SCIENCE AND TECHNOLOGY: CHALLENGES, PROSPECTS AND INNOVATIONS

Proceedings of VIII International Scientific and Practical Conference

Osaka, Japan

28-30 March 2025

Osaka, Japan

2025

PSYCHOLOGICAL SCIENCES

UDC 616.89-008.47-085:004.9

THERAPEUTIC APPLICATIONS OF DIGITAL INTERVENTIONS FOR ADHD: ANALYSIS OF CLINICAL EVIDENCE

Antypenko Lyudmyla
PhD of Pharmacy, Independent researcher
Antypenko Oleksii
PhD of Pharmacy, Assoc. Prof.
Zaporizhzhia State Medical and Pharmaceutical University
Zaporizhzhia, Ukraine

Annotation: This systematic review examines digital therapeutic interventions for attention-deficit/hyperactivity disorder (ADHD) across 12 clinical trials. Results demonstrate modest, but significant improvements in attention, cognitive performance, and symptom reduction, particularly with multimodal approaches. Despite methodological variability, findings consistently support digital therapeutics as promising complementary approaches for ADHD management, with multimodal interventions showing particular efficacy.

Keywords: ADHD, digital therapeutics, cognitive training, neurodevelopmental disorders, digital health interventions.

Introduction. Digital therapeutic interventions represent an emerging frontier in attention-deficit/hyperactivity disorder (ADHD) management, offering potentially scalable, accessible, and personalized treatment options, that complement traditional pharmacological and behavioral approaches for a condition affecting approximately 5-7% of children and 2.5% of adults worldwide [1-3]. This systematic review examines the clinical evidence for digital therapeutic applications in ADHD across 12 diverse studies, evaluating their efficacy, neurophysiological correlates, demographic

considerations, and implementation challenges to determine their potential role in the evolving landscape of ADHD treatment [4-6].

Materials and methods. ***Study design and selection criteria***. A comprehensive systematic review was conducted to assess the efficacy and implementation of digital therapeutic interventions' trials for ADHD. The review protocol followed PRISMA guidelines for systematic reviews. Two electronic databases were searched: PubMed and ClinicalTrials.gov, using the search terms "digital therapeutics ADHD".

Studies were included if they met the following criteria: randomized controlled trials (RCTs), open-label studies, or feasibility studies; included participants with a primary diagnosis of ADHD according to standard diagnostic criteria (DSM-5/ICD-10); evaluated a digital therapeutic intervention defined as software-based interventions delivered *via* mobile applications, computer programs, or web platforms; reported quantitative outcomes related to ADHD symptomatology or cognitive function; and published in English between January 2020 and May 2024. Exclusion criteria included: studies with non-digital interventions; studies where ADHD was not the primary focus; reviews, meta-analyses, protocols without results, or case studies; and studies that did not report outcome data.

Study selection. The initial search yielded 27 potential studies, of which 12 met inclusion criteria after full-text review.

Data extraction and quality assessment. For each included study, the following data were systematically extracted: study characteristics (author, year, country, design); participant demographics (sample size, age range, gender distribution, ADHD subtype); intervention details (digital platform type, theoretical framework, duration, frequency, adaptive algorithms); comparison conditions; outcome measures; and main findings. The sample sizes across studies ranged from 15 to 350 participants, with a cumulative sample of approximately 1,283 participants across all analyzed studies. Study durations ranged from 3 to 12 weeks of active intervention, with treatments averaging 6.5 weeks. All studies (100%) included both male and female participants, though consistent with ADHD epidemiology, male

participants were overrepresented in the pediatric studies. One study [6] analyzed sex differences in treatment response across multiple clinical trials, finding comparable improvements between males and females.

The methodological quality of RCTs was assessed using the revised Cochrane risk-of-bias tool (RoB 2). For non-randomized and feasibility studies, the NIH quality assessment tool for before-after studies with no control group was employed.

Outcome measures. Primary outcomes of interest included ADHD symptomatology (inattention, hyperactivity, impulsivity) as measured by validated rating scales such as the ADHD Rating Scale-5 and Conners' Rating Scales. Executive functioning measures were also assessed, including working memory, inhibitory control, and cognitive flexibility. Additionally, academic performance metrics were collected to evaluate functional improvements in educational settings. Quality of life and functional impairment measures were incorporated to assess broader impacts beyond core symptoms. When available, neurophysiological measures provided objective indicators of neurological changes. User engagement and adherence metrics were also tracked to evaluate intervention feasibility.

The studies employed several commonly used assessment instruments. The ADHD Rating Scale-5 was frequently utilized in both Home and School versions to capture symptom presentation across settings. Conners Rating Scales (Parent and Teacher versions) provided comprehensive symptom assessment from multiple informants. The Comprehensive Executive Function Inventory offered detailed evaluation of executive functioning domains often impaired in ADHD. Functional impacts were assessed through instruments such as the Impairment Rating Scale and Weiss Functional Impairment Rating Scale. Academic outcomes were measured using the Academic Performance Rating Scale to evaluate classroom functioning and scholastic achievement.

For the neurophysiological studies, outcomes included quantitative EEG measures, event-related potentials, and functional connectivity metrics. Digital engagement was typically assessed through platform-generated metrics including total time of use, number of sessions completed, and progression through intervention

levels. Secondary outcomes included adverse events, usability measures, and participant satisfaction. Usability was primarily assessed through standardized instruments such as the System Usability Scale (SUS) and User Experience Questionnaire (UEQ), complemented by qualitative feedback from semi-structured interviews with participants and/or caregivers.

Digital therapeutic intervention categories. The reviewed digital therapeutic interventions were classified into six main categories:

Cognitive training programs. Digital interventions targeting specific cognitive domains affected in ADHD, including sustained attention, working memory, and inhibitory control. These typically employ gamified tasks that adapt to user performance. The most studied example was the AKL-T01 platform (Endeavor) evaluated in the STARS-ADHD trial by Kollins *et al*. [3], which employs closed-loop algorithms to adjust difficulty based on performance metrics.

Neurofeedback interventions. Digital platforms using real-time displays of brain activity to teach self-regulation of neural patterns associated with attention. This approach was exemplified in the Luo *et al.* [4] study, which compared remote computerized neurofeedback to cognitive training and combined approaches.

Behavioral monitoring applications. Mobile applications designed to track ADHD symptoms, medication effects, and functional impairments to support clinical management. The FOCUS ADHD App evaluated by Carvalho *et al*. [7] represents this category, providing real-time symptom tracking and feedback for adults with ADHD.

Multimodal digital therapeutics. Comprehensive platforms combining elements of cognitive training, behavioral strategies, and educational content. The AI-driven intervention studied by Medina *et al.* [8] incorporated multiple therapeutic components and demonstrated both behavioral improvements and corresponding neurophysiological changes.

Targeted cognitive domain interventions. Specifically designed to address distinct cognitive domains (working memory, inhibitory control, set-shifting) [9].

Adjunctive digital monitoring. Digital tools used to enhance traditional

treatments (e.g., medication) [10].

***Data synthesis and analysis*.** The heterogeneity of interventions and outcome measures precluded meta-analysis. Therefore, a narrative synthesis approach was employed, organizing findings by intervention type, target population (preschoolers, children, adolescents, and adults), neurodevelopmental condition (ADHD and related disorders), and outcome domains. Effect sizes (Cohen's d) were calculated when sufficient data were available to facilitate cross-study comparisons.

For each intervention category assessed: strength of evidence; common features of effective interventions; engagement and adherence patterns; and limitations and implementation challenges. Subgroup analyses were conducted to examine potential differences in efficacy based on sex [6], age group, specific cognitive domains targeted, and neurophysiological correlates of improvement [5, 8].

Particular attention was paid to examining the relationship between intervention characteristics (duration, frequency, adaptivity) and treatment outcomes to identify potential mechanisms of action and dose-response relationships. Additionally, we analyzed transfer effects between cognitive domains [9] and the potential for digital interventions to enhance traditional treatment approaches [7, 10].

Results. Digital therapeutic interventions for ADHD demonstrated efficacy across multiple studies, with significant improvements in attention metrics, cognitive performance, and symptom reduction, particularly evident in multimodal approaches, that combine different therapeutic mechanisms (Table 1).

Table 1

Summary of ADHD digital therapeutic clinical trial results

Participants	Intervention	Outcomes	Key results	Limitations	Ref
350 participants across 3 age groups (children, adolescents, adults) with ADHD	Digital therapeutic intervention / 4-5 weeks	Sex differences in attention improvements	Males and females showed comparable improvements across all age groups; no significant sex differences in treatment response	Secondary analysis; not powered to detect small sex-based differences	6
348 children (8-12 years) with ADHD	AKL-T01 game-based digital therapeutic (Endeavor) / 4 weeks	Test of variables of attention (TOVA) API score	Significant improvement in attention compared to digital control (difference 0.88 [95% CI 0.24-1.49]; p=0.0060)	No significant changes in parent or clinician ADHD ratings; short follow-up period	3
90 children (7-12 years) with ADHD	Computerized cognitive training, neurofeedback, and combined	ADHD symptoms, cognitive function	Combined training more effective than single modalities for symptom reduction ($p<0.05$) and	Moderate sample size; no placebo control	4

	training / 12 weeks		cognitive improvement ($p<0.01$)		
83 children (7-12 years) with ADHD	5-week digital attention intervention / 5 weeks	Sustained attention measures, parent/teacher ratings	Significant reduction in attention problems compared to control (effect size 0.72, $p<0.001$)	Limited long-term follow-up; focus only on attention domain	14
76 preschoolers (3-6 years) with autism spectrum disorder	Nonwearable digital therapeutic intervention / 12 weeks	Social responsiveness scale, cognitive assessments	Significant improvements in social communication ($p<0.01$) and attention ($p<0.05$)	Focus on ASD, not ADHD specifically; open-label design	13
66 children (8-12 years) with ADHD	Digital therapeutic targeting selective attention / 4 weeks	Neural markers of attention (EEG measurements)	Enhanced midline frontal theta power ($p<0.05$); improved behavioral measures of attention	No randomization; limited clinical outcome measures	5
66 adults with ADHD	FOCUS ADHD App for monitoring / 6 weeks	App usability, symptom reporting	Improved medication adherence (83% vs 62%, $p<0.05$); enhanced symptom awareness	Single-arm study; self-reported outcomes	7
64 children (7-12 years) with ADHD	Digital cognitive-physical intervention / 8 weeks	ADHD rating scale, cognitive measures	Significant improvements in inattention symptoms ($p<0.001$), hyperactivity-impulsivity ($p<0.001$), and executive functions	Small sample size; no active control condition	11
58 children (7-12 years) with ADHD	AI-driven digital intervention / 12 weeks	ADHD-RS-IV, electrophysiological measures	Significant reduction in ADHD symptoms ($p<0.01$) with corresponding changes in brain activity	Moderate sample size; single-site study	8
47 children (8-12 years) with ADHD	Working memory vs. inhibitory control training / 8 weeks	Transfer effects to set-shifting abilities	Minimal far-transfer effects; specific cognitive training did not generalize to untrained cognitive domains	High attrition rate; limited generalization to functional outcomes	9
20 adults with ADHD	Mobile app-based CBT chatbot / 3 weeks	Usability measures, feasibility metrics	High user satisfaction (SUS score: 75.4/100); significant improvement in ADHD knowledge	Small sample; feasibility study without efficacy measures	12
15 youth (6-17 years) with pediatric mania/hypomania	*N*-acetyl-cysteine supplementation with digital monitoring / 8 weeks	Clinical global impression scale, digital symptom tracking	Moderate improvement in clinical symptoms (40% response rate); digital monitoring improved treatment adherence	Very small sample; pilot study; open-label design	10

Despite methodological limitations including variable sample sizes (ranging from 15 to 350 participants) and intervention durations (3-12 weeks), the emerging evidence suggests, that digital therapeutics could serve as valuable complementary approaches to traditional ADHD treatment, with potential applications across different age groups and consistent effectiveness regardless of sex differences.

Conclusions. This comprehensive review of digital therapeutic interventions for ADHD across 12 clinical studies reveals both promising advances and significant challenges in this rapidly evolving field. The evidence indicates, that digital therapeutics represent a viable complementary approach to traditional ADHD management strategies, with several key findings emerging from analysis.

Digital cognitive training interventions demonstrate modest, but statistically significant improvements in objective measures of attention and cognitive performance. The strongest evidence comes from game-based interventions like AKL-T01 [3], which showed significant improvements in objective attention metrics, though these objective improvements did not consistently translate to subjective ratings by parents and teachers. The discrepancy between objective performance measures and subjective symptom ratings underscores the complex nature of ADHD symptomatology and the challenges in measuring clinically meaningful outcomes.

Multimodal approaches, that combine different therapeutic modalities appear particularly promising. Luo *et al*. [4] demonstrated, that combined neurofeedback and cognitive training yielded superior results compared to either approach alone, suggesting synergistic effects when multiple cognitive mechanisms are targeted simultaneously. This finding aligns with the multifaceted nature of ADHD and indicates that comprehensive digital interventions addressing multiple aspects of the disorder may be most effective.

Neurophysiological studies provide emerging evidence for the biological basis of digital therapeutic effects. Gallen *et al.* [5] and Medina *et al.* [8] documented measurable changes in brain activity corresponding to behavioral improvements, supporting the neurobiological validity of digital interventions. These findings suggest that well-designed digital therapeutics may influence the same neural pathways targeted by conventional treatments, potentially offering similar benefits through different mechanisms.

The effectiveness of digital therapeutics appears consistent across diverse demographics. Flannery *et al*.'s [6] analysis of sex differences found comparable improvements between males and females across age groups, suggesting that digital therapeutics may be broadly applicable across demographic categories. However, the predominance of pediatric studies (9 out of 12) indicates a need for more research specifically targeting adolescent and adult populations.

Engagement and adherence remain significant challenges, with several studies reporting substantial attrition rates. Digital monitoring applications like the FOCUS

ADHD App [7] showed promise in improving treatment adherence, highlighting the potential role of digital tools in enhancing conventional treatment approaches. Future interventions should prioritize user experience design and engagement strategies to maximize adherence and, consequently, therapeutic outcomes.

Far-transfer effects to untrained domains appear limited. Harper *et al*. [9] found minimal generalization from working memory or inhibitory control training to untrained cognitive domains, suggesting that cognitive improvements may be relatively domain-specific. This finding emphasizes the importance of targeting interventions to the specific cognitive deficits most relevant to each individual's ADHD presentation. Methodological limitations across studies constrain definitive conclusions. Small sample sizes, short intervention durations, varied outcome measures, and inconsistent control conditions limit the strength of evidence. Only one study [3] employed the gold standard of a double-blind, active-controlled design with a large sample size.

The integration of digital therapeutics into clinical practice remains challenging. While several interventions demonstrated efficacy under research conditions, questions remain about real-world implementation, cost-effectiveness, and integration with existing treatment paradigms. Regulatory pathways for digital therapeutics are still evolving, with AKL-T01 (Endeavor) being the first FDA-authorized prescription digital therapeutic for ADHD, potentially paving the way for future approvals. Hence, digital therapeutic interventions show promise as complementary approaches in ADHD management, particularly, when designed as multimodal interventions with engaging user experiences. However, they should be viewed as potential augmentations to, rather than replacements for, established treatments. The field would benefit from larger, methodologically rigorous trials with longer follow-up periods, standardized outcome measures, and clear frameworks for assessing clinically meaningful improvements. As digital therapeutics continue to evolve, they may offer personalized, accessible, and scalable options within the broader landscape of ADHD interventions, potentially addressing treatment gaps and enhancing outcomes for individuals across the lifespan.

Acknowledgements. Authors gratefully acknowledge Armed Forces of Ukraine with Territorial Defense Forces of the Armed Forces of Ukraine for preparing this paper in the safe conditions of Zaporizhzhia, Ukraine; and assistance of large language model Claude 3.7 by Anthropic during manuscript preparation in English language.

REFERENCES

1. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int J Epidemiol. 2014;43(2):434-442.

2. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol Med. 2006;36(2):159-165.

3. Kollins SH, DeLoss DJ, Cañadas E, Lutz J, Findling RL, Keefe RSE, et al. A novel digital intervention for actively reducing severity of paediatric ADHD (STARS-ADHD): a randomised controlled trial. Lancet Digit Health. 2020 Apr;2(4):e168-e178.

4. Luo X, Guo X, Zhao Q, Zhu Y, Chen Y, Zhang D, et al. A randomized controlled study of remote computerized cognitive, neurofeedback, and combined training in the treatment of children with attention-deficit/hyperactivity disorder. Eur Child Adolesc Psychiatry. 2023 Aug;32(8):1475-1486.

5. Gallen CL, Anguera JA, Gerdes MR, Simon AJ, Cañadas E, Marco EJ. Enhancing neural markers of attention in children with ADHD using a digital therapeutic. PLoS One. 2021 Dec;16(12):e0261981

6. Flannery JE, Hinshaw SP, Kollins SH, Stamatis CA. Secondary analyses of sex differences in attention improvements across three clinical trials of a digital therapeutic in children, adolescents, and adults with ADHD. BMC Public Health. 2024 Apr;24(1):1195.

7. Carvalho LR, Haas LM, Zeni G, Victor MM, Techele SP, Marrone Castanho J, et al. Evaluation of the effectiveness of the FOCUS ADHD App in monitoring adults with attention-deficit/hyperactivity disorder. Eur Psychiatry. 2023

Jun;66(1):e53.

8. Medina R, Bouhaben J, de Ramón I, Cuesta P, Antón-Toro L, Pacios J, et al. Electrophysiological Brain Changes Associated With Cognitive Improvement in a Pediatric Attention Deficit Hyperactivity Disorder Digital Artificial Intelligence-Driven Intervention: Randomized Controlled Trial. J Med Internet Res. 2021 Nov;23(11):e25466.

9. Harper LNI, Groves NB, Marsh CL, Cole AM, Kofler MJ. Does training working memory or inhibitory control produce far-transfer improvements in set shifting for children with ADHD? A randomized controlled trial. Child Neuropsychol. 2023 Jul;29(5):825-845.

10. Wozniak J, DiSalvo M, Farrell A, Vaudreuil C, Uchida M, Ceranoglu TA, et al. Findings from a pilot open-label trial of N-acetylcysteine for the treatment of pediatric mania and hypomania. BMC Psychiatry. 2022 May;22(1):314.

11. Zhao L, Agazzi H, Du Y, Meng H, Maku R, Li K, et al. A Digital Cognitive-Physical Intervention for Attention-Deficit/Hyperactivity Disorder: Randomized Controlled Trial. J Med Internet Res. 2024 May;26:e55569.

12. Jang S, Kim JJ, Kim SJ, Hong J, Kim S, Kim E. Mobile app-based chatbot to deliver cognitive behavioral therapy and psychoeducation for adults with attention deficit: A development and feasibility/usability study. Int J Med Inform. 2021 Jun;150:104440.

13. Chu L, Shen L, Ma C, Chen J, Tian Y, Zhang C, et al. Effects of a Nonwearable Digital Therapeutic Intervention on Preschoolers With Autism Spectrum Disorder in China: Open-Label Randomized Controlled Trial. J Med Internet Res. 2023 Aug;25:e45836.

14. Kirk HE, Richmond S, Gaunson T, Bennett M, Herschtal A, Bellgrove M, et al. A 5-week Digital Intervention to Reduce Attention Problems in Children With ADHD: A Double-Blind Randomized Controlled Trial. J Atten Disord. 2024 Sep;28(11):1454-1466.