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

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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...
problems before ADHD symptoms. Recent findings regarding antidepressant resistance suggest that this approach may need to be reconsidered. The risk of antidepressant resistance was found to be >2-fold higher in patients with major depression and comorbid ADHD vs major depression alone. 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. 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.

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; 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.

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.

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). 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.

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. Significant differences in ADHD symptoms vs placebo were generally not noted until 4 weeks after treatment was initiated. Atomoxetine was associated with a bimodal response, that is, 45% of patients were much improved at study end, while 40% were considered nonresponders.

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. 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, 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. Improvements in comorbid ODD and anxiety symptoms correlated with improvements in ADHD symptoms. Atomoxetine had no significant benefit vs placebo in adults with SAD without comorbid ADHD, suggesting that previously observed benefits of ATX on comorbid anxiety were mediated by the drug’s effects on ADHD. Despite the expected improvements in ADHD symptoms, ATX effects on depressive symptoms were no different vs placebo in children and adults with comorbid MDD.

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. In adults, the most common AEs were constipation, dry mouth, nausea, decreased appetite, dizziness, erectile dysfunction, and urinary hesitation. 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), as well as warnings about severe liver injury and serious cardiovascular events. 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. Atomoxetine is contraindicated in individuals with severe cardiovascular disorders and should be avoided in children or adolescents with known serious cardiac problems.

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). Like ATX, development of dasotraline in MDD in adults was suspended due to lack of efficacy. Dasotraline dosed...
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 study24 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.
<table>
<thead>
<tr>
<th>Pharmacologic Activity</th>
<th>ADHD Status</th>
<th>Dosing</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Monoamine reuptake inhibitor</strong></td>
<td></td>
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<tr>
<td>Atomoxetine NET inhibitor</td>
<td>Approved for children ≥6 yrs and adults</td>
<td>q.d. or b.i.d.</td>
<td>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.</td>
</tr>
<tr>
<td>Dasotraline DAT, NET inhibitor</td>
<td>FDA approval rejected pending additional data</td>
<td>q.d.</td>
<td>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.</td>
</tr>
<tr>
<td>OPC-64005 SERT, NET, DAT inhibitor</td>
<td>Phase 2</td>
<td>Not reported</td>
<td>No published data.</td>
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<tr>
<td><strong>Receptor modulator</strong></td>
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<tr>
<td>Clonidine extended release α2A, α2B, α2C Agonist</td>
<td>Approved for children ≥6 yrs</td>
<td>b.i.d.</td>
<td>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).</td>
</tr>
<tr>
<td>Guanfacine extended release α2A Agonist</td>
<td>Approved for children ≥6 yrs</td>
<td>q.d.</td>
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<td><strong>Multimodal Agents</strong></td>
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<tr>
<td>Vortioxetine SERT inhibitor, 5-HT (5-HT1A, 5-HT1B, 5-HT3, 5-HT1D, 5-HT7) modulator</td>
<td>Phase 2 (approved for MDD treatment)</td>
<td>q.d.</td>
<td>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.</td>
</tr>
<tr>
<td>Mazindol controlled release SERT, DAT, NET inhibitor, 5-HT (5-HT1A, 5-HT7), muscarinic, histamine H1, μ-opioid, orexin-2 modulator</td>
<td>Phase 2</td>
<td>q.d.</td>
<td>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.</td>
</tr>
<tr>
<td>Viloxazine extended-release NET inhibitor (weak), 5-HT (5-HT2C, 5-HT2B, 5-HT7), α1B and β2 modulator</td>
<td>Completed Phase 3 trials in pediatric subjects with ADHD</td>
<td>q.d.</td>
<td>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.</td>
</tr>
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</table>

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.\textsuperscript{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.\textsuperscript{38} 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).\textsuperscript{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.\textsuperscript{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%.\textsuperscript{32}

**OPC-64005**

OPC-64005 (Otsuka) is a triple reuptake (SERT, NET, and DAT) inhibitor.\textsuperscript{53} 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).\textsuperscript{34} Study results have not been published.

**Receptor Modulators**

Extended-release formulations of the α\textsubscript{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\textsubscript{2A} receptors; clonidine has higher affinity for presynaptic α\textsubscript{2A}, α\textsubscript{2B}, and α\textsubscript{2C} receptors than for postsynaptic α\textsubscript{2A} receptors.\textsuperscript{35} Although modulators of other receptors [eg, nicotinic acid, histamine, gamma-aminobutyric acid (GABA), 5-HT, adenosine A\textsubscript{2A}] are of growing interest for their potential utility in treating ADHD, clinical trials of these receptor modulators have so far produced mixed results.\textsuperscript{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\textsuperscript{®}, Shionogi) and guanfacine-XR (Intuniv\textsuperscript{®}, 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.\textsuperscript{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.\textsuperscript{38,39} Pooled effect sizes were not significantly different for the two drugs.\textsuperscript{38} 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.\textsuperscript{38,41,42}

Several RCTs of α\textsubscript{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.\textsuperscript{43} Evidence was somewhat stronger for positive effects of guanfacine-XR on oppositional behavior scores.\textsuperscript{35,44} A meta-analysis of α\textsubscript{2}-agonist RCTs in patients with chronic tic disorders with or without ADHD demonstrated a medium-to-large effect of α\textsubscript{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.\textsuperscript{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\textsubscript{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 QTc interval was observed with guanfacine-XR vs placebo, although guanfacine-XR does not appear to interfere with cardiac repolarization associated with proarrhythmic drugs.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{®}, 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\textsubscript{1A}, partial agonist of 5-HT\textsubscript{1B}, and antagonist of 5-HT\textsubscript{3}, 5-HT\textsubscript{1D}, and 5-HT\textsubscript{7}.\textsuperscript{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.\textsuperscript{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.\textsuperscript{50} As an IR formulation, mazindol is historically considered a weak stimulant.
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.52 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.59 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-HT2C, antagonistic activity at 5-HT2A, 5-HT7, α1B, and β2 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 (NCT0324753065; NCT0324754363) were conducted in children 6 to 11 years of age (100 mg, 200 mg, 400 mg); two studies (NCT0324751764; NCT0324755665) were in adolescents 12 to 17 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).
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.46 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.65 Results from an ongoing Phase 3 study in adults with ADHD (NCT04016779) are expected in 2021.65

**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 euphoric 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 α2 receptors.69 Only one (ATX) is approved for use in adults. Atomoxetine in healthy adults.66 Cardiac AEs in SPN-812 Phase 3 study population.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

**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 α2 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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