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From Consensus Statement to Pills to Pixels: New Innovations in Attention-Deficit/Hyperactivity Disorder Care

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Abstract

Objectives: This review aims to present recent innovations and advancements in attention-deficit/hyperactivity disorder (ADHD) care, encompassing international consensus statement, new medication formulations, digital therapeutics, and neurostimulation devices.

Methods: A comprehensive literature search of relevant articles published in the past five years was conducted, emphasizing the evidence base, efficacy, safety, and practical implications of these advancements.

Results: The World Federation of ADHD Consensus Statement offers an updated diagnostic and treatment framework rooted in global scientific evidence. There are several newer ADHD medication formulations, including a nonstimulant (Viloxazine extended release) and the first transdermal amphetamine patch approved to treat ADHD. These options offer some unique benefits to personalize treatment based on symptom profile, lifestyle, preferences, and response. Digital tools offer additional means to restructure environments for individuals with ADHD, reducing impairment and reliance on others. In addition, digital therapeutics enhance access, affordability, personalization, and feasibility of ADHD care, complementing or augmenting existing interventions. Trigeminal nerve stimulation emerges as a well-tolerated nonpharmacological, device-based treatment for pediatric ADHD, with initial trials indicating effect sizes comparable to nonstimulant medications.

Conclusions: These innovations in ADHD care represent clinically significant new treatment options and opportunities for personalized care. Health care professionals should integrate these developments into clinical practice, mindful of individual patient and family needs and preferences. Future research should assess long-term outcomes, cost-effectiveness, and acceptability of these innovations.

Keywords: ADHD, psychopharmacology, digital therapeutics, nerve stimulation, consensus statement

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent and impairing neurodevelopmental disorders in childhood and adolescence, affecting over 5% of school-aged children worldwide (Polanczyk et al., 2007). There is strong scientific evidence related to prevalence, etiology, and treatment options for ADHD (NICE, 2018, Pliszka et al., 2007, Wolraich et al., 2019). However, there are many common myths or misconceptions that stigmatize the disorder, which adversely impact the well-being of people with ADHD, undermine trust in health care professionals, and hinder timely and effective care for those who struggle with the disorder. Furthermore, despite the availability of various pharmacological and nonpharmacological interventions, many patients with ADHD still face challenges in accessing and persisting with evidence-based care. Stigma, tolerability, and cost

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are all appreciable barriers to sustained treatment (Baweja et al., 2021b). Even when care is accessed, it has proved challenging to meaningfully improve long-term outcomes for many with ADHD, especially for those with other comorbid conditions or multiple stressors. Therefore, there is a need for novel treatments and alternative or complementary interventions that can address the diverse and changing needs and preferences of patients with ADHD and their families.

In recent years, there have been significant developments and innovations in ADHD care, which offer new opportunities and challenges for health care professionals. These include international consensus guidelines that provide standardized and updated recommendations for diagnosis and treatment; novel medication formulations that improve efficacy, safety, and convenience; digital therapeutics (DTx) that leverage technology to deliver evidence-based interventions in a more palatable package as well as offering novel interventions; and neurostimulation devices that modulate brain activity and enhance cognitive functions. This review aims to explore these recent advancements in ADHD care, and to provide health care professionals with practical and relevant information on how to integrate them into their clinical practice.

The World Federation of ADHD International Consensus Statement on ADHD

This consensus statement is written by a team of 87 international experts and published in Neuroscience and Biobehavioral Reviews (Faraone et al., 2021). The team compiled evidence-based statements on ADHD based on a systematic search of meta-analyses and very large cohort studies. The team selected evidence that met stringent requirements: each statement had to be supported by either a meta-analysis involving at least five studies or more than 2000 participants or large registry studies with a participant count exceeding 2000. The systematic search yielded 208 empirically supported statements about ADHD, reflecting a consensus across a wide geographic and professional spectrum. Here is the summary of the consensus statement of this World Federation of ADHD International Consensus Statement on ADHD.

Diagnosis and associated features

ADHD diagnosis, which can only be conducted by a licensed clinician, involves interviews with the parent or caregiver and the patient. While the diagnosis process has faced criticism for its perceived subjectivity, since it does not rely on biological testing, such criticism is unfounded. ADHD's validity as a mental disorder is supported by international professional consensus and its diagnostic utility, predicting related issues, outcomes, treatment responses, and genetic or neurobiological causes (Faraone et al., 2021).

Diagnosing ADHD requires sufficient hyperactive–impulsive and/or inattentive symptoms, evident across multiple settings, causing significant impairment, with an onset in early- to mid-childhood. The diagnosis must be made through a clinical interview. No rating scale, neuropsychological test, or biomarker can either rule in or rule out the diagnosis of ADHD. The clinical presentation varies, with inattention typically leading to academic and self-esteem issues, whereas hyperactivity–impulsivity is linked to social and behavioral problems. Regardless of intelligence level, ADHD can impair functioning, with a study showing that ADHD affects individuals with high, average, or low IQ similarly in terms of learning, psychiatric disorders, and substance use (Rommelse et al., 2017).

As individuals with ADHD transition into adolescence and young adulthood, the disorder continues to impact them, often with a noticeable shift to less hyperactivity and more inattentiveness (Faraone et al., 2006). Moreover, ADHD does not exist in isolation; it commonly coexists with other psychiatric disorders, including depression, bipolar disorder, and anxiety, among others (Chen et al., 2018). These comorbid conditions do not exclude an ADHD diagnosis.

People with ADHD may experience a range of nonpsychiatric medical problems more frequently than others. Studies show that ADHD is associated with an increased likelihood of obesity, allergies, asthma, and sleep disorders. Metabolic disorders, migraines, testicular dysfunction, and certain autoimmune diseases are also more common in those with ADHD (Faraone et al., 2021). These comorbid conditions could suggest shared genetic or environmental risk factors or the impact of ADHD on lifestyle choices affecting overall health.

Epidemiology

ADHD, observed worldwide in both developed and developing nations, shows a higher incidence in males. The disorder's diagnosis rates have increased, not because of a rise in occurrence but because of heightened clinical awareness over the past decades, especially for ADHD in adults. Recent meta-analyses confirm this stable prevalence, with about 5.9% of youths globally meeting ADHD diagnostic criteria and no significant differences found across continents (Willcutt et al., 2012). In adulthood, the prevalence is estimated at 2.5%, aligning with findings that the disorder's manifestations often lessen with age (Simon et al., 2009).

Interestingly, older adults show varying prevalence rates, with 2.2% identified through rating scales, which decreases with advancing age. Clinical diagnosis rates in those over 50 drops to 0.2%, and the treatment rate is even lower at 0.02% (Dobrosavljevic et al., 2020). The male-to-female ratio of ADHD in youths is $\sim$2:1, a finding consistent across both parent and teacher ratings in extensive studies (Willcutt et al., 2012). These statistics underscore the disorder's complex demographic variations and the importance of continued research and tailored health care strategies.

Causes

Most cases of ADHD arise from an accumulation of many genetic and environmental factors. Environmental influences associated with ADHD typically occur very early in life, either during fetal development or shortly after birth. In some exceptional cases, ADHD may result from severe early life deprivation, a singular genetic anomaly, or an early traumatic brain injury. Although these instances provide insight into ADHD's etiology, they do not directly aid diagnosis. Associations between environmental factors and ADHD onset are well supported, but often it is unclear if these are causal or correlated because of intertwined genetic and environmental factors. Consequently, these factors are considered correlates of ADHD, not definitive causes.

Twin studies indicate that about 75% of ADHD's causes are genetic and 25% are environmental (Faraone et al., 2021). A large genome-wide study identified multiple genetic variants with small effects contributing to ADHD, supporting a polygenic cause (Demontis et al., 2019). This genetic risk is associated with

broader psychopathology and overlaps with several psychiatric disorders (Brikell et al., 2020, Lee et al., 2019). The polygenic risk also correlates with ADHD symptoms in the general population, with those at higher risk more likely to be diagnosed with ADHD or related mental health conditions. Rare single-gene defects and chromosomal abnormalities have also been linked to ADHD (Faraone and Larsson, 2019). Genetic and environmental factors overlap between ADHD and other psychiatric and somatic disorders, suggesting shared pathophysiological pathways, although ADHD also has unique genetic risks. Large family studies further suggest genetic or familial links between ADHD and certain autoimmune diseases, developmental conditions, and intellectual disability (Faraone and Larsson, 2019, Li, 2021).

Research has reported association of some environmental toxicants with ADHD. Meta-analyses have shown correlations between lead exposure and ADHD symptoms, with higher blood lead levels significantly increasing the odds of the disorder (Nilsen and Tulve, 2020). Maternal smoking during pregnancy has been associated with a higher incidence of ADHD, but this link has been shown to be because of the genetic risk for ADHD, which also influences maternal smoking. Exposure to secondhand smoke, artificial food dyes, acetaminophen during pregnancy, and certain medications, such as valproate, has also been associated with ADHD. In addition, phthalates and organophosphate pesticides, neurotoxic substances, have been associated with higher ADHD rates. Air pollution studies have yielded mixed results, with some pollutants linked to increased ADHD-related hospital admissions. Nutrient deficiencies, particularly lower levels of ferritin and omega-3 fatty acids, have been observed in individuals with ADHD. Events during pregnancy and birth, such as prematurity, low birth weight, hypertensive disorders, and maternal preeclampsia, have been associated with a greater likelihood of ADHD in offspring. Social factors, including family adversity, stress, and lower socioeconomic status, have also shown dose–response relationships with the risk of ADHD. Conversely, family cohesion and community support appear to mitigate the risk of more severe ADHD (Faraone et al., 2021).

Brain structure and function

Research on the brains of individuals with ADHD reveals two main types of findings: one based on performance in psychological tests and the other on neuroimaging studies. Although differences have been identified between those with and without ADHD, they are generally subtle and not distinct enough to be used for diagnostic purposes. These brain differences are not attributable to medication effects and may diminish as some individuals outgrow ADHD symptoms.

Those diagnosed with ADHD often face cognitive challenges as evidenced by moderately lower IQs and academic skills, specifically in reading, spelling, and arithmetic (Frazier et al., 2004). ADHD is associated with difficulties in working memory, attention, verbal memory, and problem-solving, with a tendency toward impulsive decision-making and preference for immediate rewards (Marx et al., 2018, Schoechlin and Engel, 2005). Although these impairments are more pronounced in children and adolescents, they tend to lessen with age (Ramos et al., 2020). Cognitive training has shown moderate improvements in working memory and inhibitory control in preschoolers with ADHD (Pauli-Pott et al., 2021). No significant sex differences in ADHD symptoms and associated cognitive deficits have been found in youths (Loyer Carbonneau et al., 2020).

Neuroimaging studies have found small to very small differences in the brains of individuals with ADHD compared with those without. Structural MRI data revealed slightly reduced cortical surface areas and some smaller subcortical regions in children with ADHD, which were not seen in adolescents or adults (Hoogman et al., 2019, Hoogman et al., 2017). Functional MRI studies showed underactivation in areas associated with inhibitory control, but these findings are not consistent across all ages and tasks. White matter differences suggesting connectivity issues have been found. Medications for ADHD do not account for the neuroimaging findings (Faraone et al., 2021). Overall, these neuroimaging findings, while indicative of some differences, are subtle and not specific enough to be used for diagnostic purposes or to establish a clear pathophysiology.

The impact of ADHD

ADHD, especially when not treated, leads to serious distress and/or impairments in living. Although many severe adverse outcomes are associated with ADHD, the typical patient does not experience all, or even most, of these problems.

Children with ADHD experience substantial deficits in emotional and social functioning, with schooling also severely affected (Lee et al., 2016). Studies have shown that children with ADHD are substantially more likely to encounter difficulties with emotional regulation, conduct, and peer relationships (Strine et al., 2006). They are also more prone to struggle with social interactions, manifesting in peer rejection and difficulty with social cues and cooperation (Ros and Graziano, 2018). In addition, there is a notable increased likelihood of engaging in bullying behaviors (Montes and Halterman, 2007). These factors combined point to a considerable need for support in managing the complex emotional and social dimensions of ADHD. Furthermore, parents of children with ADHD also report a moderate decrease in their quality of life compared with those with typically developing children (Dey et al., 2019). This highlights the extensive influence of ADHD on the day-to-day well-being of individuals with the disorder and their families.

People with ADHD have a significantly higher risk of accidental injuries compared with those without the condition. They are more prone to burns, with the risk doubling for children under six (Yeh et al., 2020), and have an increased likelihood of serious transport accidents, physical injuries, and vehicular crashes (Chang et al., 2014a, Ruiz-Goikoetxea et al., 2018, Vaa, 2014). High school and college athletes with ADHD are three times more likely to suffer concussions (Nelson et al., 2016). Even after accounting for driving mileage, those with ADHD are more likely to be involved in crashes (Vaa, 2014). ADHD is associated with an increased risk of premature death, primarily due to accidents and suicidality (Sun et al., 2019). Treatment with medications, such as methylphenidate (MPH), does not increase, and may even decrease, the risk of repeated suicide attempts (Huang et al., 2018).

Individuals with ADHD are found to have a higher likelihood of involvement in the criminal justice system. They are more likely to be convicted of crimes and incarcerated (Mohr-Jensen et al., 2019). The prevalence of ADHD in prison populations is reported to be around 20%, substantially higher than the general population (Young et al., 2015). In addition, those with ADHD are more likely to engage in and be victims of physical dating violence (McCauley et al., 2015). There is also an increased vulnerability to making false confessions and being victims of violent crimes

(Christoffersen, 2019, Gudjonsson et al., 2016). These findings underscore the need for targeted interventions and support within legal and correctional systems for individuals with ADHD.

Adults with ADHD are twice as likely to delay high school graduation, with the risk persisting even when adjusting for other psychiatric disorders (Breslau et al., 2011). School children on ADHD medication still face significant educational challenges, including lower achievement and higher dropout rates, despite adjustments for socioeconomic and psychiatric factors (Fleming et al., 2017). ADHD also correlates with poorer language performance in various domains among youths (Korrel et al., 2017). These educational difficulties highlight the impact of ADHD on academic outcomes and the importance of specialized support for affected individuals.

Individuals with ADHD have a significantly higher likelihood of developing substance use disorders. They are nearly three times more likely to become nicotine dependent and have a 50% higher risk for drug or alcohol use disorders compared with those without ADHD (Lee et al., 2011). The association with alcohol-use disorders and nicotine-related disorders is similarly elevated, as confirmed by a meta-analysis (Groenman et al., 2017). In Sweden, a study revealed that people with ADHD have a threefold increased risk of drug use disorders, even when controlling for demographic factors (Sundquist et al., 2015).

Girls with ADHD are more likely to experience teen pregnancies (Østergaard et al., 2017). ADHD increases the risk of various risky behaviors, including problem gambling and reckless driving (Bernardi et al., 2012). Adults with ADHD are at a higher risk for developing dementia (Tzeng et al., 2017). Children with ADHD are more susceptible to poisoning, including self-poisoning (Ruiz-Goikoetxea et al., 2018). Adolescents with ADHD see a reduction in employment and earnings (Fletcher, 2014), and youths with ADHD are more likely to be victims of sexual crimes even when accounting for other risk factors (Christoffersen, 2022). These findings suggest that ADHD can have widespread and significant impacts on various aspects of life beyond typical behavioral challenges.

Owing to these impairments, ADHD incurs substantial economic costs globally, impacting individual patients, their families, and societies. European studies show per-patient costs reaching over €14,000 annually with national costs exceeding €1 billion (Le et al., 2014). In the United States, ADHD is associated with national annual costs ranging from $143 to $266 billion, mostly due to adult ADHD (Doshi et al., 2012). In addition, individuals with ADHD have higher rates of lost workdays and increased health care costs compared with those without the disorder (Graaf et al., 2008, Swensen et al., 2003). Overall, the economic burden of ADHD is significant, reflecting direct health care costs and broader impacts on productivity and well-being.

Medication treatments for ADHD

Stimulants like amphetamines (AMPH) and MPH have been shown to significantly improve symptoms in both children and adults. Nonstimulant medications, such as atomoxetine, extended-release guanfacine, extended-release clonidine, and extended-release viloxazine, also yield significant improvements that are, on average, less than those for stimulants (Cortese et al., 2018). Medication treatments not only address core symptoms but also show benefits in related areas, such as emotional dysregulation and anxiety, albeit to a lesser degree (Coughlin et al., 2015, Lenzi et al., 2018). Moreover, stimulants have been effective in reducing aggression and oppositional behaviors, particularly in youths (Pringsheim et al., 2015). The effectiveness of these treatments is widely recognized in comprehensive guidelines by various health care associations, which detail protocols for medication use in ADHD management (NICE, 2018, Pliszka et al., 2007, Wolraich et al., 2019).

Naturalistic studies highlight the significant impact of ADHD medication on reducing associated impairments both short and long term (Boland et al., 2020). Medication has been shown to improve academic performance, with gains in grade points and increased likelihood of completing secondary school (Jangmo et al., 2019). It is also linked to reductions in criminality, injuries, and serious transport accidents (Dalsgaard et al., 2015, Lichtenstein et al., 2012). In terms of health, medication for ADHD decreases risks for traumatic brain injuries and fractures and lowers the risk of suicide and depression (Chang et al., 2016, Chen et al., 2014, Chen et al., 2017). Moreover, treatment has been associated with a reduction in substance use/use disorders and teenage pregnancies (Chang et al., 2014b, Hua et al., 2021). Overall, the use of ADHD medication appears to protect against the untreated ramification of ADHD across various aspects of life.

ADHD medications, while effective in managing symptoms, come with potential adverse effects. Sleep disruption, appetite and weight loss, and abdominal pain are common side effects associated with stimulant use (Holmskov et al., 2017, Kidwell et al., 2015). Growth in height and weight may be delayed with stimulant treatment, although this is often reversible (Faraone et al., 2008). Cardiovascular events, although rare, may be more frequent in stimulant users (Dalsgaard et al., 2014). MPH use during pregnancy has been linked to an increased risk of cardiac malformations in infants (Koren et al., 2020). However, ADHD medication is not associated with an increased risk of all-cause death, heart attack, or stroke (Liu et al., 2019). These findings underscore the importance of careful monitoring and management of medication in individuals with ADHD.

The misuse and diversion of prescribed stimulant medications, particularly among college students, is a notable public health issue. Although often used for perceived academic or occupational performance enhancement, there is little evidence that it improves academic outcomes for non-ADHD individuals (Faraone et al., 2020) with the preponderance of data suggesting the "expectation" of effect is what drives the actual performance component (Wilens and Kaminski, 2019). Nonmedical use is linked to lower educational attainment and is often preceded by the use of other substance or prescription drugs nonmedically (McCabe et al., 2017). Intentional misuse can lead to serious medical consequences, including critical care admissions and, in rare cases, death (Faraone et al., 2019).

Nonmedication treatments

Behavioral and cognitive-behavioral therapies for ADHD offer varying results. Parent training moderately reduces parent-reported ADHD symptoms but shows less impact on teacher-reported symptoms (Rimestad et al., 2019). Cognitive behavioral therapy (CBT) in adults has moderate self-reported benefits, yet only small improvements are seen with active controls and blind assessment (Knouse et al., 2017). Cognitive training and organizational skill interventions in children yield small-to-moderate improvements in executive functioning and inattention symptoms (Bikic et al., 2017, Scionti et al., 2020). Meditation-based therapies and social skills training have not shown significant effects on ADHD core

symptoms or social skills as measured by teachers (Storebø et al., 2019, Zhang et al., 2018). Although behavioral therapies do not substantially improve ADHD symptoms, they can be beneficial for other related issues. For most patients, combining medication with behavioral treatments is optimal.

Computer-based cognitive training and neurofeedback have shown mixed results for ADHD. Although some studies suggest a small reduction in inattention, they generally do not significantly impact hyperactivity–impulsivity or overall ADHD symptoms when assessed by blinded evaluators (Micoulaud-Franchi et al., 2014). Cognitive training may improve verbal working memory, but it does not improve academic outcomes or have lasting effects (Cortese et al., 2015). Most existing studies have methodological limitations, such as a lack of active controls, making it difficult to ascertain the true efficacy of these interventions for ADHD.

Omega-3 fatty acid supplements show small improvements in ADHD symptoms in well-controlled trials (Puri and Martins, 2014). Dietary interventions, such as food color restriction, have been associated with a small reduction in symptoms but not when appropriate controls are used (Nigg et al., 2012). Exercise may lead to moderate symptom reduction, but this effect is not consistently supported after accounting for publication bias, although it may help with associated anxiety and depression (Vysniauske et al., 2020).

Newer ADHD Medication

Before 2001, providers had few formulation choices of MPH and mixed AMPH salts, and there were no nonstimulant drugs that the U.S. Food and Drug Administration (FDA) approved to treat ADHD. In 2002, atomoxetine was the first nonstimulant medication to be approved. Then in 2009, guanfacine extended-release was marketed, and shortly thereafter in 2011, clonidine extended-release was approved. Since 2000, approximately two dozen stimulant formulations have been approved by the FDA. All are various MPH or AMPH compounds that differ in available isomers (racemic or the d-isomer), technology used to deliver drug (uncoated and coated beads, uncoated and coated microscopic particles, multilayer tablets, and osmotic pressure), and dosage form (tablets, capsules, oral suspensions, oral disintegrating tablets, chewable tablets, and transdermal patches) (Childress, 2022).

Since 2020, four new drugs have been approved by the FDA for the treatment of ADHD. Three are stimulants: one is a combination of a d-MPH immediate-release (IR) and serdexmethylphenidate (SDX, Azstarys); the second is an AMPH extended-release (ER) chewable tablet (Dyanavel XR Tablet, or AMPH|-ERCT); and the third is a transdermal AMPH patch (Xelstrym) (DRUGS@FDA, 2021a, DRUGS@FDA, 2021b, DRUGS@FDA, 2022a). All are FDA approved for patients six years of age and older. One nonstimulant, a new chemical entity, viloxazine extended-release (Qelbree, or VLX-ER) was approved for children and adolescents in 2021 and for adults in 2022 (DRUGS@FDA, 2022b). Each drug will be discussed briefly.

SDX and dexmethylphenidate

SDX/d-MPH is composed of 30% d-MPH-IR and 70% SDX prodrug (Kollins et al., 2021a). SDX is gradually metabolized to d-MPH in the lower intestine and is listed as a Schedule IV controlled substance by the Drug Enforcement Administration, whereas d-MPH has a Schedule II designation. The combination effectively provides IR and ER d-MPH. After ingestion, d-MPH concentrations rise rapidly and peak at about 2 hours, and then d-MPH is continually released as the d-MPH bond is cleaved from SDX in the lower intestine. The drug has a single d-MPH peak with a half-life of 11.7 hours (Kollins et al., 2021a).

Onset and duration of efficacy of d-MPH/SDX was demonstrated in a laboratory classroom trial that enrolled children 6–12 years of age (Kollins et al., 2021a). The study included up to a 7-week screening period, a 3-week dose-optimization period, a 1-week double-blind placebo-controlled period, and a 5-day follow-up visit. Participants started a dose of SDX/d-MPH of 39.2 mg/7.8 mg/day (equivalent to d-MPH-ER 30 mg) and could stay at the initial dose, decrease to 26.1 mg/5.2 mg/day, or increase to 52.3/10.4 mg/day to achieve an optimal symptom improvement and tolerability. Symptom improvement was evaluated using the ADHD Rating Scale-5. At the end of the dose-optimization phase, more than 93% of participants were taking either 39.2 mg/7.8 mg or 52.3 mg/10.4 mg strengths. The primary efficacy endpoint was the change from predose at baseline to the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale-combined scores collected postdose and averaged across the laboratory classroom day. Data were collected at predose and 0.5–13 hours postdose. The study met its primary endpoint. Key secondary measures included the Permanent Product Measure of Performance (PERMP)—a 10-minute skill-adjusted math test—attempted and correct—administered during 25-minute classroom periods. Participants on SDX/d-MPH completed significantly more math problems than their counterparts taking placebo beginning at 30 minutes after dosing and through 13 hours after dosing.

The most common adverse events (AEs) ≥5% occurring during dose optimization included decreased appetite, insomnia, affect liability, upper abdominal pain, headache, and irritability.

Amphetamine extended-release chewable tablets

The AMPH-ERCT is composed of d- and l-AMPH in a 3.2:1 ratio complexed with sodium polystyrene sulfonate to form millions of particles (DRUGS@FDA, 2021a, Pardo et al., 2020). The drug has both IR and ER complexes in which positively charged ions in gastrointestinal fluid displace ions on the drug complexes and release AMPH. The IR complexes are uncoated, and the ER complexes have variable thickness coatings that control drug release through diffusion and ion exchange. The AMPH-ERCT demonstrated bioequivalence to AMPH ER oral suspension (AMPH EROS or Dyanavel XR oral suspension) in a single-dose pharmacokinetic study (Pardo et al., 2020). AMPH EROS is bioequivalent to mixed AMPH salts ER (DRUGS@FDA, 2021a).

The efficacy of AMPH-ERCT was evaluated in a double-blind, placebo-controlled study for adults with ADHD aged 18–60 years that included a screening period of up to 6 weeks and a 5-week forced-dose titration phase (Cutler et al., 2022a). For participants on receiving active drug, titration began with 5 mg/day and then was increased weekly to 10 mg/day, 15 mg/day, and 20 mg/day. During the last 2 weeks of the dose titration phase, participants remained on 20 mg/day. At the end of week 5, participants participated in laboratory classroom during which they completed the PERMP at predose and multiple postdose time points beginning at 30 minutes after dosing continuing through 14 hours after dosing. The difference in mean PERMP total scores averaged across all postdose assessments was the primary efficacy endpoint. PERMP scores were also significantly improved from hour 1 through hour 8 and at hour 13.

Small elevations in systolic and diastolic blood pressure were associated with active AMPH-ERCT treatment and not clinically significant. The most common AEs reported for participants on active drug included insomnia, irritability, initial insomnia, anxiety, decreased appetite, dry mouth, nausea, headache, dizziness, and fatigue. A total of five subjects (8.1%) reported tachycardia as an AE. AEs may have been increased as participants were not optimized to a dose—all were titrated to the maximum dose of 20 mg/day.

For patients, recommended dosing of AMPH-ERCT should start at 2.5 mg/day or 5 mg/day, and dosage may be increased every 4–7 days by 2.5 mg to 10 mg/day to a maximum dose of 20 mg/day (DRUGS@FDA,2021a). A dose comparison between mixed AMPH salts ER and AMPH-ERCT is shown in Table 1(DRUGS@FDA, 2001).

Dextroamphetamine transdermal system

The dextroamphetamine transdermal system (d-ATS) consists of three layers. The outer layer is a silicone-release liner that is discarded when the patch is applied to skin, the next layer is an acrylic AMPH-containing adhesive matrix, and the third is a polyester and polyurethane laminate film (DRUGS@FDA, 2022a). The patch can be applied to multiple skin sites, including the hip, upper arm, chest, upper back, and flank without altering the d-AMPH pharmacokinetics.

The onset and duration of efficacy of the d-ATS was evaluated in a double-blind, placebo-controlled, crossover study in children and adolescents aged 6–17 years (Cutler et al., 2022b). The study consisted of a 28-day screening period followed by 4 weeks of dose optimization. The starting dose was 5 mg/9 hours and could be increased by 5 mg/day weekly until an optimal dose was reached. Participants then completed a 2-week crossover period during which they randomly were assigned to drug or placebo each for 1 week. The primary efficacy endpoint was d-ATS SKAMP total score compared with placebo with onset and duration of effect as secondary endpoints. The optimal d-ATS dose was 5 mg/day for 7% of participants, 10 mg/day for 33% of participants, 15 mg/day for 39% of participants, and 20 mg/day for 21% of participants. After dose optimization, participants were randomized into the double-blind phase. When worn for 9 hours, efficacy was demonstrated at 2 hours after patch application through 12 hours.

Treatment-emergent AEs were reported by ~96% of participants (Cutler et al., 2022b). The most common AEs were decreased appetite, insomnia, and headache. Irritated mood, appetite loss, and abdominal pain caused discontinuation for three subjects during the dose-optimization period. AEs related to patch application included pain (10%), pruritis (7.3%), burn (2.7%), erythema (1.8%), discomfort (0.9%), edema (0.9%), and swelling (0.9%) during dose optimization. Pain/discomfort at the application site usually resolved in 2–4 hours after patch removal. Heart rate and blood pressure changes were consistent with amphetamine treatment. Simulations using pharmacokinetic data concluded that a shorter patch wear time is associated with a shorter duration of d-AMPH effect (Cutler et al., 2022b).

The recommended starting dose is 4.5 mg/9 hours, and the d-ATS can be titrated weekly in 4.5 mg increments (DRUGS@FDA, 2022a). The maximum dose is 18 mg/9 hours.

Table 1. A Dose Comparison Between Mixed AMPH Salts ER and AMPH-ERCT

AMPH-ERCT	*Mixed AMPH salts ER capsule (AMPH base)*
2.5 mg AMPH base	5 mg (3.1 mg AMPH base)
5 mg AMPH base*	10 mg (6.3 mg AMPH base)
10 mg AMPH base*	15 mg (9.4 mg AMPH base)
12.5 mg AMPH base	20 mg (12.5 mg AMPH base)
15 mg AMPH base*	25 mg (15.6 mg AMPH base)
20 mg AMPH base*	30 mg (18.8 mg AMPH base)

AMPH-ERCT, AMPH extended-release chewable tablet; ER, extended release.

VLX-ER

VLX-ER is a norepinephrine reuptake inhibitor with serotonin (5HT) receptor-modulating properties. It is a 5-HT_{2C} agonist and a 5-HT_{2B} antagonist. The IR formulation was marketed as an antidepressant in Europe (Findling et al., 2021, Yu, 2020, Yu et al., 2020). VLX-ER is metabolized by CYP2D6. It is a strong inhibitor of CYP1A2, thus increasing exposure to caffeine and melatonin, and is a weak inhibitor of CYP2D6 and CYP3A4 (Yu, 2020, 2021). VLX-ER did not interact pharmacokinetically with MPH or AMPH in single-dose pharmacokinetics studies (Faison et al., 2021a, Faison et al., 2021b).

Five double-blind, placebo-controlled studies with VLX-ER, including more than 1100 participants were conducted in children and adolescents 6 to 17 years of age using the ADHD-Rating Scale-5 (Johnson et al., 2020, Nasser et al., 2021a, Nasser et al., 2020, Nasser et al., 2021b, Nasser et al., 2021c). After screening, all participants were randomized to VLX-ER or placebo for 6 or 8 weeks depending on the trial. VLX-ER started at 100 mg for children and at 200 mg for adolescents in these forced-dose trials. In children aged 6 to 11 years, VLX-ER was effective at doses of 100 mg to 400 mg/day with significant improvement compared with placebo in ADHD symptoms as early as one week after beginning treatment. For adolescents aged 12–17 years, VLX-ER 400 mg was effective compared with placebo at 2 weeks after onset of treatment and the 200 mg dose was effective beginning at 3 weeks. The most common treatment emergent AEs reported in ≥5% of patients and ≥2 times placebo were somnolence, decreased appetite, and fatigue. Mild increases in blood pressure and heart rate were noted consistent with VLX-ER's mechanism of action.

VLX-ER was also evaluated as an add-on treatment for stimulants in an 8-week, open-label study. Participants aged 6–17 years who had partial response to AMPH or MPH were enrolled. During the first 4 weeks, VLX-ER was administered in the morning, and during the second 4 weeks, it was administered in the evening. All subjects continued their same stimulant dose that they were taking before participating in the study. The VLX-ER and stimulant combination improved ADHD symptoms greater than stimulants alone, whether VLX-ER was dosed in the morning or evening (Childresset al., 2023).

VLX-ER dosing for patients aged 6–11 years should begin at 100 mg/day and can be increased by 100 mg/day per week up to a maximum of 400 mg/day. For patients aged 12–17 years. the VLX-ER dose should begin at 200 mg and can be increased after 1 week to 400 mg/day. The capsule contents can either be sprinkled on applesauce or pudding or swallowed whole.

Digital Interventions

Delivery of digital interventions for assessment and treatment of ADHD offer an opportunity for improved access to care, greater precision and personalization of care, and a novel platform for treatment of both symptoms and functional impairment. The majority of patients have a smartphone and access to Wi-Fi, and digital health solutions for assessment and treatment opens the potential for a treatment that can be scalable and accessible, even when there is limited access to a local clinician experienced in treating ADHD.

DTx

A DTx is defined by the Digital Therapeutics Alliance as a device that will "deliver medical interventions directly to patients using evidence-based software therapeutic interventions to treat, manage, and prevent a broad spectrum of diseases and disorders" (Tremain et al., 2020). There are now a growing number of ADHD-specific DTx, including among others EndeavorRx, EndeavorOTC, Braingame, Revibe Connect, Sylar's Run, NeuroSigma, ACTIVATE, Smartmind, Airplane, Neuroracer, and Dragon. DTx can be sold direct-to-consumer (DTC), where there is no requirement for clinical evidence to support the product or authorized by the FDA for nonprescription over-the-counter (OTC) use. Prescription Digital Therapeutics (PDTx) require clinician initiation and oversight. Clinicians who wish to practice evidence-based medicine in guiding their patients on the opportunity cost of both time and money in investing in these products have very little empirical data to work from. Regulated and cleared OTC and PDTx might be a starting place for clinicians wanting to ensure that the DTx they recommend to patients are evidence based.

Meta-analyses of effectiveness of DTx for youth with ADHD

Two meta-analyses have looked at the efficacy of digital therapies in children with ADHD. He and colleagues looked at 31 studies with 2169 participants (1665 boys and 504 girls) aged 4–17 years. Individual studies had a minor effect on pooled estimations (He et al., 2023). The results indicated an effect size for improvement based on five studies of attention symptoms of 0.25 and for hyperactivity and impulsivity of 0.13. Meta-analysis of the effect of DTx on the total score of ADHD Rating Scale (ADHD-RS; DuPaul et al., 1998) based on six studies was 0.24. The authors concluded that DTx may have "possible efficacy on improving clinical symptoms of pediatric ADHD."

A second systematic review and meta-analysis of DTx and ADHD looked at attention as the primary outcome and hyperactivity and impulsivity as a secondary outcome as reported by parents and teachers, as well as comparing DTx to medication and control through indirect meta-analysis (Oh et al., 2024). The study looked at children and youth less than 18 years with ADHD treated with a DTx. Three interventions were compared: game-based DTx, medication, and control groups (defined as a game with no specific effectiveness for ADHD or a placebo). Twenty randomized controlled trials (RCTs) were found that met these criteria, comprising 1402 participants. The standardized mean difference (SMD) outcome on attention as reported by the teacher was 0.21, as compared with the SMD of the effect of medication on attention of 0.62. The authors conclude that game-based DTx significantly improved attention as compared with controls but less than medication.

Limitations of both meta-analyses included RCTs with small sample size and high heterogeneity among outcome endpoints, evaluation indicators, and type of control group.

PDTx

The EndeavorRx was the first videogame cleared by the FDA in 2020. The Software Treatment for Actively Reducing Severity of ADHD trials initially included an open-label proof of concept study of 40 children with ADHD and 40 children without ADHD looking at the test of variable of attention (TOVA), behavior rating inventory of executive function (BRIEF), and Cambridge neuropsychological test automated battery as outcomes. Significant improvements were observed on a computerized attention task for the ADHD group and also improvement in working memory with an effect size of 0.39 (Davis et al., 2018).

The next study was an RCT with 180 children, age 8–12 years in active treatment versus 168 in a control group in which the sham intervention was a word game. Subjects were asked to participate for 25 minutes a day for 5 days a week. The primary outcome was the change on a subtest of the computerized TOVA, called the attention performance index (TOVA API), which is a composite measure of reaction time and reaction time variability for frequent and infrequent targets. The results showed statistically significant superiority of the digital intervention on this primary outcome, with no serious adverse events or discontinuations (Kollins et al., 2020). A third study looked at efficacy over a longer time as well as in combination with medication (Kollins et al., 2021b). The treatment was well tolerated with no serious adverse events and suggested additional treatment benefit.

The designs employed in the EndeavorRx trials create challenges for clinicians trying to generalize the findings to real-world practice. Specifically, it is difficult as a clinician to judge whether improvement from using a computer program as measured by a computerized test looking at reaction time has real life benefit. The correlation between the TOVA-API and actual classroom performance is modest, whereas there is no significant correlation between the TOVA and parent or child report of clinical improvement in ADHD symptoms with stimulant (Manor et al., 2008). Notably, a recent systematic review and meta-analysis has explored the clinical utility of continuous performance tests (such as the TOVA) and found that they are only modest to moderate in their ability to differentiate ADHD from non-ADHD samples (Arrondo et al., 2023). In addition, outcome measure is similar to the training tasks, further questioning the generalizability of treatment effects.

These concerns could be addressed by the results of secondary outcomes included in the study, including a responder analysis on the Impairment Rating Scale. The authors selected a 1-point difference on the IRS as the definition of a "responder" for comparing active versus sham treatment groups. The RCT found a modest difference (48% treatment response vs. 37% control response) on the IRS. There was also no significant difference between the active and control interventions on ADHD symptoms as measured by the ADHD-RS, on executive function as measured by the BRIEF, or on the Clinical Global Impressions—Improvement (CGI-I) scale rated by the clinician. The responder analysis comparing active versus sham treatment showed improvement in the ADHD-RS of 24% versus 19% of subjects and clinician-rated improvement in 17% versus 16% of subjects. Nonetheless the authors concluded, "This study shows that a digital intervention can significantly increase attentional functioning of children with ADHD" (Kollins et al., 2020). The FDA cleared the intervention

as PDTx, and in 2023, the company announced that the product would be marked for children, adolescents, and adults without requiring a physician prescription as EndeavorOTC. The requirement for a physician prescription limited access, and the intent was to reach a wider audience. Clearance for the OTC market authorizations are still pending with the FDA. Endeavor Rx is listed as not intended to be used as a stand-alone therapeutic and is not a substitution for your child's medication.

Another area where it is difficult to extrapolate from the methodological standards of pharmacological research to digital research is the definition and evaluation of adverse events. Current DTx research has looked at adverse events using the kind of somatic complaints that are associated with medications, such as headaches or dizziness. This may not be the best way to conceptualize the true risks of DTx.

Digital health technologies

Apps and onboard sensors (e.g., accelerometers and gyroscope) found on wearable devices such as a Fitbit or Apple Watch provide data to the user on activity, sleep, calories, heart rate, and an ever-increasing range of other health parameters. Although these tools are not ADHD specific, they have nonetheless changed the landscape for providing assistive technology to support individuals with ADHD. Apps to support organization, time management, on-task behavior, reading, and writing have particular importance in remediating ADHD impairments.

Executive function: Digital health technologies (DHTs) are becoming increasingly important as a support for organization, prioritizing, and task management for everyone. DHTs have the potential to play a critical role in building external, compensatory environmental structures to manage executive dysfunction. Tools such as alarms, timers, lists, "find my" locators, organizers, and financial management apps may provide support in skills that are uniquely challenging for individuals with ADHD. Devices, such as Air Tags, Tile, or "Find My," in Apple are effective in managing difficulty with losing important items such as keys, wallets, and devices. Reminders in iCal, Google Calendar, or Outlook help with planning, forgetfulness, being on time, and task management. Devices can provide feedback on effective use of time, by, for example, tracking screen time versus productive time. The transition from print materials to electronic materials mitigates the challenges of not having the right materials in the right place at the right time. Cloud-based programs such as Dropbox, Box, iCloud, or Microsoft Cloud mean that individuals with ADHD have access to their electronic work files from anywhere. Digital devices now also include "do not disturb" features that prevent distraction during work, sleep, or driving.

Written output: Dictation tools such as Siri can mitigate limitations associated with written output, which impacts more than half of patients with ADHD (Mayes et al., 2019). The ability to simply say "hey Siri" and have a reminder on your watch or phone helps individuals with limited working memory manage tasks, reminders, and other demands in the moment. This is more compatible with ADHD than carrying around an agenda, creating handwritten lists on sticky notes, or trying to rely on memory.

Reading: Another common co-occurring difficulty in patients with ADHD is difficulty with reading, or even simple avoidance and dislike of reading. The availability of written materials in audio format has provided access to information that bypasses the need to read. Individuals with ADHD can now 'listen' to books, textbooks, magazines, newspapers, podcasts, and just about anything else. This means they can learn while walking, running, driving, doing housework, or other "activities" that allow them to move and feel 'busy' is typically more ADHD friendly than sitting still.

Driving: The digital safety features and use of map programs decrease the risk of getting lost, alerts drivers to potential safety concerns, and allows drivers who are impatient to avoid traffic congestion. These apps are useful to everyone; what makes them uniquely relevant to ADHD is how they can level the playing field for the impairments which are uniquely challenging to ADHD individuals.

The clinician's role in DHTs

Clinicians supporting patients with functional impairments associated with ADHD need to be familiar with the potential of digital interventions, and any available evidence on the cost, risk, and benefit these tools provide. ADHD support associations have provided patient guides to support understanding and access to digital health apps for ADHD (Additude, 2019). Websites such as www.mindapps.org are collating and rating various digital health interventions for mental health in general, and ADHD in particular (Camacho et al., 2022).

Clinicians also need to be aware of DHTs when evaluating for ADHD symptoms. When asked if they have difficulty waiting, patients with ADHD may respond, "not if I have my phone." When asked if they have difficulty losing things, patients may respond, "I have Air Tags (or Tiles) on my purse and keys, so even when I lose them, I can find them." These responses illustrate symptoms, which are still present, but no longer impairing, because the patient has adopted digital compensatory strategies. This raises the question of whether the clinicians should consider the symptoms as present if they are well compensated by technology. We would argue that when a patient acknowledges sufficient difficulty with a particular symptom to lead them to commit to finding and using a DHT to compensate, that symptom is significant, even when the compensatory strategy mitigates impairment.

Clinicians who support digital literacy in their patients as a new and powerful avenue for intervention set the patient up to maintain improvement without ongoing need for intervention. When the device nags instead of a supervising adult, this also protects against the frustration that can otherwise be experienced by mothers, spouses, or teachers who are functioning as the patient support for executive function. Keeping someone with ADHD on task is frustrating and demanding and often experienced by the child, youth, or adult as annoying. DHTs can do the same thing, without the negative affect, while maintaining the support indefinitely without fatigue. Similarly, in CBT for ADHD or group, where the clinician is recommending use of an agenda, the patient would return saying they forgot to write things down in the calendar, or that they lost or forgot the agenda altogether. Now a clinician can set up an adult with ADHD to have a calendar on their wrist and train them to dictate their appointments, tasks, shopping lists, and so on. Likewise, a clinician might have had the teacher write down the homework in the child's agenda, but the backpack and the books never made it home. Now, direct parent–teacher communication with online access to the work might mean training the parent to be able to use Google Classroom.

DHT raises the hope of providing a scalable, less expensive way to manage some of the challenges associated with ADHD. However, head-to-head comparison of digital versus analog

strategies for management of time and behavior has mostly not been tested in controlled, randomized, clinical trials.

Trigeminal Nerve Stimulation

In 2019, trigeminal nerve stimulation (TNS) became the first FDA-cleared, nonpharmacological, device-based monotherapy for treatment of ADHD in children aged 7–12 years. TNS is safe and effective at reducing core symptoms of ADHD in ~50% of children (McGough et al., 2019).

Among children randomized to active TNS, 4 weeks of nightly therapy resulted in an average decrease of 27% in the ADHD-RS total score compared with 14% reduction in the sham TNS group, which was a significant group effect (McGough et al., 2019). Both inattentive and hyperactive behaviors showed levels of change similar to the ADHDRS total score across both groups. When examining TNS clinical responders as defined by the CGI-I = 1 or 2, the rate of symptom reduction on the ADHDRS total score was 38% versus 13% for nonresponders (Loo et al., 2021). Overall, these data support the clinical observation that TNS treatment is an effective treatment for improving core ADHD symptoms for ~50% of children, among whom there is, on average, a ~38% reduction in total symptoms.

In the initial RCT of TNS, adverse events were mild to moderate in clinical significance and not different between active and sham conditions. The active group exhibited significant increases in weight and pulse relative to the sham condition, but the end-of-treatment changes remained within the normal range (McGough et al., 2019). The most common treatment-related side effect was headache (9% in active and 3% in sham). In addition, skin rash among children with sensitive skin or skin discoloration among children with darker pigment may occur. Recommendations for remediation of these symptoms are given in Table 2. There were no serious adverse events, nor were there any side effects that led to participant withdrawal from the trial. This result was also reported in a recent review and meta-analysis of 48 TNS treatment studies across clinical conditions, including migraine, major depression, epilepsy, and ADHD (Westwood et al., 2023). Overall, TNS was well tolerated across studies with a favorable adverse event profile. All data thus far support the conclusion that TNS is a minimal risk treatment with few side effects.

Clinical effects: Among responders, inattentive symptoms show the biggest change with TNS. Several families reported improved sleep, either due to shorter sleep onset, longer sleep duration, and/or feeling more rested in the morning. The day-to-day executive functioning reportedly improved, which might drive overall improvement, particularly in inattention. Similarly, effects on better emotion regulation and improvement in emotion reactivity and dysregulation were also reported.

Mechanism of action: TNS involves mild stimulation that affects brain activity indirectly through the trigeminal nerve, a cranial nerve in the forehead. The TNS increases activity in brain areas involved in ADHD. Electroencephalography (EEG) data suggested that the main effect was related to broadband increase in brain spectral power over the middle and right frontal areas, which was significantly associated with change in hyperactive and impulsive symptoms (McGough et al., 2019). Furthermore, lower EEG power in the slower wave frequencies, that is, theta and alpha bands, particularly when coupled with parent ratings of impaired executive functioning, resulted in modest prediction (area under the curve = 0.83) of TNS responder status (Loo et al., 2021). These brain regions have been linked to cognitive and emotional control and response inhibition (Voigt, 2019, Wagner et al., 2018).

TNS initiation: There are various resources, including physician brochure, order form (for the device and electrodes), and technical assistance, available by the device manufacturer, Neurosigma (https://www.monarch-etns.com/). There is also a brochure on the website for patients. A manual comes with the device and the website has a video that demonstrates proper usage. A prescription for the device should be submitted through the Neurosigma website and tech support is also available through the website for technical challenges with the device. It is useful for the clinician to understand the technical aspects of the device, but this is not critical. Table 2 highlights the common troubleshooting issues and solutions that have been used to address the problems.

The two main treatment parameters are stimulation level (dose) and timing.

Dose: The stimulation range is 0–10milliamps (mA), with 0.2 mA steps. The stimulation should be high enough that the child can feel the tingling sensation on the forehead but maintained at their comfort level. It should not cause pain or discomfort (headache), as this would make it difficult for the child to sleep with the device on throughout the night. Comfort levels appear to differ greatly across individuals. Thus, the parent should start the stimulation at the lowest level and slowly increase by each 0.2 mA step while asking the child if he or she feels the tingling. Once the child can feel it, the parent should stop increasing the stimulation level when it starts to feel uncomfortable. If the child reports that the stimulation is uncomfortable, the parent reduces the stimulation level by one 0.2 mA step. Currently, there are no data on an "optimal" stimulation level, but generally it is above 1 and less than 5. Sometimes, parents consider increasing stimulation level, but it is not necessary to use higher stimulation levels to achieve a good clinical outcome. There may be some variation in stimulation level over the course of treatment, which does not seem to influence treatment outcome.

Timing: The standard timing for device use is ~7–9 hours every night while the child sleeps (i.e., put on electrode right before bed and take off upon waking up in morning). If having problems making nightly sleep work, the child can also start use for a couple of hours before bedtime and continue during sleep. Treatment for 4–6 weeks is usually sufficient to observe if treatment is effective. The onset of treatment effect for most people is slow, with gradual improvements occurring over weeks.

TNS treatment maintenance: Once a positive response to TNS has been established in the initial 4–6 weeks of treatment, TNS effects can be monitored by ADHD symptom rating scales every 1–2 months or according to clinician or family preference. Consistent use (~5 nights/week) of TNS has been reported to have the best outcomes. In an ongoing 1-year open label extension of TNS, long-term compliance with TNS is variable, such as other ADHD medication and psychosocial treatments.

Long-term safety and outcomes within ADHD have not been systematically studied, but 1+ year of TNS treatment has not indicated any significant safety concerns (Westwood et al., 2023). As with other medical treatments, TNS does not remedy family issues, parental lack of discipline, or comorbid learning problems. Multimodal treatments are still needed to address these issues.

Currently, there are no published studies to date on the effect of TNS with ADHD medications. However, in research studies on adults with other conditions such as migraine, depression, and

Table 2. Troubleshooting TNS: Common Questions and Issues with Potential Responses and Solutions

Question	*Response*
What does the stimulation feel like?	The stimulation feels like a tingling on the forehead.
Should I try to increase the stimulation level so treatment will be effective?	No, it is unknown whether a higher stimulation level is necessary for effectiveness. The child's comfort should be prioritized to reduce resistance.
Does TNS make it difficult for the child to sleep?	The data so far suggest that TNS may result in better sleep for some children, with shorter sleep onset and longer sleep duration.
Is it okay if the stimulation level varies on some nights?	Yes, this is ok. The child's comfort level should be prioritized.
Can we reuse the electrodes?	The electrodes are single use and should be discarded after each use.
Issue	***Possible Solutions***
Skin rash under electrode	Treat rash (wash area after removing the electrode and/or use cortisone cream).
Skin discoloration under electrode	Discoloration improves with discontinuation of device and electrode use for ~2 weeks and normal exposure to sun.
Eye twitch Headache Stimulation is painful	Reduce TNS stimulation level 1–3 steps (0.2 mA each step) until twitch is resolved.
Electrode will not stay on forehead for the whole night.	Forehead should be clean and dry before applying electrode. A headband over the electrode or medical tape on the sides of the electrode may help with adherence through the night.
Electrode falls off due to excessive sweating	Try to reduce the cause of sweating as much as possible. If sweating only occurs during sleep, the TNS device may be used for an hour or two before bed.
The wires become tangled because the child is a restless sleeper.	The wires can be taped together in the back of the head or neck. Or, the device and wires can be placed behind the child's head or pillow (instead of attached to pajamas). Or, a cord-shortening device may be used on the wires to reduce tangling.

TNS, trigeminal nerve stimulation.

epilepsy (Westwood et al., 2023), TNS device use with medications has been safe and effective.

Discussion

This review aims to provide an overview of the recent innovations and advancements in ADHD care, including international consensus statement, new medication formulations, DTx, and neurostimulation devices. By understanding and integrating established clinical standards and practices with recent advances, health care professionals optimize the assessment and treatment of ADHD in youth.

The World Federation of ADHD Consensus Statement focuses on evidence-based assertions about ADHD gathered from a global perspective; with 208 empirically supported statements, which challenge concerning misconceptions, reduce stigma, and provide a foundation for standardization of assessment and treatment. These consensus statements provide valuable insights on the disorder's nature, course, outcome, causes, and treatment strategies supported by a strong evidence base to the health care professionals. However, it is essential to note that this document does not encompass areas where the evidence base is still evolving, such as large-scale studies or meta-analyses. Their absence does not inherently discount the potential importance of those effects but rather highlights the need for future investigation. There has been appreciable study on the long-term tolerability of CNS stimulants over the past few years, which is not captured in the 2021 consensus statement (Zhang et al., 2022). In addition, numerous recent studies have contributed further insights into ADHD. In a systematic review, pharmacological interventions were the most effective intervention for mitigating executive function in youth with ADHD, closely followed by psychological and digital interventions (Wilens et al., 2024). A multicohort study revealed that prescription stimulant misuse, rather than appropriate medical use of stimulants, is associated with subsequent substance use disorders, particularly methamphetamine and cocaine use disorders (McCabe et al., 2023). A population-based cohort study found no impact on neurodevelopment and growth in offspring exposed to ADHD medication (Bang Madsen et al., 2023). Recent studies have also shown that stimulants use may cause mild growth suppression in children with ADHD that lasts as long as the medication is used (Baweja et al., 2021a).

The four newest additions to drugs approved to treat ADHD offer some unique benefits for patients. VLX-ER is a new chemical entity choice for patients who do not want to take a CNS stimulant. The initial clinical trials of this agent observed good overall tolerability with few participants discontinuing treatment due to adverse events. Onset of effect occurs as soon as one week, and it can be dosed once daily at any time of the day. SDX/d-MPH is the only MPH prodrug/d-MPH combination on the market. The IR d-MPH gives the combination a rapid onset of effect at 30 minutes while the continuous metabolism of SDX to d-MPH allows for extended duration of effect through 13 hours after dosing. The d-ATS is the only transdermal AMPH on the market. It may be preferable for patients who cannot swallow medications or for those wanting to flex the effect duration daily. The AMPH-ER chewable

tablet may be more appealing for patients who want an easily ingestible option for AMPH-ER that covers the morning into the evening. These new medication formulations offer health care providers more options and flexibility to tailor treatment for each patient, based on symptom profile, lifestyle, preferences, and response. In addition to these, there are two new medications: Centanafadine sustained-release (a serotonin–norepinephrine–dopamine reuptake inhibitor) and Solriamfetol (a dopamine–norepinephrine reuptake inhibitor) have shown effectiveness in RCTs in adults with ADHD (Adler et al., 2022, Surman et al., 2023). These new developments further expand the range of options available to health care providers for patient treatment.

Digital tools provide additional means to restructure the environment for individuals with ADHD to manage impairment and reliance on others. Empirical research looking at the impact of digital tools is still in its infancy with little controlled data at present. DTx may represent potentially novel and palatable treatments that can improve access, affordability, personalization, and feasibility of ADHD care, as well as complement or augment existing pharmacological and nonpharmacological interventions. The best methods to evaluate their efficacy and safety are still being determined. Additional potential barriers to the effective use of digital interventions include a patient's reluctance to engage in treatment that does not include human interaction (Waller and Gilbody, 2009) and limited insurance reimbursement.

TNS is a well-tolerated treatment for pediatric ADHD, with effect size in the initial trials found to be comparable nonstimulant medications. This presents a valuable clinical tool, particularly for families preferring nonpharmacological interventions or children with suboptimal medication responses or tolerability concerns. Short-term treatment compliance has been good with parents and children reporting high levels of satisfaction. However, the long-term safety and outcomes of TNS in ADHD have not been systematically studied, and the insurance reimbursement may not be available or sufficient.

ADHD is a complex and heterogeneous disorder that affects millions of children and adolescents worldwide. The field of ADHD care has witnessed remarkable innovations and advancements in recent years, such as the World Federation of ADHD Consensus Statement, new medication formulations, DTx, and neurostimulation devices. These developments offer more treatment options, potentially enabling greater personalization of care. The expanding array of treatments challenges clinicians to keep up with the rapidly growing evidence base, but awareness of new treatment options may translate to meaningful benefits for patients and families.

Authors' Contributions

R.B.: Conceptualization, investigation, and writing—original draft preparation (lead). S.V.F.: Investigation and original draft preparation (Consensus Statement section). A.C.C.: Investigation and writing—original draft preparation (Newer Medication section). M.D.W.: Investigation and writing—original draft preparation (Digital Intervention section). S.K.L.: Investigation and writing—original draft preparation (Trigeminal Nerve Stimulation section). T.E.W.: Conceptualization and writing—reviewing and editing. J.G.W.: Conceptualization and writing—reviewing and editing (lead). All authors approved the final article as submitted and agree to be accountable for all aspects of the work.

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