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Advances in Clinical Research on the Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD)

Xu Han

College of Nursing and Health, Zhengzhou University, Zhengzhou, China
1620435390@qq.com

Abstract. Attention-Deficit/Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental condition, often persisting into adulthood, that necessitates multimodal treatment strategies. Despite extensive research, its pathophysiology remains poorly understood, and the absence of validated biomarkers necessitates reliance on clinical assessment and behavioral evaluation for diagnosis. Pharmacotherapy remains the cornerstone of treatment: central nervous system stimulants such as methylphenidate and amphetamine derivatives demonstrate robust first-line efficacy across age groups, supported by diverse formulations including immediate- and extended-release preparations and transdermal patches. Non-stimulant agents—atomoxetine, α_2-adrenergic agonists, and the recently approved viloxazine ER—serve as alternatives for patients with stimulant intolerance or comorbidities, albeit with slightly lower efficacy, while rational combination regimens offer enhanced outcomes and improved tolerability. Non-pharmacological interventions provide essential adjunctive benefits: cognitive-behavioral therapy (CBT) improves psychosocial functioning when integrated with medication; neuromodulation techniques, including repetitive transcranial magnetic stimulation (rTMS), have demonstrated significant attentional improvements; and complementary strategies such as aerobic exercise and Traditional Chinese Medicine modalities (e.g., acupuncture and acupoint stimulation) show preliminary promise. Future priorities include biomarker-guided personalized pharmacotherapy, development of novel agents with reduced abuse potential, large-scale validation of neuromodulation and complementary therapies, and implementation of multimodal treatment frameworks. High-quality, longitudinal studies remain critical to refining evidence-based ADHD management and improving long-term patient outcomes.

Keywords: ADHD, Pharmacotherapy, Non-Pharmacological, Neuromodulation

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder characterized by persistent patterns of inattention, hyperactivity, and impulsivity [1]. It typically emerges during childhood, with an estimated global prevalence of approximately 5%, and persists into adulthood in nearly 65% of diagnosed individuals, making it one of the most prevalent psychiatric conditions among children [2]. Beyond core symptoms, ADHD imposes a substantial

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burden on family dynamics, and healthcare systems, with an estimated global economic cost exceeding hundreds of billions annually.

Despite decades of research, the precise pathophysiological mechanisms underlying ADHD remain incompletely understood, and no definitive neurobiological biomarkers have been established for diagnostic purposes [3]. Neuroimaging studies have reported structural and functional alterations in specific brain regions of individuals with ADHD compared with typically developing peers [1,4]. However, clinical diagnosis continues to rely primarily on symptom recognition, standardized rating scales [5], and adjunctive assessments such as magnetic resonance imaging (MRI) [6].

Additionally, ADHD is commonly associated with other psychiatric and neurodevelopmental disorders, further complicating its clinical presentation and therapeutic management. As a result, contemporary treatment paradigms increasingly emphasize individualized, multimodal approaches to optimize outcomes [7].

This review aims to summarize recent clinical advances in ADHD management, with a focus on pharmacological therapies (stimulant and non-stimulant agents, combination strategies), non-pharmacological interventions (psychological/educational approaches, neuromodulation, exercise, and Traditional Chinese Medicine-based modalities), and integrative frameworks, and it highlights emerging directions for biomarker-guided personalization and long-term outcome optimization.

2. Pharmacotherapy interventions

Pharmacotherapy remains a core component of evidence-based ADHD management and is consistently recommended in national and international clinical guidelines [1,3,8]. Current practice primarily targets pediatric and adult populations, while data on efficacy and safety in older adults remain scarce. In children, treatment goals focus on improving attention and impulse control, whereas adult management often addresses broader functional impairment and comorbidities such as anxiety and depression [3,9]. For elderly patients, use is largely extrapolated from adult protocols, with careful physician supervision due to the absence of specific regulatory approvals and heightened concerns about adverse effects [10,11]. The primary categories include central nervous system (CNS) stimulants and non-stimulant medications, each with distinct mechanisms of action, therapeutic benefits, and limitations (Table 1).

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Table 1. Overview of pharmacotherapy in ADHD. Summary of central nervous system (CNS) stimulant and non-stimulant medications used in ADHD management, including their mechanisms of action, representative drugs, advantages, disadvantages, and supporting references.

Drug Category	Mechanism of Action	Key Interventions	Advantages	Disadvantages	Reference Citations
Central Nervous System (CNS) Stimulant	Increase synaptic levels of dopamine and norepinephrine, enhancing prefrontal and striatal function.	(1) Methylphenidate (MPH): Immediate-release, extended-release, oral suspension, transdermal patch.(2) Amphetamine (AMPH) derivatives.	(1) Robust efficacy: Large-scale trials (e.g., 10,000+ children) show significant symptom reduction within ~28.8 days.(2) Multiple formulations allow tailored dosing for daily needs.	(1) Common adverse effects: Appetite suppression, insomnia, increased heart rate. (1) High interindividual response variability; requires personalized selection.	[13, 14, 15, 16, 17]
Non-Stimulant Medications	(1) Act on alternative neurotransmitter systems: Atomoxetine inhibits norepinephrine reuptake; (2) α_2-adrenergic agonists (clonidine, guanfacine) modulate α_2 receptors; (3) viloxazine modulates serotonin and norepinephrine.	(1) Atomoxetine (selective norepinephrine reuptake inhibitor).(2) α_2-adrenergic agonists: Extended-release clonidine, guanfacine.(3) Extended-release viloxazine (serotonin–norepinephrine modulator).	(1) Suitable for patients with stimulant intolerance or comorbidities (e.g., tic disorders, sleep disturbances).(2) Lower abuse potential; better for long-term adherence.	(1) Generally less potent than stimulants.(2) Efficacy slightly lower; may take longer to show effects.	[14, 18, 19, 20, 21]

2.1. Central Nervous System (CNS) stimulants

Methylphenidate (MPH) and amphetamine (AMPH) derivatives are first-line agents in both pediatric and adult ADHD [12]. By increasing synaptic dopamine and norepinephrine, they enhance prefrontal and striatal function. Large-scale randomized controlled trials, including one involving over 10,000 children, have confirmed their robust efficacy, with MPH significantly reducing core symptom scores after a mean treatment duration of 28.8 days compared with placebo [13].

Stimulants are available in multiple formulations-immediate-release, extended-release, oral suspension, and transdermal patch-each with distinct pharmacokinetics [14]. MPH demonstrates low bioavailability and high interindividual variability, with inactive metabolites, whereas AMPH undergoes oxidative metabolism to yield active metabolites. Adverse effects, including appetite suppression, insomnia, and increased heart rate, are common to both classes [14]. Considerable heterogeneity in patient response underscores the importance of individualized agent and formulation selection [15–17].

2.2. Non-stimulant medications

Non-stimulants offer viable alternatives for patients with stimulant intolerance or significant psychiatric comorbidities. Atomoxetine, a selective norepinephrine reuptake inhibitor, was the first non-stimulant approved for ADHD across age groups [14]. Extended-release formulations of clonidine and guanfacine, both α2-adrenergic receptor agonists, are particularly useful for managing impulsivity, sleep disturbances, and comorbid tic disorders [14]. More recently, extended-release viloxazine, a multimodal serotonin-norepinephrine modulator with additional effects on

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noradrenergic signaling, has been approved in the US and Europe, demonstrating favorable efficacy and tolerability in multiple randomized trials [18]. While generally less potent than stimulants in reducing core ADHD symptoms, non-stimulants present advantages in lowering abuse potential, addressing a broader range of comorbidities, and supporting long-term treatment adherence, particularly in patients with complex clinical profiles [19,20].

2.3. Combination therapy and future directions

Growing insights into ADHD neurobiology have prompted a shift from monotherapy toward individualized, multimodal pharmacological strategies. Rational combination of stimulants and non-stimulants may improve symptom control in patients with partial response to single agents, while enabling lower stimulant doses and mitigating adverse effects [21].

Evidence from systematic reviews indicates that rational polypharmacy can enhance efficacy while lowering stimulant doses and reducing adverse effects (Table 2). In summary, pharmacotherapy remains a cornerstone intervention for ADHD with significant clinical value. Future research priorities include the development of novel agents with reduced abuse liability, optimization of personalized dosing regimens, and integration of biomarker-based monitoring to guide treatment selection.

Table 2. Summary of representative clinical trials on ADHD medications. Trials and clinical studies evaluating pharmacological interventions for ADHD, stratified by drug category, population, main findings, and reference sources.

Drug Category	Representative Drugs	Study Population	Key Conclusions	Reference Citations
Central Nervous System (CNS) Stimulants	Methylphenidate (MPH)	Children	Large-scale randomized controlled trials (involving over 10,000 children) confirmed its robust efficacy, with significant reduction in core symptom scores after a mean treatment duration of 28.8 days compared with placebo.	[13]
	Methylphenidate hydrochloride sustained-release tablets	Children	It improves cognitive function in children with ADHD and has certain treatment safety.	[17]
Non-Stimulant Medications	Atomoxetine hydrochloride	Children	Compared with methylphenidate, it has certain effects in the treatment of children with attention deficit hyperactivity disorder and impacts CORT and 25-(OH)D levels.	[19]
	Methylphenidate hydrochloride sustained-release tablets combined with Atomoxetine hydrochloride	Children	The combination of atomoxetine hydrochloride capsules and methylphenidate hydrochloride sustained-release tablets is effective and safe in the treatment of ADHD in children.	[16]
	Extended-release viloxazine	Not specified (based on approval information)	It demonstrated favorable efficacy and tolerability in randomized trials and has been approved for ADHD treatment in the US and Europe.	[18]
	Non-stimulant medications (overall category)	Children, Adolescents	They serve as viable alternatives for patients with stimulant intolerance or significant psychiatric comorbidities, with advantages in reducing abuse potential, addressing comorbidities, and supporting long-term adherence.	[19, 20, 21]

3. Non-pharmacological interventions

In addition to pharmacotherapy, non-pharmacological approaches occupy a pivotal role in the comprehensive management of ADHD, encompassing psychological and educational interventions, alongside emerging physical therapies and traditional medical practices (TCM) modalities (Table 3).

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Such interventions not only provide symptomatic relief but also contribute to long-term skill development, improved psychosocial functioning, and better academic performance. Furthermore, the integration of these approaches with pharmacotherapy has been shown to produce synergistic benefits, underscoring their importance in multimodal treatment frameworks.

Table 3. Comparative overview of non-pharmacological interventions for ADHD. Summary of psychological/educational, emerging physical, and TCM approaches, including specific interventions, target populations, principal outcomes, and key citations.

Intervention Category	Specific Interventions	Study Population	Key Findings	Reference Citations
Psychological and Educational Interventions	Cognitive Behavioral Therapy (CBT), behavioral training, parental skills training, classroom optimization	Children; Adults (limited data)	(2) CBT combined with pharmacotherapy improves core symptoms and social functioning in children. (2) Standalone CBT shows limited efficacy in adults. (2) Educational interventions enhance executive functioning and social adaptation in children.	[22]
Emerging Physical Therapies	Non-Invasive Brain Stimulation (NIBS): repetitive Transcranial Magnetic Stimulation (rTMS), Transcranial Direct Current Stimulation (tDCS); Aerobic exercise (running, swimming, cycling)	Children; Mixed populations	(2) rTMS (targeting left dorsolateral prefrontal cortex) significantly ameliorates attentional deficits (meta-analysis of 1,987 participants). (2) Aerobic exercise improves attention, impulse control, and emotional regulation with rapid symptom relief and high adherence.	[23, 25, 26, 27]
Traditional Chinese Medicine (TCM)	Acupuncture, intradermal needle therapy, ear copper scraping, auricular acupressure, modified Kongsheng Zhenzhong Dan combined with press-needle therapy	Children	(2) Acupuncture and related therapies improve attention and behavioral regulation by enhancing cerebral blood flow.(2) Ear scraping and auricular acupressure show short-term symptomatic benefits.(2) Evidence primarily from small, single-center studies.	[28, 29, 30, 31, 32]

3.1. Psychological and educational interventions

Psychotherapy constitutes the foundational component of ADHD management, with cognitive behavioral therapy (CBT) and behavioral training being the most widely utilized modalities. CBT focuses on improving attention regulation, impulse control, and emotional management through structured cognitive restructuring and behavioral techniques. While standalone CBT has shown limited efficacy in adults with ADHD, particularly in reducing core symptoms, combining CBT with pharmacotherapy or other behavioral strategies has demonstrated additive benefits for symptom control, emotional regulation, and social functioning in several randomized controlled trials [22]. Educational interventions remain a cornerstone for pediatric ADHD, targeting not only affected children but also their caregivers and teachers. These programs typically incorporate parental skills training, classroom environment optimization, and structured learning strategies designed to enhance executive functioning, improve academic performance, and facilitate social adaptation across home and school settings.

3.2. Emerging physical therapies

Non-Invasive Brain Stimulation (NIBS): NIBS involves the modulation of neural activity in targeted brain regions via external stimulation devices, most commonly employing repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) [23,24]. These modalities likely exert therapeutic effects by modulating cortical excitability and restoring functional connectivity within prefrontal-limbic networks. A meta-analysis including 1,987

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participants reported that rTMS significantly ameliorates attentional deficits, particularly when applied to the left dorsolateral prefrontal cortex [25].

Exercise Interventions: Multiple studies indicates that aerobic exercise modalities (e.g., running, swimming, cycling) can improve attention, impulse control, and emotional regulation in individuals with ADHD [26,27]. Compared with cognitive training, aerobic exercise may offer advantages in the rapidity of symptom relief and adherence to treatment, findings supported by multi-center trials conducted in China.

3.3. Traditional Chinese Medicine (TCM) non-pharmacological therapies

According to TCM theory, ADHD is often attributed to "insufficiency of kidney essence" and "inadequate nourishment of the brain." Interventions such as acupuncture and intradermal needle therapy, which aim to enhance cerebral blood flow and brain perfusion, have been associated with improvements in attention and behavioral regulation among children with ADHD [28–31]. Additional techniques, including scraping therapy and auricular acupressure, have demonstrated short-term symptomatic benefits [32]. However, the current evidence is predominantly derived from single-center studies with limited sample sizes, underscoring the need for rigorous validation through large-scale, multi-center randomized controlled trials prior to widespread clinical adoption.

4. Future perspectives

Clinical management of ADHD has progressively evolved into a comprehensive paradigm, with psychotherapy constituting the cornerstone and pharmacotherapy serving as a principal modality. Among pharmacological options, CNS stimulants remain the most widely prescribed agents with robust evidence of efficacy. Future development is expected to emphasize precision-targeted compounds and individualized dosing strategies aimed at minimizing adverse effects and reducing dependence liability. Non-stimulant agents and therapies acting on alternative neurotransmitter systems warrant further investigation through adequately powered, multi-center randomized controlled trials.

In the domain of non-pharmacological interventions, CBT remains the primary psychological treatment, demonstrating significant efficacy in pediatric populations but limited effectiveness in adults. This underscores the need for refinement through integration with linguistics, neuropsychology, and related disciplines. Emerging modalities, including NIBS, TCM approaches such as acupuncture and acupoint stimulation, have yielded encouraging preliminary results. However, the small sample sizes and methodological heterogeneity of existing studies necessitate rigorous validation in large-scale RCTs.

Future advancements in ADHD management are anticipated in several domains: (1) Elucidation of pathophysiological mechanisms and identification of reliable biomarkers to enable truly personalized pharmacotherapy; (2) Development of novel psychotropic agents with reduced abuse potential[33, 34]; (3) Enhancement of treatment monitoring accuracy and medication adherence via advances in neuroimaging and pharmacokinetic assays; (4) Technological optimization and clinical standardization of NIBS as a non-pharmacological therapeutic option; and (5) Implementation of evidence-based multimodal treatment strategies combining pharmacotherapy, psychotherapy, physical interventions, and lifestyle modifications to maximize therapeutic outcomes and potentially alter disease trajectories.

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