been

studied in these populations), due to their known antidepressant effects. All of the nonstimulants could be options for individuals with ADHD and SUD because stimulant use can be (but is not necessarily) problematic in this population. Note, however, that the above suggestions are based on clinical acumen and have received only minimal investigation.

The α-2 agonists additionally have a labeled indication for adjunctive therapy (in the United States) and can aid in mitigating increases in HR and BR or sleep disturbances that often accompany stimulant treatment. Moreover, nonstimulant medications can be used alone or in combination with stimulants to provide medication coverage throughout the day and into the evening, compensating for the restricted time-action properties of stimulants in some patients, and limiting stimulant dose. Although unstudied, the latter strategy could be useful for potentially mitigating long-term AEs of stimulants, such as growth retardation, in selected individuals.

It is important to note that while both stimulants and nonstimulants are FDA-approved for ADHD, important characteristics of clinical response often vary across the different drug classes, including the nature of response, approach to titration, expected time to onset of clinical improvement, and temporal characteristics of the treatment.

SUMMARY

There are 2 classes of FDA-approved nonstimulant medications for ADHD—the selective noradrenergic reuptake inhibitors and the α-2 adrenergic agonists. In addition, several other medication classes have been used off-label with reported efficacy and several more are being developed. Although the nonstimulant medications are, on average, not as broadly or robustly effective as the psychostimulants, they can be very helpful in treating certain patients with ADHD (and associated comorbidities)—either as monotherapy or as adjunctive agents. Controlled clinical trials comparing nonstimulant and stimulant medications that examine not only the impact on core symptoms but also a range of associated clinical and contextual variables will be essential to guide the clinical use of nonstimulants in ADHD.

There is considerable interest in developing new classes of nonstimulant medications, based on our growing knowledge regarding the multiplicity of neural circuits and neurotransmitter systems that are implicated in the pathophysiology and/or maintenance of attention, cognitive, behavioral, and emotional control—all of which are central to ADHD. It is expected that current and yet to be developed nonstimulants will have an important role in the treatment of selected subgroups of ADHD patients in the years ahead, potentially offering better opportunities to match treatments to specific clinical and neurobiological patient characteristics.

CLINICS CARE POINTS

- Currently approved nonstimulants have moderate effect sizes, although somewhat lower on average than for stimulants. More robust response is seen in a subgroup of those treated. Duration of action is typically longer than for stimulants.
- Nonstimulants can be used in monotherapy or combined treatment. Combining nonstimulants with stimulants can be an effective strategy for extending duration of coverage, improving efficacy, and limiting side effects of both medication classes.
- Atomoxetine has been shown to be effective in treating children and adults with anxiety disorders and might be a parsimonious choice for this population.

- Alpha-2 agonists improve both inattention and hyperactive–impulsive symptoms, with slightly better response to hyperactivity/impulsivity symptoms, and are often used to treat behavioral overarousal, aggression, tics, and insomnia either as comorbidity or as they emerge in treatment with stimulants.
- Norepinepherine reuptake inhibitors have cardiovascular effects more similar to stimulants than to α-2 adrenergic agonists; the α-2s may be used off-label alone or in combination with stimulants in selected adults due to their favorable cardiovascular profile.
- Among the norepinepherine reuptake inhibitors, Viloxazine extended release has documented antidepressant activity and has a longer half-life compared with ATX (except in CYP 2D6 poor metabolizers). Might this be an effective medication for depression comorbid with ADHD?
- Bupropion, an antidepressant also labeled for smoking cessation, may be particularly useful in the treatment of comorbid ADHD and depression, with evidence that it may be used successfully in context of substance use disorder.

DISCLOSURE

In the past year, Dr Newcorn is/has been an advisor and/or consultant for Adlon Therapeutics, Corium, Lumos, Medice, Myriad Neuroscience, NLS, OnDosis, Rhodes, Shire/Takeda, and Supernus. He has received research support from the National Institute on Drug Abuse, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Adlon and Shire. He also has received honoraria from for disease state presentations from Otsuka and Takeda, and served as a consultant for the US National Football League. Dr Krone has nothing to disclose. Dr Dittman has nothing to disclose.

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