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Current and future nonstimulants in the treatment of pediatric ADHD: monoamine reuptake inhibitors, receptor modulators, and multimodal agents

Andrew J. Cutler[1], Gregory W. Mattingly[2], Rakesh Jain[3] and Welton O'Neal[4]*

[1]Neuroscience Education Institute and Department of Psychiatry, SUNY Upstate Medical University, Sarasota, FL, USA, [2]Department of Psychiatry, Washington University School of Medicine, Washington University, St. Louis, MO and Midwest Research Group, St. Charles, MO, USA, [3]Department of Psychiatry, Texas Tech Health Sciences Center School of Medicine – Permian Basin, Midland, TX, USA, and [4]Medical Affairs, Supernus Pharmaceuticals, Inc., Rockville, MD, USA

Review

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Author for correspondence:
*Welton O'Neal, PharmD
Email: woneal@supernus.com

Abstract

Attention-deficit/hyperactivity disorder (ADHD), the single most common neuropsychiatric disorder with cognitive and behavioral manifestations, often starts in childhood and usually persists into adolescence and adulthood. Rarely seen alone, ADHD is most commonly complicated by other neuropsychiatric disorders that must be factored into any intervention plan to optimally address ADHD symptoms. With more than 30 classical Schedule II (CII) stimulant preparations available for ADHD treatment, only three nonstimulants (atomoxetine and extended-release formulations of clonidine and guanfacine) have been approved by the United States Food and Drug Administration (FDA), all of which focus on modulating the noradrenergic system. Given the heterogeneity and complex nature of ADHD in most patients, research efforts are identifying nonstimulants which modulate pathways beyond the noradrenergic system. New ADHD medications in clinical development include monoamine reuptake inhibitors, monoamine receptor modulators, and multimodal agents that combine receptor agonist/antagonist activity (receptor modulation) and monoamine transporter inhibition. Each of these "pipeline" ADHD medications has a unique chemical structure and differs in its pharmacologic profile in terms of molecular targets and mechanisms. The clinical role for each of these agents will need to be explored with regard to their potential to address the heterogeneity of individuals struggling with ADHD and ADHD-associated comorbidities. This review profiles alternatives to Schedule II (CII) stimulants that are in clinical stages of development (Phase 2 or 3). Particular attention is given to viloxazine extended-release, which has completed Phase 3 studies in children and adolescents with ADHD.

The Challenge of ADHD

As the most common neurodevelopmental disorder of childhood, attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity, and impulsivity. ADHD is associated with an increased risk of academic, social, and family problems, as well as emotional dysregulation in children and increased risk of substance abuse, motor vehicle/traffic accidents, and teenage pregnancy in adolescents.[1] ADHD that persists into adulthood has been associated with lower occupational and economic performance, psychiatric comorbidity (eg, depression, substance abuse, emotional lability, and anxiety disorders), increased rates of marital problems/divorce, and more negative assessments of self-worth and self-esteem.[1] Although ADHD-related impairments during school and work are generally the primary focus of intervention, ADHD behaviors at the beginning and end of the day can be just as impairing as well as stressful and frustrating for affected individuals and their families.[1]

Comorbidities: the rule, not the exception, in ADHD

ADHD rarely occurs in isolation. In the National Survey of Children's Health, parents reported that 64% of children/adolescents with current ADHD had at least one other mental, emotional, and/or behavioral disorder.[2] The most common are behavioral/conduct disorder, anxiety problems, depression, autism spectrum disorder, and Tourette syndrome.[2] The incidence of psychiatric comorbidity in adults with ADHD reportedly approaches 90%, with anxiety, depression, and substance abuse being the most common.[3]

Patients with ADHD and significant comorbid mood or anxiety symptoms are frequently encountered by clinicians. The traditional practice has been to prioritize mood and anxiety

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problems before ADHD symptoms. Recent findings regarding antidepressant resistance suggest that this approach may need to be reconsidered.[4] The risk of antidepressant resistance was found to be >2-fold higher in patients with major depression and comorbid ADHD vs major depression alone.[4] Concomitant ADHD treatment was associated with a significantly lower risk of antidepressant resistance, leading to the conclusion that prompt and regular treatment of ADHD in dual-diagnosis patients may reduce the risk of antidepressant resistance.[4] Because the functional impairments of ADHD can exacerbate underlying mood disorders, anxiety disorders, and substance abuse, the careful treatment of ADHD may provide a more favorable environment for effective treatment of these psychiatric comorbidities.[1]

Shortcomings of stimulant therapy

While stimulants (ie, methylphenidates, amphetamines) have been the primary pharmacologic therapy in ADHD for decades, they are not suitable in many situations, including the 25% to 30% of patients who do not achieve optimal symptom reduction or do not tolerate stimulants;[5] some patients with comorbidities (eg, anxiety, depression, and tics) or conditions (eg, sleep disorders, eating problems) in which stimulant effects are of concern; in patients requiring 24-hour symptomatic coverage; and in situations where there is a risk of nonmedical use, drug diversion, or abuse of these Schedule II (CII) drugs. Because CII drugs have a high potential for abuse and severe psychological or physical dependence, nonmedical use/diversion of stimulants is not a trivial issue, particularly in light of data that nearly 60% of college undergraduates with current prescriptions for stimulants reported having given away or selling their stimulant medication at least once.[6] In children, adverse effects of long-term, continuous stimulant use on growth trajectories that may modestly reduce adulthood height and increase weight and body mass index are also cause for concern.[7]

Nonstimulants currently approved for ADHD by the FDA are limited to atomoxetine (ATX) and extended-release formulations of guanfacine (guanfacine-XR) and clonidine (clonidine-XR). Of these, only ATX is approved for use in adults. This limited scope of nonstimulant options is likely to expand in the next several years since several agents are in clinical development and have successfully completed Phase 2 and/or Phase 3 studies. Each candidate is unique in terms of chemical structure and putative molecular targets (Figure 1; Table 1). Based on these pharmacologic profiles, nonstimulants can be broadly classified as (1) monoamine reuptake (transporter) inhibitors (eg, ATX); (2) receptor modulators (guanfacine-XR, clonidine-XR); and (3) multimodal agents.

We review clinical characteristics of the marketed and experimental alternatives to CII stimulants that have demonstrated efficacy in double-blind, placebo-controlled Phase 2 or Phase 3 studies. Pipeline alternatives to CII stimulants include several monoamine reuptake inhibitors (dasotraline, centanafadine sustained release, OPC-64005) and multimodal nonstimulants (vortioxetine, viloxazine extended-release), as well as a multimodal stimulant (mazindol controlled release) with lower abuse potential (CIV).

Monoamine Reuptake (Transporter) Inhibitors

Atomoxetine

Atomoxetine (Strattera®, Eli Lilly) is a selective noradrenergic reuptake inhibitor with high affinity for presynaptic norepinephrine transporters (NET).[8,9] Although ATX was first evaluated in the 1980s as a potential treatment of major depressive disorder (MDD) in adults, development in depression was abandoned due to lack of efficacy.[10]

Atomoxetine was the first nonstimulant medication approved by the FDA for the treatment of ADHD based on a series of double-blind, randomized controlled trials (RCTs) in children ≥6 years of age, adolescents, and adults. In a large, comprehensive meta-analysis incorporating data from 24 RCTs in pediatric ADHD, the effect size for total ADHD symptom improvement with ATX was 0.64.[11] Significant differences in ADHD symptoms vs placebo were generally not noted until 4 weeks after treatment was initiated.[11] Atomoxetine was associated with a bimodal response, that is, 45% of patients were much improved at study end, while 40% were considered nonresponders.[11]

Several RCTs have examined ATX efficacy and safety in children and/or adolescents with ADHD and specific comorbidities, for example, oppositional defiant disorder (ODD), anxiety disorders, depressive disorders, tic disorders, and autism spectrum disorders.[12,13] Overall, comorbid disorders did not appear to compromise the efficacy of ATX in reducing ADHD symptoms. Atomoxetine not only did not exacerbate comorbidity symptoms in RCTs,[12,13] it appeared to have the potential for positive effects on some comorbid symptoms, for example, reducing tic severity and ODD symptoms in children and social anxiety disorder (SAD) in children and adults.[13] Improvements in comorbid ODD and anxiety symptoms correlated with improvements in ADHD symptoms.[13] Atomoxetine had no significant benefit vs placebo in adults with SAD without comorbid ADHD,[14] suggesting that previously observed benefits of ATX on comorbid anxiety were mediated by the drug's effects on ADHD.[15] Despite the expected improvements in ADHD symptoms, ATX effects on depressive symptoms were no different vs placebo in children and adults with comorbid MDD.[13]

The most common adverse events (AEs) of ATX in pediatric ADHD RCTs were gastrointestinal symptoms (vomiting, abdominal pain, nausea, and diarrhea), nervous system symptoms (dizziness, headache, somnolence, sedation, and drowsiness), fatigue, and anorexia.[11] In adults, the most common AEs were constipation, dry mouth, nausea, decreased appetite, dizziness, erectile dysfunction, and urinary hesitation.[16] Safety concerns cited in ATX prescribing information include a boxed warning about suicidal ideation in children and adolescents (risk ratio, ATX vs placebo, 2.92[17]), as well as warnings about severe liver injury and serious cardiovascular events.[16] Cardiovascular effects of ATX include increases in blood pressure (BP) and heart rate (HR). A comprehensive safety review by the manufacturer found clinically significant increases in HR (≥20 beats per minute [bpm]) and/or BP (≥15-20 mm Hg) in 8% to 12% of children and adolescents.[18] Atomoxetine is contraindicated in individuals with severe cardiovascular disorders and should be avoided in children or adolescents with known serious cardiac problems.[16]

Dasotraline

Dasotraline (Sunovion) is considered a dual reuptake inhibitor based on its preferential inhibition of dopamine transporters (DAT) and NET and weaker inhibition of serotonin transporters (SERT).[*20] Like ATX, development of dasotraline in MDD in adults was suspended due to lack of efficacy.[21,22] Dasotraline dosed

[*]Some sources have identified dasotraline as a triple reuptake inhibitor.[19]

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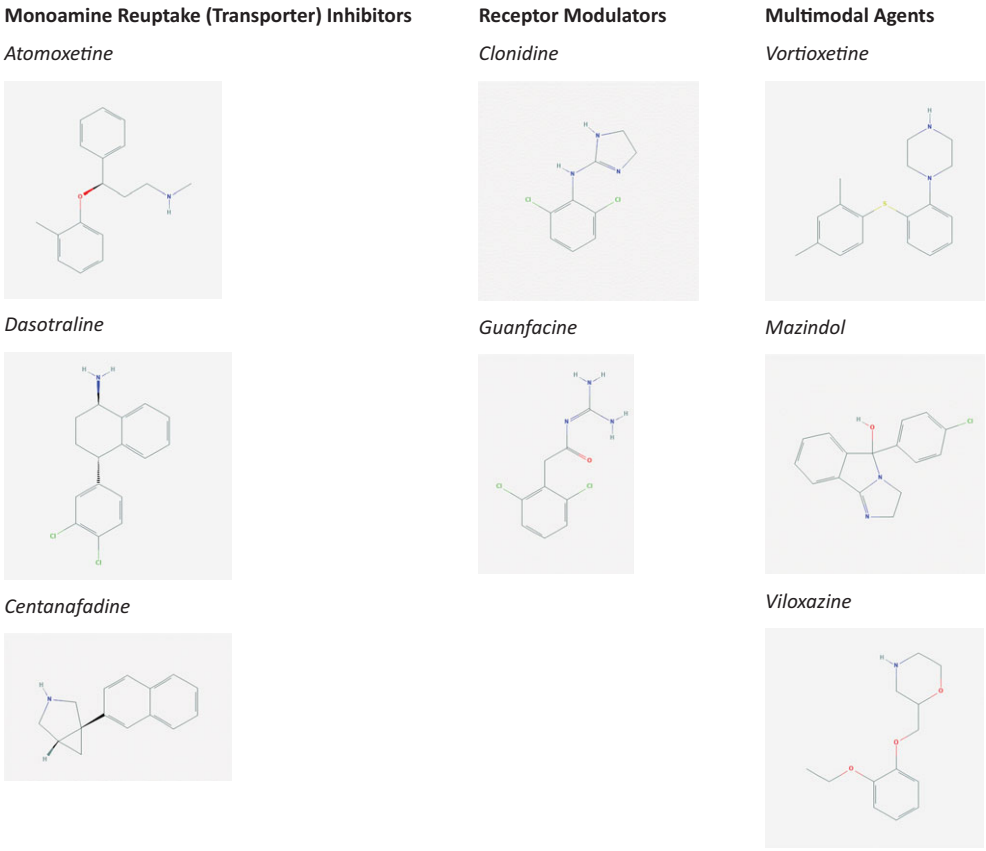

Figure 1. Molecular structure of currently approved and pipeline nonstimulant medications for attention-deficit/hyperactivity disorder.

q.d. was subsequently evaluated in a series of RCTs in adults and children with ADHD, starting with a proof-of-concept Phase 2 study in adults treated with 4 mg or 8 mg (estimated DAT receptor occupancy, 56% and 71%, respectively).[23] Only 8 mg dasotraline was superior to placebo (effect size, 0.41) in improving total ADHD symptoms but was not well tolerated (discontinuation due to AEs, 28%) in this exploratory study. Subsequent Phase 3 RCTs in ADHD evaluated 2 to 6 mg dasotraline.

In children and adolescents with ADHD, 4 mg dasotraline was significantly superior to placebo in two RCTs, with an effect size of 0.85 in methylphenidate-responsive patients in a 2-week laboratory classroom study[24] and 0.48 in a 6-week fixed-dose study.[25] In the fixed-dose study, superiority of dasotraline over placebo emerged within the first week. The lower dose of 2 mg dasotraline was not significantly superior to placebo,[25] while evaluation of 6 mg was terminated due to unexpected neuropsychiatric AEs, including hallucinations.[24] In a Phase 3 study in adults, improvement with 4 mg dasotraline failed to show a significant difference vs placebo in improving total ADHD symptoms while the difference with 6 mg dasotraline trended toward significance.[26] In a posthoc analysis of pooled data from the two RCTs in adults, improvements in ADHD symptoms were significantly greater with dasotraline (4, 6, and 8 mg/day) vs placebo.[26]

The most common AEs with 2 and 4 mg dasotraline in children/adolescents were insomnia, irritability, decreased appetite, and decreased weight.[25] Psychosis-related symptoms (hallucinations, delusions) were reported in 5% of children receiving 4 mg and in 10% receiving 6 mg.[24,25] Mean BP changes were minimal (≤3 mmHg).[25] No clinically meaningful ECG changes were observed in children. The most common AEs in adults were insomnia, decreased appetite, and dry mouth.

Results of the dasotraline-ADHD clinical development program were reviewed by the FDA, which rejected approval pending additional efficacy and tolerability data.[27] Dasotraline has also been evaluated as a treatment of binge eating disorder in adults. As of this writing, results of this clinical development program were under review by the FDA.[28]

Centanafadine

Centanafadine (CTN, Otsuka) is a triple reuptake inhibitor (NET > DAT > SERT) that is being developed as a sustained-release (SR) formulation for b.i.d. dosing in ADHD.[29,30] In a microdialysis study in conscious rats, CTN increased extracellular NE, DA, and serotonin (5-HT) concentrations from baseline by approximately twofold in the prefrontal cortex; striatal extracellular DA was also increased nearly twofold.[29] A study in healthy volunteers supported dose-related brain occupancy of CTN-SR on NET, SERT, and DAT.[31] NET occupancy with CTN-SR was equivalent to that of a typical dose of ATX; DAT occupancy was similar to that of a typical long-acting methylphenidate dose. In light of the ability of CTN-SR to increase DA, the drug's abuse potential was evaluated in an exploratory crossover-design study in healthy recreational stimulant users, comparing an immediate-release (IR) formulation of CTN with d-amphetamine and lisdexamfetamine.[29,30] The subjective effects profile of CTN-IR was different from that of the stimulants. With CTN-IR, aversive effects (dislike) during the initial period when CTN exposure was rapidly increasing were followed by increased "like" mean scores that were numerically lower vs stimulants. Results were interpreted as indicators of low abuse potential for CTN-SR.

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Table 1. Currently Approved and Pipeline Nonstimulant Medications for Attention-Deficit/Hyperactivity Disorder (ADHD).

	Pharmacologic Activity	ADHD Status	Dosing	Comments
Monoamine reuptake inhibitor				
Atomoxetine	NET inhibitor	Approved for children ≥6 yrs and adults	q.d. or b.i.d.	Inconsistent, delayed (≥4 wks) treatment effect; bimodal response. Positive effects on certain ADHD comorbidities (tics, ODD, and SAD symptoms, but not depressive symptoms in comorbid MDD). Notable safety issues: suicidal ideation, liver toxicity, and cardiovascular effects.
Dasotraline	DAT, NET inhibitor	FDA approval rejected pending additional data	q.d.	Significant treatment effect in children (4 mg) and adults (4, 6, 8 mg); early onset of effect (1 wk). Dose-related psychosis symptoms (hallucinations, delusions) observed in children. Most common AEs in children: insomnia, irritability, decreased appetite, decreased weight. Most common AEs in adults: insomnia, decreased weight, dry mouth.
Centanafadine sustained release	NET, DAT, SERT inhibitor	Phase 3	b.i.d.	Limited clinical information. Significant treatment effect in Phase 2 studies in adults. Low abuse potential (human abuse liability study).
OPC-64005	SERT, NET, DAT inhibitor	Phase 2	Not reported	No published data.
Receptor modulator				
Clonidine extended release	α_{2A}, α_{2B}, α_{2C} Agonist	Approved for children ≥6 yrs	b.i.d.	Repurposed antihypertensive agents. Primarily used as adjunct to stimulants. Early onset of effect (wk 1 or 2). Positive effects on comorbid oppositionality/conduct disorder and tics. Notable safety issues: cardiovascular effects (both agents), syncope (guanfacine-XR) and abrupt discontinuation (clonidine-XR).
Guanfacine extended release	α_{2A} Agonist	Approved for children ≥6 yrs	q.d.	
Multimodal Agents				
Vortioxetine	SERT inhibitor, 5-HT (5-HT_{1A}, 5-HT_{1B}, 5-HT_3, 5-HT_{1D}, 5-HT_7) modulator	Phase 2 (approved for MDD treatment)	q.d.	Repurposed antidepressant shown to improve cognitive processing speed in depressed individuals. No clear efficacy signal (ADHD symptom reduction) in Phase 2 study in adults with ADHD. No additional RCTs in ADHD underway.
Mazindol controlled release	SERT, DAT, NET inhibitor, 5-HT (5-HT_{1A}, 5-HT_7), muscarinic, histamine H_1, μ-opioid, orexin-2 modulator	Phase 2	q.d.	Repurposed obesity treatment (Schedule IV). Significant treatment effect in Phase 2 study in adults with ADHD; early onset of effect (1 wk). Most common AEs: dry mouth, nausea, fatigue, increased HR, decreased appetite, constipation. HR and BP increased.
Viloxazine extended-release	NET inhibitor (weak), 5-HT (5-HT_{2C}, 5-HT_{2B}, 5-HT_7), α_{1B} and β_2 modulator	Completed Phase 3 trials in pediatric subjects with ADHD	q.d.	Repurposed antidepressant. Significant treatment effect in Phase 3 studies in children and adolescents with ADHD; early onset of effect (1 wk). The most common treatment-related AEs in the Phase 3 trials of SPN-812 (≥5% incidence) were somnolence, headache, decreased appetite, fatigue, nausea, and upper abdominal pain. No significant adverse cardiovascular effects.

Abbreviations: AEs, adverse events; BP, blood pressure; DAT, dopamine transporters; HR, heart rate; MDD, major depressive disorder; NET, norepinephrine transporters; ODD, oppositional defiant disorder; SAD, social anxiety disorder; SERT, serotonin transporters.

Results of two Phase 2 studies have been published.[30] In a pilot, single-blind, flexible-dose (target dose, 500 mg/day), 4-week study in adults with ADHD (N = 41), CTN-SR was associated with significant reductions in ADHD symptoms vs baseline.[30] A Phase 2b double-blind, crossover study (3-week treatment period; 1-week washout) in 85 adults compared CTN-SR (target dose, 400–800 mg/day) and placebo. CTN-SR was significantly superior to placebo (effect size, 0.66).[30] The most frequently reported treatment-related AEs were decreased appetite (24%), headache (23%), and nausea (20%); 10% of subjects discontinued CTN-SR due to AEs. Clinically significant ECG changes were not observed.

Two recently completed Phase 3 double-blind RCTs found significant differences favoring 200 (100 mg b.i.d.) and 400 mg/day (200 mg b.i.d.) CTN-SR over placebo in reducing ADHD symptoms after 6 weeks of treatment in adults.[32] The most common AEs occurring more frequently with CTN-SR vs placebo were decreased appetite, headache, nausea, dry mouth, upper respiratory tract infection, and diarrhea. The incidence of individual AEs did not exceed 7%.[32]

OPC-64005

OPC-64005 (Otsuka) is a triple reuptake (SERT, NET, and DAT) inhibitor.[33] A Phase 2 flexible-dose study in adults with ADHD compared OPC-64005 (titrated up to 30 mg/day) with placebo and ATX (titrated up to 80 mg/day).[34] Study results have not been published.

Receptor Modulators

Extended-release formulations of the α_2 adrenoreceptor agonists guanfacine and clonidine are the only FDA-approved ADHD therapies that have pharmacologic activities seemingly limited to receptor modulation. Guanfacine appears to be selective for postsynaptic α_{2A} receptors; clonidine has higher affinity for presynaptic α_{2A}, α_{2B}, and α_{2C} receptors than for postsynaptic α_{2A} receptors.[35] Although modulators of other receptors [eg, nicotinic acid, histamine, gamma-aminobutyric acid (GABA), 5-HT, adenosine A_{2A}] are of growing interest for their potential utility in treating ADHD, clinical trials of these receptor modulators have so far produced mixed results.[36] None have advanced to Phase 3 trials in patients with ADHD and are therefore unlikely to be clinically available for several years, if at all.

Clonidine-XR (Kapvay®, Shionogi) and guanfacine-XR (Intuniv®, Shire) were approved by the FDA for use not only as monotherapy in children and adolescents (6–17 years old) with ADHD but also as adjuncts to stimulants, which is their primary use in clinical practice.[37] Clonidine-XR is dosed b.i.d.; guanfacine-XR is dosed q.d. In pivotal RCTs of clonidine-XR and guanfacine-XR as monotherapy in youth with ADHD, effect sizes ranged from 0.43 to 0.86.[38,39] Pooled effect sizes were not significantly different for the two drugs.[40] In fixed-dose clonidine-XR and guanfacine-XR monotherapy studies, improvements in ADHD symptoms were significantly greater vs placebo by week 1 or 2, with ADHD symptoms typically improving further over the duration of the 8- and 9-week studies.[38,41,42]

Several RCTs of α_2-agonist efficacy in ADHD also assessed effects on scores for oppositional behavior and conduct problems in children with or without comorbid ODD or CD. Based on a meta-analysis, evidence was weak that the small effect of clonidine (clonidine-IR and clonidine-XR combined) on oppositionality/conduct scores was clinically important.[43] Evidence was somewhat stronger for positive effects of guanfacine-XR on oppositional behavior scores.[43,44] A meta-analysis of α_2-agonist RCTs in patients with chronic tic disorders with or without ADHD demonstrated a medium-to-large effect of α_2 agonists (clonidine-IR) in studies enrolling patients with tics and ADHD vs no significant benefit in trials excluding patients with ADHD, suggesting a potential benefit in youth with ADHD and comorbid tic disorders.[45]

The more common AEs associated with clonidine-XR and guanfacine-XR are sedation/somnolence, fatigue, and gastrointestinal symptoms (nausea, abdominal pain). Consistent with the therapeutic use of α_2-agonists as antihypertensives, clonidine-XR and guanfacine-XR can cause dose-related decreases in BP and HR. A small but statistically significant prolongation of QTcF interval was observed with guanfacine-XR vs placebo, although guanfacine-XR does not appear to interfere with cardiac repolarization associated with proarrhythmic drugs.[40,46] Safety concerns about the cardiovascular effects are reflected in prescribing information, that is, clonidine-XR and guanfacine-XR should be used with caution in patients at risk of hypotension, bradycardia, and, in the case of guanfacine-XR, syncope.[46,47] Heart rate and BP should be monitored before and after initiating therapy with these agents, while patients should avoid becoming dehydrated or overheated. Prescribing information for clonidine-XR also warns about the risk of abrupt discontinuation and the risk of allergic reactions in patients with a history of allergic reactions, including contact sensitization, with transdermal clonidine.[47]

Multimodal Agents

Multimodal agents are defined here as drugs that combine transporter (eg, NET, SERT, and DAT) modulation/inhibition with receptor modulation (agonist and/or antagonist) activity. Several such agents are being evaluated as potential ADHD treatments.

Vortioxetine

Vortioxetine (VORT, Trintellix®, Lundbeck, and Takeda) is approved for the treatment of MDD in adults and has been suggested to improve cognitive processing speed in depressed individuals. It is a SERT inhibitor, agonist of 5-HT_{1A}, partial agonist of 5-HT_{1B}, and antagonist of 5-HT_3, 5-HT_{1D}, and 5-HT_7.[48] A Phase 2 proof-of-concept RCT of 10 or 20 mg/day q.d. in adults with ADHD failed to detect a significant difference of VORT vs placebo in improving total ADHD symptoms, although it was significantly superior in reducing patient-rated functional impairment due to ADHD.[49] A post hoc analysis that excluded nonadherent patients (32%) resulted in more pronounced changes from baseline in total ADHD symptom scores for both VORT doses; similar patterns were observed in other parameters. The AE profile in this exploratory study was consistent with the known profile of VORT, with the most common AE being nausea. No additional studies of VORT in ADHD are currently underway.

Mazindol

Immediate-release mazindol (MZD-IR) was marketed for the short-term treatment of obesity in adults but was withdrawn from the market for commercial reasons in the early 2000s.[50] As an IR formulation, mazindol is historically considered a weak stimulant

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(CIV) due to a lower potential for abuse and addiction vs the classical CII stimulants. In more contemporary studies, MZD displays multimodal pharmacologic activities that include NET, DAT, and SERT inhibition (relative affinity, 100:12:2),[51] as well as modulation of serotonin (5-HT_{1A}, 5-HT_7), muscarinic, histamine H_1, μ-opioid, and orexin-2 receptors.[50]

In a pilot, 1-week, open-label study in children with ADHD (N = 21) and MZD-IR (1 mg q.d.) was associated with significant improvement in ADHD scores.[52] Almost all patients (19/21) reported ≥1 AE. The most common AEs were decreased appetite (severe in four patients), drowsiness, intestinal distension, and upper abdominal pain; insomnia was not reported. In a Phase 2 flexible-dose, 6-week RCT in adults with ADHD, mazindol controlled-release (MZD-CR, Nolazol®, NLS Pharmaceutics) was associated with significantly greater improvements in ADHD scores vs placebo (effect size, 1.09).[50] The proportion of patients with excellent response (≥50% change from baseline) at 6 weeks was 55% vs 16%. A significant difference favoring MZD-CR was observed at the end of week 1. As expected of an agent previously marketed for short-term weight loss, weight was decreased as early as week 1; mean weight loss was 1.7 kg after 6 weeks. The most common AEs were dry mouth, nausea, fatigue, increased HR, decreased appetite, and constipation. Mean increases of ~3 to 6 mmHg in diastolic and systolic BP (DBP and SBP) and ~7 to 11 bpm in HR were observed. Phase 3 RCTs in ADHD are planned.[53]

Viloxazine

Viloxazine as an immediate-release formulation was first marketed as an antidepressant in Europe for more than two decades before being discontinued for commercial reasons. Antidepressant efficacy was established in multiple double-blind RCTs in adults with depressive disorders with/without comorbid anxiety.[54] Conducted in the 1970s, these RCTs used tricyclic antidepressants (TCAs) as the active control. In these studies, viloxazine immediate-release (150–300 mg/day) and TCAs improved symptoms of depression and comorbid symptoms such as anxiety.[54,55] Significant improvements in depression scores were generally noted within the first week of treatment with viloxazine immediate-release, indicating an early onset of effect.[54]

The tolerability/safety profile of viloxazine immediate-release that emerged during more than two decades of use in adults was relatively benign for the therapeutic class. Compared with TCAs, viloxazine immediate-release had a better tolerability/safety profile, particularly with regard to sedation and anticholinergic effects.[53,54,55] Viloxazine immediate-release was associated with fewer cardiovascular effects,[56] including minimal detrimental effects on BP.[57] Viloxazine immediate-release was not associated with dose-related depression of cardiac contractility in healthy volunteers; symptoms did not include cardiac complications in postmarketing reports of viloxazine immediate-release overdose.[58]

The therapeutic effects of viloxazine in depression were historically attributed to NET inhibition. Early preclinical studies, however, found a more complex pharmacologic profile involving the potentiation of 5-HT without inhibiting SERT.[54] In contemporary preclinical studies using more sophisticated methods, extracellular 5-HT concentrations in the prefrontal cortex were increased >5-fold by viloxazine by an unknown mechanism that likely involves 5-HT receptor modulation.[59] Prefrontal cortex dopamine and norepinephrine concentrations were also increased >5-fold. Monoamine transmitter concentrations were minimally increased in the nucleus accumbens. In addition to moderate NET inhibition, viloxazine exhibited agonistic activity at 5-HT_{2C}, antagonistic activity at 5-HT_{2B}, and weak antagonistic activity at 5-HT_7, α_{1B}, and β_2 receptors.[59]

Double-blind, placebo-controlled RCTs have consistently demonstrated a treatment effect significantly favoring viloxazine over placebo in reducing ADHD symptoms, starting with a Phase 2a proof-of-principle study of viloxazine immediate-release (100 mg t.i.d) in adults.[60] A Phase 2b dose-ranging RCT in children found that viloxazine extended-release (SPN-812, Supernus Pharmaceuticals) at dosages of 200, 300, and 400 mg dosed q.d. was significantly superior to placebo in improving ADHD symptoms, with effect sizes of 0.547, 0.596, and 0.623, respectively.[61] SPN-812 was subsequently evaluated in four Phase 3 double-blind, placebo-controlled, fixed-dose RCTs in children and adolescents with ADHD. Two studies (NCT032475305[62]; NCT03247543[63]) were conducted in children 6 to 11 years of age (100 mg, 200 mg, 400 mg); two studies (NCT03247517[64]; NCT03247556[65]) were in adolescents 12 to17 years of age (200 mg, 400 mg, 600 mg). Depending on target dose, SPN-812 was titrated over 1 to 3 weeks (starting dose: 100 mg in children; 200 mg in adolescents); the target dose was maintained for at least 5 weeks. Across the four studies (N=1354, intent-to-treat population), subjects were treated with SPN-812 (100 mg, n = 147; 200 mg, n = 359; 400 mg, n = 299; 600 mg, n = 97) or placebo (n = 456). In three Phase 3 studies, subjects consistently displayed greater ADHD symptom improvement with SPN-812 vs placebo. Differences vs placebo in the change from baseline in ADHD-RS-5 Total score at end of study (EOS) were statistically significant with once-daily 100 and 200 mg SPN-812 in one Phase 3 trial conducted in children, and with 200 mg and 400 mg SPN-812 in two Phase 3 trials – one conducted in children and one conducted in adolescents. In the fourth study, the primary endpoint was not met; one of the two (400- and 600-mg/day) doses of SPN-812 (600-mg/day) did not separate from placebo. This was possibly due to a higher placebo response observed in this study, which may have confounded the treatment response. For 100-400 mg SPN-812, symptom improvement was observed as early as the first week of treatment. ADHD symptoms steadily improved over the entire course of double-blind treatment. Core ADHD symptom domains—inattention and hyperactivity/impulsivity—were improved to similar degrees. Parent-assessed outcomes generally mirrored those of investigators. Parents perceived greater ADHD symptom improvement, greater reduction of functional impairment, and less stress with SPN-812 treatment vs placebo. The proportion of patients in the Phase 3 studies with 50% or greater improvement in ADHD-RS-5 Total score compared to baseline (50% responder rate) and proportion of patients "much improved" or "very much improved" per the CGI-I scale were also assessed. The 50% responder rate ranged from 34.2% to 48.2% at EOS; 45.0% to 60.6% of patients were categorized as "much" or "very much improved" per CGI-I scale at EOS. SPN-812 was well tolerated. Discontinuation rate due to treatment-related AEs was <5% for SPN-812 treatment groups within each study. The most common treatment-related AEs in the Phase 3 trials of SPN-812 (≥5% incidence) were somnolence, headache, decreased appetite, fatigue, nausea, and upper abdominal pain. The treatment-related AEs usually emerged within the first month of treatment and most resolved with continued treatment. The most common AEs leading to SPN-812 discontinuation (≥2 subjects) were somnolence (n = 7), fatigue (n = 3), nausea (n = 3), tachycardia (n = 3), decreased appetite (n = 2), and headache (n = 2).

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A recently published study evaluated the effect of SPN-812 on QTc interval in healthy adult subjects. The study demonstrated that supratherapeutic (1800 mg q.d.) dose of SPN-812 had no significant effect on cardiac repolarization or other ECG parameters, suggesting that it does not pose a risk of cardiac arrhythmias in healthy adults.[66] Cardiac AEs in SPN-812 Phase 3 study populations were infrequent, with only two incidences of tachycardia and one incidence of ECG T-wave inversion leading to discontinuation and considered related or possibly related to treatment across all four studies.[62-65] During intensive monitoring of suicidality, suicidal ideation and suicidal behavior were infrequent occurrences, with no incidence of suicidal ideation considered related to treatment and only one incidence of suicidal attempt in an SPN-812 treatment group considered possibly related to treatment.[62-65]

The Phase 3 clinical program in pediatric population has been completed.[67] Results from an ongoing Phase 3 study in adults with ADHD (NCT04016779) are expected in 2021.[68]

Why More Options to Schedule II Stimulants Are Needed

We propose several reasons that all clinicians should develop a deeper appreciation of nonstimulants in the treatment of ADHD in both children/adolescents and adults and the need for a broader array of options. First, while stimulants are highly effective in reducing ADHD symptoms, a substantial number of patients either fail to respond and/or have unacceptable side effects when treated with stimulants. In such scenarios, the use of nonstimulants is both appropriate and well supported by various treatment guidelines. Second, stimulants often are less than ideal treatment options in ADHD patients with commonly occurring symptoms such as insomnia, poor appetite, subsyndromic anxiety or depression, and failure to thrive. Nonstimulants are treatment options in such patients—either as monotherapy or as cotherapy with stimulants. In addition, continuous, even coverage of ADHD symptoms is often a clinical necessity. However, even the longest acting stimulant formulation often fails to provide adequate duration of coverage. In such situations, nonstimulants can be useful—again, either as monotherapy or combination therapy. Finally, the potential euphorigenic effects and abuse liability that make CII stimulants medications may negatively impact acceptance and adherence due to complex procedures in renewing a CII medication as well as misinformation, biases, or uncertainty about the use of stimulants to treat ADHD.

With more than 30 CII stimulant preparations commercially available, the field of ADHD is currently limited to just three FDA-approved nonstimulant agents that either modulate the norepinephrine reuptake pump or stimulate norepinephrine α_2 receptors.[69] Only one (ATX) is approved for use in adults. Atomoxetine has inconsistent and delayed efficacy, with a bimodal distribution of response, and carries significant warnings involving suicidal ideation, liver injury, and cardiovascular effects. The use of clonidine-XR and guanfacine-XR is limited by sedation and somnolence, particularly when used as monotherapy, while safety concerns include cardiovascular warnings, such as hypotension, bradycardia, and the risk of syncope in the case of guanfacine-XR.

In light of the complex neurobiology of ADHD, novel nonstimulant options are needed that may be more suited to the diverse needs of pediatric and adult patients with ADHD and its associated comorbidities, including patients with comorbid psychiatric disorders such as depression or anxiety. Several promising alternatives to CII stimulants with different mechanisms of action are in clinical development, with one such agent currently being reviewed by the FDA. These new agents may be of benefit in ADHD patients in whom treatment has been limited by comorbidities that make stimulants inappropriate as first-line therapy or have inadequate response or side effects with currently available treatment options. Finally, the concept of ADHD symptom remission is gathering more traction in both psychiatry and pediatrics. If clinicians are to accept this as a "gold standard" for all patients with ADHD, then a deeper appreciation of the strengths and weaknesses of both simulants and nonstimulants is necessary.

Conclusions

ADHD medication development has focused on engineering novel systems for CII stimulants—liquids, capsules, sprinkles, chewables, and prodrugs—that have different pharmacokinetics due to different stimulant formulation release profiles. In contrast, current development of novel medications is exploring new molecular entities with different structures and molecular targets. These molecules differ markedly from the older agents by targeting reuptake inhibition of multiple monoamines, modulation of receptors other than noradrenergic α_2 neurotransmitter receptors, and multimodal agents that combine reuptake inhibition with direct receptor modulation. Interest in these new agents include their potential for rapid onset of action and a more favorable safety profile. Hopefully, future research will also assess each of these agent's ability to beneficially influence the diverse clinical needs and comorbidities associated with ADHD, including their effects on mood, sleep, anxiety, combined with the potential for lower abuse liability.

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References

1. Mattingly GW, Anderson RH. Optimizing outcomes in ADHD treatment: from clinical targets to novel delivery systems. *CNS Spectr*. 2016;**21**(S1): 45–59.
2. Danielson ML, Bitsko RH, Ghandour RM, *et al.* Prevalence of parent-reported ADHD diagnosis and associated treatment among U.S. children and adolescents, 2016. *J Clin Child Adolesc Psychol*. 2018;**47**(2):199–212.
3. McGough JJ, Smalley SL, McCracken JT, *et al.* Psychiatric comorbidity in adult attention deficit hyperactivity disorder: findings from multiplex families. *Am J Psychiatry*. 2005;**162**(9):1621–1627.
4. Chen M-H, Pan T-L, Hsu J-W, *et al.* Attention-deficit hyperactivity disorder comorbidity and antidepressant resistance among patients with major depression: a nationwide longitudinal study. *Eur Neuropsychopharmacol*. 2016;**26**(11):1760–1767.
5. Connor D. Stimulant and nonstimulant medications for childhood ADHD. In: Barkley RA, ed. *Attention-Deficit/Hyperactivity Disorder: A Handbook for Diagnosis and Treatment*. New York, NY: Guilford Press; 2015:666–685.
6. Gallucci AR, Martin RJ, Usdan SL. The diversion of stimulant medications among a convenience sample of college students with current prescriptions. *Psychol Addict Behav*. 2015;**29**(1):154–161.
7. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. *Lancet*. 2020;**395**(10222):450–462.
8. Wong DT, Threlkeld PG, Best KL, Bymaster FP. A new inhibitor of norepinephrine uptake devoid of affinity for receptors in rat brain. *J Pharmacol Exp Ther*. 1982;**222**(1):61–65.
9. Bymaster FP, Katner JS, Nelson DL, *et al.* Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacol*. 2002;**27**(5):699–711.
10. Food & Drug Administration. Strattera Clinical Safety Review. 2002. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-411_Strattera_medr_P3.pdf. November 16, 2020.
11. Schwartz S, Correll CU. Efficacy and safety of atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder: results from a comprehensive meta-analysis and metaregression. *J Am Acad Child Adolesc Psychiatry*. 2014;**53**(2):174–187.
12. Garnock-Jones KP, Keating GM. Atomoxetine: a review of its use in attention-deficit hyperactivity disorder in children and adolescents. *Paediatr Drugs*. 2009;**11**(3):203–226.
13. Clemow DB, Bushe C, Mancini M, *et al.* A review of the efficacy of atomoxetine in the treatment of attention-deficit hyperactivity disorder in children and adult patients with common comorbidities. *Neuropsychiatr Dis Treat*. 2017;**13**:357–371.
14. Ravindran LN, Kim DS, Letamendi AM, Stein MB. A randomized controlled trial of atomoxetine in generalized social anxiety disorder. *J Clin Psychopharmacol*. 2009;**29**(6):561–564.
15. Koyuncu A, Alkin T, Tükel R. The relationship between social anxiety disorder and ADHD. *Child Adolesc Psychopharmacol News*. 2016;**21**(4): 1–6.
16. Strattera [prescribing information]. Indianopolis, IN: Eli Lilly & Co; 2017. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021411s048lbl.pdf. February 1, 2020.
17. Bangs ME, Tauscher-Wisniewski S, Polzer J, *et al.* Meta-analysis of suicide-related behavior events in patients treated with atomoxetine. *J Am Acad Child Adolesc Psychiatry*. 2008;**47**(2):209–218.
18. Bushe CJ, Savill NC. Systematic review of atomoxetine data in childhood and adolescent attention-deficit hyperactivity disorder 2009–2011: Focus on clinical efficacy and safety. *J Psychopharmacol*. 2013;**28**(3):204–211.
19. Nageye F, Cortese S. Beyond stimulants: a systematic review of randomised controlled trials assessing novel compounds for ADHD. *Expert Rev Neurother*. 2019;**19**(7):707–717.
20. Hopkins SC, Sunkaraneni S, Skende E, *et al.* Pharmacokinetics and exposure-response relationships of dasotraline in the treatment of attention-deficit/hyperactivity disorder in adults. *Clin Drug Investig*. 2016;**36**(2):137–146.
21. Sepracor [press release]. Sepracor provides update on clinical trials for SEP-225289 and LUNESTA® Pediatrics. Accessed at: https://wwwbusinesswirecom/news/home/20090701006146/en/Sepracor-Update-Clinical-Trials-SEP-225289-LUNESTA®-Pediatrics. July 1, 2009.
22. ADIS Insight. Dasotraline - Sumitomo Dainippon Pharma. ADIS Insight. 2019;Update 07 Aug 2019. Accessed at: https://adisinsight.springer.com/drugs/800023450. February 1, 2020.
23. Koblan KS, Hopkins SC, Sarma K, *et al.* Dasotraline for the treatment of attention-deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled, proof-of-concept trial in adults. *Neuropsychopharmacology*. 2015;**40**(12):2745–2752.
24. Wigal SB, Hopkins SC, Koblan KS, *et al.* Efficacy and safety of dasotraline in children with ADHD: a laboratory classroom study. *J Atten Disord*. 2019;**24**(2):192–204.
25. Findling RL, Adler LA, Spencer TJ, *et al.* Dasotraline in children with attention-deficit/hyperactivity disorder: a six-week, placebo-controlled, fixed-dose trial. *J Child Adolesc Psychopharmacol*. 2019;**29**(2):80–89.
26. Adler L, Kollins S, Hopkins S, *et al.* Dasotraline for the treatment of attention deficit/hyperactivity disorder in adults: pooled analysis of two double-blind studies. *Neuropsychopharmacology*. 2015;**40**:22745–22752.
27. Sunovion [press release]. FDA issues a complete response letter for New Drug Application for dasotraline for the treatment of ADHD. Accessed at: https://news.sunovion.com/press-releases/press-releases-details/2018/FDA-Issues-a-Complete-Response-Letter-for-New-Drug-Application-for-Dasotraline-for-the-Treatment-of-ADHD/default.aspx. November 16, 2020.
28. Sunovion [press release]. Sunovion announces acceptance by the U.S. FDA of the New Drug Application for dasotraline for the treatment of adults with moderate-to-severe binge eating disorder. Accessed at: https://news.sunovion.com/press-releases/press-releases-details/2019/Sunovion-Announces-Acceptance-by-the-US-FDA-of-the-New-Drug-Application-for-Dasotraline-for-the-Treatment-of-Adults-with-Moderate-to-Severe-Binge-Eating-Disorder/default.aspx. November 16, 2020.
29. Robertson BA, Shram M, Schoedel KA. Early stage assessment of the abuse potential of centanafadine, a triple reuptake inhibitor: preclinical and clinical study results. Poster presented at: 53rd Annual Meeting of the American College of Neuropsychopharmacology. 2014. Accessed at: http://www.neurovance.com/wp-content/uploads/2014/03/Neurovance_CTN_HAL_ACNP_2014.pdf:7–11. February 1, 2020.
30. Wigal S, Wigal T, Hobart M, *et al.* Safety and eficacy of centanafadine sustained-release in adults with attention-deficit hyperactivity disorder: Results of Phase 2 studies. *Neuropsych Dis Treat*. 2020;**16**:1411–1426.
31. Jennings D, Barret O, Wisniewski G, *et al.* Centanafadine SR (CTN-SR) demonstrates brain occupancy at norepinephrine transporter (NET), serotonin transporter (SERT) and dopamine transporter (DAT) using single photon emission tomography (SPECT) in healthy volunteers (HVS). Poster presented at 2016 American Society of Clinical Psychopharmacology, May 30–June 2, 2016; Scottsdale, AZ. Accessed at: https://ascpmeeting.org/wp-content/uploads/2014/07/2016-Oral-Abstract-Book-FINAL-with-cover-page.pdf. February 1, 2020.
32. Otsuka [press release].Otsuka announces positive top-line results from two Phase 3 studies of centanafadine for the treatment of attention-deficit hyperactivity disorder (ADHD) in adult patients. Accessed at: https://www.otsuka-us.com/discover/otsuka-announces-positive-top-line-results-from-two-phase-3-studies-of-centanafadine. February 1, 2020.
33. Otsuka Group. Pipeline Information. 2019. Accessed at: https://www.otsuka.com/en/rd/pharmaceuticals/pipeline/pdf.php?financial=652. February 1, 2020.
34. Otsuka. A phase 2, multicenter, randomized, double-blind, active- and placebo-controlled trial of the safety and efficacy of OPC-64005 in the treatment of adult attention-deficit/hyperactivity disorder. Accessed at: https://clinicaltrials.gov/ct2/show/NCT03324581. February 1, 2020.
35. Arnsten AFT. Toward a new understanding of attention-deficit hyperactivity disorder pathophysiology. *CNS Drugs*. 2009;**23**(1):33–41.
36. Childress A, Tran C. Current investigational drugs for the treatment of attention-deficit/hyperactivity disorder. *Expert Opin Investig Drugs*. 2016; **25**(4):463–474.
37. Daughton JM, Kratochvil CJ. Review of ADHD pharmacotherapies: advantages, disadvantages, and clinical pearls. *J Am Acad Child Adolesc Psychiatry*. 2009;**48**(3):240–248.

https://doi.org/10.1017/S1092852920001984 Published online by Cambridge University Press

38. Jain R, Segal S, Kollins SH, Khayrallah M. Clonidine extended-release tablets for pediatric patients with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2011;**50**(2):171–179.
39. Huss M, Chen W, Ludolph AG. Guanfacine extended release: a new pharmacological treatment option in Europe. *Clin Drug Investig*. 2016;**36**(1):1–25.
40. Hirota T, Schwartz S, Correll CU. Alpha-2 agonists for attention-deficit/hyperactivity disorder in youth: a systematic review and meta-analysis of monotherapy and add-on trials to stimulant therapy. *J Am Acad Child Adolesc Psychiatry*. 2014;**53**(2):153–173.
41. Biederman J, Melmed RD, Patel A, *et al.* A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics*. 2008;**121**(1):e73
42. Sallee FR, McGough J, Wigal T, *et al.* Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2009;**48**(2):155–165.
43. Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder: a systematic review and meta-analysis. Part 1: Psychostimulants, alpha-2 agonists, and atomoxetine. *Can J Psychiatry*. 2015;**60**(2):42–51.
44. Findling RL, McBurnett K, White C, Youcha S. Guanfacine extended release adjunctive to a psychostimulant in the treatment of comorbid oppositional symptoms in children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2014;**24**(5):245–252.
45. Weisman H, Qureshi IA, Leckman JF, *et al.* Systematic review: pharmacological treatment of tic disorders – efficacy of antipsychotic and alpha-2 adrenergic agonist agents. *Neurosci Biobehav Rev*. 2013;**37**(6):1162–1171.
46. Intuniv [prescribing information]. Lexington, MA: Shire Pharmaceuticals, Inc., Revised 02/2013. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022037s009lbl.pdf. February 1, 2020.
47. Kapvay [prescribing information]. Atlanta, GA: Shionogi Pharma, Ltd. 2010. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022331s001s002lbl.pdf. February 1, 2010.
48. Trintellix [prescribing information]. Deefield, IL: Takeda Pharmaceuticals America, Inc. Revised 07/2019. Accessed at: https://general.takedapharm.com/trintellixpi/. February1, 2020.
49. Biederman J, Lindsten A, Sluth LB, *et al.* Vortioxetine for attention deficit hyperactivity disorder in adults: a randomized, double-blind, placebo-controlled, proof-of-concept study. *J Psychopharmacol*. 2019;**33**(4):511–521.
50. Wigal TL, Newcorn JH, Handal N, *et al.* A double-blind, placebo-controlled, Phase II Study to determine the efficacy, safety, tolerability and pharmacokinetics of a controlled release (CR) formulation of mazindol in adults with DSM-5 attention-deficit/hyperactivity disorder (ADHD). *CNS Drugs*. 2018;**32**(3):289–301.
51. Zhou J. Norepinephrine transporter inhibitors and their therapeutic potential. *Drugs Future*. 2004;**29**(12):1235–1244.
52. Konofal E, Ahao W, Laouénan C, *et al.* Pilot Phase II study of mazindol in children with attention deficit/hyperactivity disorder. *Drug Des Devel Ther*. 2014;**8**:2321–2332.
53. NLS [press release]. NLS Pharmaceutics announces the completion of the merger between NLS Pharma Ltd., NLS1 Pharma Ltd. and NLS-0 Pharma, unifying the global operations and sevelopment of Nolazol. Accessed at: https://www.globenewswire.com/news-release/2019/03/19/1757387/0/en/NLS-Pharmaceutics-Announces-the-Completion-of-the-Merger-between-NLS-Pharma-Ltd-NLS-1-Pharma-Ltd-and-NLS-0-Pharma-Unifying-the-Global-Operations-and-Development-of-Nolazol.html. November 16, 2020.
54. Pinder RM, Brogden RN, Speight TM, Avery GS. Viloxazine: a review of its pharmacological properties and therapeutic efficacy in depressive illness. *Drugs*. 1977;**13**(6):401–421.
55. Ban TA, McEvoy JP, Wilson WH. Viloxazine: a review of the literature. *Int Pharmacopsychiatry*. 1980;**15**:118–123.
56. Thompson C, Isaacs G. Is viloxazine an antidepressant? A placebo-controlled double-blind study in major depressive disorder presenting in a general hospital. *Hum Psychopharmacol*. 1991;**6**(1):31–38.
57. Bayliss PF, Duncan SM. The clinical pharmacology of viloxazine hydrochloride-a new anti-depressant of novel chemical structure. *Br J Clin Pharmacol*. 1974;**1**(5):431–437.
58. Warrington SJ, Padgham C, Lader M. The cardiovascular effects of antidepressants. *Psychol Med Monogr Suppl*. 1989;**16**:1–40.
59. Yu C, Garcia-Olivares J, Candler S, *et al.* New insights into the mechanisms of action of viloxazine: serotonin and norepinephrine modulating properties. *J Exp Pharmacol*. 2020;**12**:285–300.
60. Johnson JK, Saylor K, Brittain ST, *et al.* Double-blind, randomized, placebo-controlled study of immediate-release viloxazine (SPN-812 IR) as a novel non-stimulant therapy in adults with attention-deficit/hyperactivity disorder (ADHD). Poster presented at: Annual Meeting of the American Academy of Child & Adolescent Psychiatry; October 26–31, 2015; San Antonio, TX.
61. Johnson JK, Liranso T, Saylor K, *et al.* A Phase II double-blind, placebo-controlled, efficacy and safety study of SPN-812 (extended-release viloxazine) in children with ADHD. *J Atten Disord*. 2020;**24**(2):248–358.
62. Nasser A, Liranso T, Adewole T, *et al.* A Phase III, randomized, placebo-controlled trial to assess the efficacy and safety of once-daily SPN-812 (viloxazine extended release) in the treatment of attention-deficit/hyperactivity disorder in school-aged children. *Clin Ther*. 2020. Aug;42(8):1452–1466.
63. Nasser A, Hull JT, Chowdhry FA, *et al.* Phase 3, double-blind, placebo-controlled study (P303) assessing efficacy and safety of extended-release viloxazine in children with ADHD. *CNS Spectr*. 2020;**25**(2):273–274.
64. Nasser A, Hull JT, Chowdhry FA, *et al.* A Phase 3, randomized, double-blind, placebo-controlled study (P302): efficacy and safety of extended-release viloxazine in adolescents with ADHD. *CNS Spectr*. 2020;**25**(2):272–273.
65. Supernus. Evaluation of SPN 812 ER 400 and 600 mg efficacy and safety in adolescents with ADHD - a double-blind, placebo-controlled, pivotal trial. Accessed at: https://clinicaltrials.gov/ct2/show/NCT03247556. November 16, 2020.
66. Nasser A, Faison SL, Liranso T, *et al.* Evaluation of the effect of SPN-812 (viloxazine extended-release) on QTc interval in healthy adults. *J Clin Psychiatry*. 2020;**81**(6):20m13395. doi: 10.4088/JCP.20m13395.
67. Nasser A, Hull JT, Chaturvedi S, *et al.* The efficacy and safety of SPN-812 (viloxazine extended-release) for the treatment of ADHD in children and adolescents, including a post-hoc analysis of those results. Presented at the 2020 Annual Conference for the American Academy of Child and Adolescent Psychiatry (virtual).
68. Supernus. A Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group flexible-dose study of the efficacy and safety of SPN-812 in adults with attention-deficit/hyperactivity disorder (ADHD). Accessed at: https://clinicaltrials.gov/ct2/show/NCT04016779. November 16, 2020.
69. Mattingly G, Wilson J, Ugarte L, Glaser P. Individualization of attention-deficit/hyperactivity disorder treatment: pharmacotherapy considerations by age and co-occurring conditions. *CNS Spectr*. 2020. Feb 14;1–20. doi: 10.1017/S1092852919001822.