SPECIAL ARTICLE: NOVEL UPDATES IN ADHD
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A Review and an Update on Pharmacological Treatment of Children With Attention-Deficit/Hyperactivity Disorder

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This review highlights the current and emerging pharmacological treatments for attention-deficit/hyperactivity disorder. Stimulants such as methylphenidate are the first-line treatment for improving attention and behavior. Non-stimulants, such as atomoxetine serve as alternative options, particularly for patients with comorbid conditions or those intolerant to stimulants. Emerging treatments, not yet available in Korea, include the methylphenidate prodrug, delayed-release/extended-release methylphenidate, and transdermal dextroamphetamine, that provide innovative delivery systems for sustained symptom control. Additionally, novel drugs such as viloxazine and centanafadine show promise as alternatives with potentially fewer side effects, broadening the spectrum of available therapies. As these new medications become accessible, they may help develop more personalized treatment plans tailored to individual patient needs and potential side effects.

Keywords: Attention-deficit/hyperactivity disorder; Pharmacotherapy; New medication; Prodrug; Transdermal; Viloxazine; Centanafadine.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention and hyperactivity/impulsivity. The prevalence of ADHD has been increasing in recent years, with a global prevalence of 10.2% reported in 2016 [1]. Longitudinal studies suggest that between half to two-thirds of children with ADHD continue to experience symptoms into adulthood [2].

Pharmacological treatment of ADHD was first reported in the early to mid-20th century with the use of stimulants [3]. Since then, various medications have been identified and used in treatment. Despite the availability of non-pharmacological interventions, treatment guidelines recommend pharmacotherapy as the first-line therapy, except for very young children [4,5]. This is because evidence shows that pharmacotherapy is more effective than other treatments in reducing ADHD symptoms [6]. However, it is important to note that non-pharmacological therapies remain essential in cases where pharmacotherapy is insufficient or causes significant adverse effects.

This article reviews the current pharmacological treatments for ADHD and the new treatment options that are not yet available in Korea. A summary of the pharmacological treatments is presented in Table 1.

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PHARMACOLOGICAL TREATMENTS FOR ADHD IN KOREA

Stimulants

Stimulant medications increase the concentration of dopamine and norepinephrine in the synaptic cleft of the prefrontal cortex. These medications not only improve inattention and hyperactivity/impulsivity but also reduce problematic behaviors and help maintain appropriate peer relationships [7,8]. Stimulants are considered as the first-line treatment option in clinical guidelines because they are more effective and have a faster onset of action compared to that of the non-stimulants [4,9]. Two classes of stimulants exist: methylphenidate and amphetamine formulations. However, amphetamines are not available in some countries, including Korea.

Methylphenidate

Methylphenidate is categorized based on its duration and mechanism of action into immediate release (IR), extended release (ER), and osmotic controlled-release oral delivery system (OROS) formulations.

Table 1. Summary of pharmacological treatment of ADHD

	FDA approval	KMFDS approval	Formulation	Effect size*	Note
Stimulants					
Methylphenidate	O	O	IR, ER, prodrug, DR/ER, transdermal	SMD=0.78 (0.62 to 0.93)	DR/ER (methylphenidate, 2018 FDA) Prodrug (serdexmethylphenidate, 2021 FDA)
Dexamphetamine†	O	X	IR, ER, prodrug, transdermal	SMD=1.02 (0.85 to 1.19)	Transdermal (dextroamphetamine, 2022 FDA)
Non-stimulants					
Atomoxetine	O	O	-	SMD=0.56 (0.45 to 0.66)	
Clonidine	O	O	ER, oral suspension	SMD=0.71 (0.24 to 1.17)	Oral suspension (clonidine, 2024 FDA)
Guanfacine	O	X	ER	SMD=0.67 (0.50 to 0.85)	
Viloxazine	O	X	ER	-	ER (viloxazine, 2021 FDA)
Centanafadine	X	X	-	-	Phase 3 clinical trial
Bupropion	X	X	ER	SMD=0.96 (0.22 to 1.69)	
Modafinil	X	X	-	SMD=0.62 (0.41 to 0.84)	

*effect size based on clinician's rating on ADHD core symptom from Cortese et al. [14]; †includes lisdexamfetamine and mixed amphetamine salts. ADHD, attention-deficit/hyperactivity disorder; DR/ER, delayed-release/extended-release; ER, extended-release; FDA, U.S. Food and Drug Administration; IR, immediate-release; KMFDS, Korean Ministry of Food and Drug Safety; SMD, standardized mean difference

IR methylphenidate reaches its peak plasma concentration 1–3 h after ingestion, with effects lasting approximately 4 h. This implies that dosing two to three times a day may be necessary, that can be inconvenient. If medication intake is not monitored, the child's attention may diminish shortly, and potentially worsening symptoms of hyperactivity due to rebound effects.

To address the disadvantages of IR methylphenidate, various ER methylphenidate formulations have been developed. These formulations maintain their effects for approximately 6–8 h, allowing children to avoid taking medication during school hours and improving adherence. In Korea, Medikinet, that contains a 50:50 ratio of IR to ER methylphenidate, is available. This formulation provides a rapid onset of effects by quickly reaching its initial peak concentration, followed by a second peak concentration 3–4 h after ingestion. This medication is recommended to be swallowed whole; however, it can be sprinkled on liquid food if needed.

Concerta utilizes OROS technology to regulate the rate of drug release. Peak concentration is reached 1–2 h post ingestion, providing therapeutic effects for up to 12 h with a single dose [10]. This extended duration of action is particularly beneficial in clinical practice for children and adolescents who experience functional impairments into the afternoon and evening.

The treatment response rate for methylphenidate is approximately 70%, demonstrating greater efficacy compared to non-stimulants [7,11]. Methylphenidate treatment has been associated with notable improvements in neurocognitive tests and overall quality of life [12,13]. When assessed for symptom improvement, the effect size for methylphenidate has been found to be large in youths while moderate in adults [14].

Commonly reported side effects of methylphenidate include loss of appetite, abdominal pain, headache, insomnia, and irritability. Most side effects are mild and temporary, and appear primarily during the early stages of treatment [4]. However, if symptoms persist, they should be monitored and addressed by reducing the dosage or switching to a different class of medication [7]. In cases where a particular medication is most effective, but causes significant side effects, additional medications can be prescribed to mitigate these side effects.

Stimulant treatment may lead to small reductions in height and weight, but these effects tend to diminish over time, with minimal long-term clinical effects [15]. Growth monitoring is recommended to address individual differences. Stimulants can also reduce total sleep time and delay sleep onset, making it advisable to assess sleep quality before starting treatment. Sleep issues can often be managed by adjusting medication formulation [16]. Although hypertension may occur,

large studies have found no increased risk of serious cardiovascular events, such as heart attack or stroke in children and young adults receiving stimulant medications [17].

Non-stimulants

Atomoxetine

Atomoxetine was the first nonstimulant medication approved by the U.S. Food and Drug Administration (FDA) in 2002 for ADHD treatment, more effective than placebo in treating ADHD in children, adolescents, and adults [18]. Atomoxetine is a selective norepinephrine reuptake inhibitor that inhibits presynaptic norepinephrine transporters.

Atomoxetine has a slower effect than that of stimulant medications, and it may take 6 weeks to reach its maximum therapeutic effect. The dosage starts at 0.5 mg/kg/day and is gradually increased at weekly intervals to a therapeutic dose of 1.2 mg/kg/day, with a maximum dosage of 1.4 mg/kg/day. The clinical side effects should be prioritized when determining an appropriate therapeutic dosage. Notably, in cases of oppositional defiant disorder, improvements were observed at a dosage of 1.8 mg/kg/day [19]. Although the side effects increased with higher doses, the medication demonstrated excellent safety and tolerability at all doses.

Atomoxetine has a lower risk of drug abuse and provides long-lasting effects with a single dose, covering late evening and early morning. It is also useful in cases where side effects such as insomnia or appetite suppression are severe with stimulant medications, or when comorbid conditions, such as tic or anxiety disorders, are present. Research has shown that atomoxetine significantly reduces both ADHD symptoms and anxiety in patients with ADHD and anxiety disorders [20]. Additionally, atomoxetine has proven useful as an adjunct treatment for individuals who partially respond to stimulants [21].

The most common side effects of atomoxetine include gastrointestinal symptoms, such as decreased appetite, abdominal pain, vomiting, and indigestion, and sleep-related symptoms, such as drowsiness [22]. These side effects tend to decrease over time. Otherwise, management by adjusting dosage or switching medications may be required. Gradually increasing the dose and dividing the administration into morning and evening can help reduce early side effects [23]. Routine blood tests and electrocardiograms are not recommended unless clinically indicated. Slight increase in blood pressure and heart rate are possible, although the extent of the increase may vary from patient to patient [24]. Reversible changes in liver enzyme levels and an increased risk of suicidal ideation with atomoxetine use have been documented in boxed warnings, and parents or guardians should be instructed to report these changes. As with methylphenidate, atomoxetine can affect final adult height, thus regular monitoring of weight and height is recommended [25]. For adolescent and adult patients, side effects such as erectile dysfunction, ejaculation issues, and menstrual pain should also be considered [26].

Clonidine

The alpha-2 adrenergic receptor agonists used for the treatment of ADHD include clonidine and guanfacine, originally approved for the treatment of hypertension. ER Clonidine is currently available in Korea. Although the effect size for symptom reduction is smaller than that of stimulant medications, it is comparable to that of atomoxetine, and many patients achieved symptom improvement [27]. ER Clonidine can be used as a monotherapy or as an adjunct to stimulants and can be helpful in cases where patients experience side effects such as tics, sleep disturbances, or mood swings during stimulant or atomoxetine treatment.

The full therapeutic effect of ER-clonidine may take 1 to 2 weeks to become apparent [27]. The manufacturer documents that ER clonidine differs from IR clonidine in terms of its pharmacokinetic profile and should not be substituted on a mg-per-mg basis. Initial dose is 0.1 mg at bedtime, with weekly increments of 0.1 mg/day, up to a maximum of 0.4 mg/day. Doses should be administered twice daily, with a bedtime dose equal to or greater than the morning dose. When discontinuing ER clonidine, tapering by 0.1 mg every 3 to 7 days is necessary to prevent withdrawal symptoms.

The most common side effects of ER clonidine include drowsiness and fatigue [28]. ER clonidine has been reported to slightly lower blood pressure and heart rate, but this did not lead to medication discontinuation in most patients [29]. Changes in QT intervals were minor and consistent with the established pharmacological effects of ER clonidine [29]. As these cardiovascular effects are dose-dependent, it is important to gradually increase the dosage as recommended. If taken in excessive amounts, there is a risk of hypotension and sudden discontinuation may lead to rebound hypertension.

Other medications

Bupropion

Bupropion, an FDA-approved medication for treating depression and smoking cessation, has also shown significant effectiveness in reducing ADHD symptoms [30]. A systematic review of four randomized studies comparing bupropion and methylphenidate found that the efficacy of bupropion was comparable to that of the methylphenidate [30]. However, a meta-analysis comparing bupropion to other ADHD

medications indicated that it had a smaller effect than other drugs when compared against a placebo [31]. Similar to its use in depression treatment, the effects of bupropion for ADHD typically become noticeable over a period of 6 to 8 weeks. Common side effects of bupropion include mild insomnia, loss of appetite, irritability, drowsiness, fatigue, headaches, and, in some cases, worsening of tics.

Modafinil

Modafinil, a drug approved by the Korean Ministry of Food and Drug Safety (KMFDS) for the treatment of narcolepsy, has been reported to significantly reduce ADHD symptoms in children and adolescents [32]. However, it has not been approved by either the FDA or KMFDS for ADHD treatment. Modafinil can cause side effects, such as headaches, anxiety, irritability, and insomnia.

NEW TREATMENT OPTIONS FOR ADHD

Stimulants

Serdexmethylphenidate: methylphenidate prodrug

Serdexmethylphenidate was the first methylphenidate prodrug approved by the FDA in 2021 for the treatment of ADHD in patients aged six years and older. The medication is a combination of 30% dexmethylphenidate, an IR stimulant, and 70% serdexmethylphenidate, a prodrug metabolized in the gastrointestinal tract to produce dexmethylphenidate over time. This dual-action formula provides both immediate and sustained release of the active compound, treating ADHD symptoms throughout the day. The recommended starting dose for children over six years is 39.2 mg of serdexmethylphenidate and 7.8 mg of dexmethylphenidate once daily, with the option to increase the dosage weekly up to 52.3 mg/10.4 mg. Medication can be taken without food, and the capsules may be swallowed whole or sprinkled onto food such as applesauce. No dosage adjustments were required for individuals with kidney or liver impairment.

A randomized, double-blind study with children aged 6–12 years reported serdexmethylphenidate to be safe and effective, providing smooth and gradual ADHD symptom relief throughout the day [33]. The prodrug design allows the maintenance of plasma concentrations of dexmethylphenidate throughout the waking hours, offering continuous symptom management from morning to evening without the need for multiple doses [34]. Similar to other central nervous system stimulants, serdexmethylphenidate carries warnings for potential cardiac effects, including sudden death in children with preexisting heart conditions, along with the risks of abuse, dependence, and growth suppression with long-term use. Other possible side effects include decreased appetite, insomnia, abdominal pain, irritability, and increased heart rate or blood pressure.

Delayed-release/extended-release methylphenidate

Delayed-release/extended-release (DR/ER) methylphenidate was FDA-approved in 2018 and is prescribed for patients aged six and older to treat ADHD. It is the first recommended stimulant to be taken in the evening. DR/ER methylphenidates do not contain IR methylphenidates. As a result, less than 5% is released within the first 10 h of medication intake. Approximately half of the medication is released 10–14 h after dosing, and the rest between 14–20 h. This prolonged release provides symptom coverage from morning to evening, making it particularly beneficial for patients who struggle with morning ADHD symptoms before typical medications are administered. The duration of the drug effect can be extended by increasing the dose without increasing the maximum concentration [35]. This unique property allows clinicians to adjust the duration of medication based on the required symptom control, providing a customizable treatment option for patients with ADHD.

The initial dose of DR/ER methylphenidate starts at 20 mg, with weekly titrations up to 100 mg. In a clinical trial, 8 pm was the most common dosing time for patients [36]. Capsules can be swallowed whole or sprinkled on food without chewing. Like other stimulants, DR/ER methylphenidate carries warnings related to the risk of abuse and dependence, along with the potential cardiovascular issues. Common side effects include insomnia, nausea, weight loss, anxiety, irritability, and increased blood pressure. Psychosis, manic symptoms, and decreased height can also be a potential adverse effect.

Dextroamphetamine patch

In May 2022, the FDA approved the first transdermal dextroamphetamine administration for ADHD treatment [37]. The dextroamphetamine patch requires 2 h to become effective and remains effective for up to 12 h. Peak levels are reached within 6–9 h of dosing, and 90% of the drug is delivered within 9 h. The transdermal delivery system allows for flexible control of dosing, where patches can be applied when required and removed early, if needed. Additionally, transdermal delivery minimizes first-pass metabolism and reduces the risk of drug–drug interactions. This is also helpful for children who are unable to ingest the pills.

The prescription directions state that the patch should be worn for no longer than 9 h and applied once daily. The recommended starting dose of 4.5 mg per 9 h can be titrated weekly to a maximum of 18 mg per 9 h. During clinical tri-

als, a significant proportion of patients reported irritation at the application site, which resolved spontaneously [38]. The patch can be placed on various body parts such as the hip, upper arm, chest, or upper back; however, to avoid skin irritation, the application site should be changed with each new patch. The patch shares similar warnings with other amphetamine-based medications. Adverse reactions commonly reported in pediatric patients include decreased appetite, headache, insomnia, and nausea, whereas adults may experience dry mouth, diarrhea, and anxiety. The risks of cardiovascular reactions, increased heart rate, blood pressure, psychiatric symptoms, and growth suppression should also be noted.

Non-stimulants

Viloxazine extended-release

Viloxazine ER was approved by the FDA in 2021 for treating pediatric ADHD and subsequently for adult ADHD in 2022. Viloxazine ER is a selective norepinephrine reuptake inhibitor initially developed as an antidepressant before being repurposed as a treatment for ADHD [39]. Studies have demonstrated that the pharmacokinetics of viloxazine ER vary with body weight, with larger individuals exhibiting lower drug exposure [40]. If doses are missed, plasma concentrations rapidly return to normal once the medication is resumed, even after a gap of up to four days. Phase 3 trial data suggested that viloxazine ER may help improve peer relations [41], learning [42], and executive function [43] in children. Although it takes approximately six weeks for full efficacy, early improvements within two weeks are predictive of a good response [44].

A starting dose of 100 mg daily for children aged 6–11 and 200 mg daily for those aged 12 and older are recommended. The dose can be titrated weekly to a maximum of 400 mg except in patients with renal impairment, where the maximum dose is 200 mg. Common adverse effects include somnolence, decreased appetite, fatigue, nausea, and irritability. There is also a boxed warning for suicidal thoughts and behaviors in pediatric patients, similar to the warnings for atomoxetine and antidepressants. Viloxazine ER can interact with medications metabolized by CYP1A2.

Centanafadine

Centanafadine is an investigational drug that has shown promising results in phase 3 clinical trials, and is currently under consideration for FDA approval [45,46]. It functions as a triple monoamine reuptake inhibitor, targeting norepinephrine, dopamine, and serotonin transporters. Centanafadine is believed to address core ADHD symptoms similarly to stimulants but with fewer side effects. It increases dopamine levels in the prefrontal cortex and striatum, with the highest activity observed in norepinephrine reuptake inhibition, 6 times less activity for dopamine, and 14 times less activity for serotonin.

In phase 2 trials involving 41 patients, common adverse events included diarrhea, headache, decreased appetite, and dry mouth, with some patients experiencing rashes, leading to discontinuation in a few participants [46]. The dermatologists determined that these rashes were not life threatening. Phase 3 trials further demonstrated the efficacy and safety of centanafadine in adults with ADHD, with headache and decreased appetite as the most common side effects [45]. Overall, centanafadine is a potential alternative for patients who cannot tolerate stimulants or require additional medication for symptom management.

CONCLUSION

In conclusion, the treatment landscape for ADHD continues to evolve, with a range of pharmacological options available to address the diverse needs of patients. Stimulants remain the cornerstone of ADHD management due to their well-established efficacy and rapid onset of action. However, non-stimulants such as atomoxetine and clonidine provide valuable alternatives, particularly for individuals who cannot tolerate stimulants or have comorbid conditions, such as anxiety or tic disorders. Emerging treatments, including serdexmethylphenidate, DR/ER methylphenidate, and transdermal dextroamphetamine, offer innovative methods for sustained symptom control and improved adherence by meeting individual patient needs. Novel agents, such as viloxazine and centanafadine, offer promise as effective alternatives with potentially fewer side effects. Tailoring ADHD treatment to individual patient profiles remains critical, underscoring the importance of regular monitoring for efficacy, side effects, and long-term outcomes. Continued development and introduction of safer and more effective medications for ADHD will enhance patient care, offering hope for improved symptom control and quality of life.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Taeyeop Lee, Hyo-Won Kim. Supervision: Hyo-Won Kim. Writing—original draft: Taeyeop Lee. Writing—review & editing: Taeyeop Lee, Hyo-Won Kim.

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