

Emerging Therapies for Attention-Deficit/Hyperactivity Disorder

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Among the most important recent developments in attention-deficit/hyperactivity disorder (ADHD) research is the development of new therapies that better address the needs of individuals living with the condition.¹ Although an increasing array of short-acting and long-acting psychostimulant formulations are FDA-approved and exhibit large effect sizes for core ADHD symptoms, these first-line therapies also carry an array of well-characterized side effects, which are variably present across individuals.² Adverse effects of stimulants include decreased appetite and weight loss, decreased growth velocity, insomnia, increased heart rate and blood pressure, headaches, stomachaches, and mood changes/irritability/affective blunting.³ Additionally, as US Drug Enforcement Administration (DEA) Schedule II drugs, stimulants have “a high potential for abuse,” and their diversion is an increasingly prevalent problem.^{4,5} Because of these risks, some patients with ADHD will refuse stimulants, whereas some doctors will not prescribe them.

Non-stimulant alternatives for ADHD, such as atomoxetine and α_2 agonists, have their own profile of advantages and limitations, which further justify the development of novel therapeutics. Approximately 40% of pediatric patients prescribed atomoxetine experience persistent ADHD symptoms and require alternative or additional clinical interventions. Further, the effect

size in adults is more modest.^{6,7} The α_2 agonists (clonidine extended release [ER], guanfacine ER) are FDA-approved in children but not adults, though there is a positive controlled trial with guanfacine ER in adults conducted in Japan.⁸ All of the non-stimulant medications for ADHD are thought to take time to exert their fullest effects,¹ although the best responders to atomoxetine may begin to show effects within the first few weeks of treatment.⁹

Since 2020, a number of newer stimulant formulations with potential advantages over traditional options have emerged and gained regulatory approval. One such option contains a combination of serdexmethylphenidate (SDX), an extended-duration prodrug of dexamethylphenidate (d-MPH), and d-MPH in a 70/30 molar ratio. SDX has a Schedule IV designation from the DEA and may have value in recipients where the perceived risk for abuse is elevated.¹⁰

Within the expanding stimulant class, researchers have also encountered success with transdermal treatments. By administering ADHD pharmacotherapies through patches, caregivers can monitor and confirm drug delivery, thereby addressing suboptimal medication adherence. Additionally, this route enables greater customization of therapy duration, can often reduce dosing frequency, and minimizes the risk of drug-drug interactions.¹¹ In a phase 2, randomized, placebo-controlled study, investigators

noted that patches of transdermal dextroamphetamine at doses of 4.5, 9, 13.5, and 18 mg significantly improved ADHD symptoms versus placebo as measured by total score on the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale while having a systemic safety profile similar to oral amphetamines.¹²

The development of novel non-stimulant medications in ADHD has been a major interest over the past two decades; however, several investigational non-stimulant drugs failed because of a lack of efficacy or unacceptable tolerability profiles.^{13,14} The recent approval of viloxazine ER (VER) offers a viable non-stimulant option. VER is a norepinephrine reuptake inhibitor and has agonist activity at several postsynaptic 5-HT receptors. In a phase 3 clinical trial assessing VER in pediatric patients with ADHD, researchers observed statistically significant improvements in behavior among recipients randomized to the 100 mg/d and 200 mg/d viloxazine groups after 2 weeks of treatment.¹⁵ These positive findings corroborate data from a phase 3 clinical trial of VER conducted among adults with ADHD, in which participants randomized to viloxazine at doses ranging between 200 and 600 mg experienced improvements on the Adult ADHD Investigator Symptom Rating Scale.¹⁶ Several other investigational, non-stimulant drugs, such as centanafadine, are undergoing examination in late-stage clinical trials.¹⁷

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In addition to the new pharmacologic agents, several devices have been developed for ADHD treatment. While it remains to be determined how these new interventions will be best utilized, there is potential to augment response in patients refractory to recommended stimulants and non-stimulants—or as an alternative to these medications. Already used in Europe and Canada to treat depression, the Monarch e-TNS (trigeminal nerve stimulation) system received approval from the US Food and Drug Administration (FDA) in April 2019 in ADHD. Users of the Monarch e-TNS system wear a patch at night across the forehead, which delivers an electrical signal to brain areas associated with concentration and impulse control.¹⁸ FDA authorities additionally cleared a digital therapeutic, EndeavorRx, in June 2020 to supplement multimodal treatment programs for pediatric patients aged 8 to 12 years with ADHD.¹⁹ Several other devices are being developed and in clinical trials.^{20,21}

While patients with ADHD today still face numerous unmet needs, the armamentarium is continuing to expand. These encouraging advances are transforming ADHD management and warrant consideration from clinicians, especially among those with patients possessing unmet needs.

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