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DIGITAL THERAPEUTICS: BRIDGING THE GAP BETWEEN EVIDENCE-BASED SOFTWARE INTERVENTIONS AND CLINICAL PRACTICE—CURRENT APPLICATIONS, REGULATORY LANDSCAPE AND EMERGING TECHNOLOGIES

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ABSTRACT

Digital therapeutics (DTx) are a paradigm shift in the way that healthcare is delivered today, with evidence-based software therapy that delivers a clear therapeutic mechanism of action in measurable disease prevention, management and treatment. This in-depth review pulls together existing evidence regarding digital therapeutics applications in children and adults and reviews their effectiveness in the field of neurodevelopmental disorders, psychiatric disorders, and management of chronic diseases. We systematically reviewed and analyzed RCTs and clinical evidence to show that prescription digital therapeutics have a good safety profile and similar effect sizes as conventional interventions. Both EndeavorRx and Luminopia have created regulatory history as the first FDA-cleared digital therapeutics for attention-deficit/hyperactivity disorder and amblyopia, respectively, with over 60% response rates in the pediatric patient populations. New applications such as AI- based personalization, virtual reality integration and wearable biosensor systems offer revolutionary prospects for scalable, accessible therapeutic delivery. There are still substantial implementation challenges such as complex reimbursement environments, low provider comfort with digital solutions and health

equity gaps that exist among socioeconomic groups. In this review the need for the integrated implementation methods, strong and active post-market surveillance systems and patient-centred design approaches is emphasized, with the aim of getting the transformative potential of digital therapeutics in precision medicine and personalized healthcare delivery.

KEYWORDS: Digital Therapeutics; Evidence-Based Software; FDA-Approved DTx; AI Personalization; Pediatric neurodevelopment.

1. INTRODUCTION

Technology has revolutionized the healthcare system, but access to evidence-based interventions has been limited due to the need for in-person behavioral and specialist consultation. Digital therapeutics was identified as a new therapeutic category that was separate from general wellness apps - a clinical proof-based software-based therapeutic intervention that is delivered through software with a therapeutic mechanism of action that is comparable to that of a pharmaceutical or a behavioral intervention.[1] Prescription digital therapeutics have clinical validation and FDA review processes that are much more stringent than those for consumer health applications, resulting from rigorous clinical validation and therapeutic efficacy by means of randomized controlled trials and real-world evidence generation. The global digital therapeutics market shows exponential growth, with projections of expansion from 4–7 billion in 2023 and reaching more than10.1 billion in 2024, thus the growth trajectory is faster than the independent forecasts.[2] There is a growing and important recognition of unmet healthcare needs; advances in technologies allowing developmentally appropriate intervention; and changing regulatory pathways that offer opportunities for innovation, all of which are fueling the fast-growing pediatric market. This review offers an extensive synthesis of the clinical evidence for digital therapeutics in various therapeutic areas, considers regulatory pathways and issues related to implementation, as well as future opportunities for emerging technologies to transform the delivery of therapeutics in precision medicine.

2. DIGITAL THERAPEUTICS – CLINICAL CLASSIFICATION AND THERAPEUTIC MECHANISMS

Digital therapeutics represent a unique category of health care apps, distinct from fitness and wellness apps because they have been designed using evidence to show therapeutic mechanisms of action. The key difference is the differences in regulatory classification and clinical validation requirements.[3] Digital therapeutics are prescription apps that go through

formal clinical trials and FDA review processes; the timeline for FDA clearance is usually much faster than the timespan of pharmaceutical drug development. The developmental appropriateness demands pediatric DDTs differ from those geared toward adults, requiring age-specific interface design that can address these developmental milestones such as fine motor skill development, attention span, and cognitive maturation trajectories.[4]

Relying on the caregiver's involvement and interfaces that are simplified for younger children, gamified interactive features for school-aged children, and higher levels of autonomy for adolescents while at the same time prioritizing privacy issues and stigma reduction. Particularly caregiver involvement, simplified interfaces for younger children, gamified interactive features for school aged children, and increased autonomy for adolescents, while keeping increasing attention to privacy concerns and stigma reduction. Therapeutic mechanisms are based on adaptive algorithms that adjust the level of difficulty in real time according to the performance of each user, guaranteeing level of difficulty and sustainability of level of engagement and cognitive challenge.[5] Real time biometric monitoring features incorporated into digital platforms allow for ongoing assessment of engagement and in turn allow for real-time therapeutic parameter modification, which would not be possible if it were reliant on external assessments. This ability is a hallmark of its unique difference from traditional therapeutic interventions and provides an objective measure of treatment adherence as well as symptom modification throughout treatment.

3. CLINICAL EVIDENCE OF DIGITAL THERAPEUTICS IN VARIOUS THERAPEUTIC DOMAINS

3.1 Attention-Deficit Hyperactivity Disorder

In this module, the transformation of clinical trial evidence into what works in real-world practice, with a focus on Attention-Deficit Hyperactivity Disorder is addressed.

Attention-deficit/hyperactivity disorder (ADHD) is the most extensively researched disorder in the field of digital therapeutics, with EndeavorRx as the first FDA-approved digital therapeutic for an indication in pediatrics.[5] The intervention was initially FDA approved in June 2020 (DEN200026) for ages 8-12 years with primarily inattentive or combined presentation ADHD and expanded to the ages 8-17 years in December 2023 based on a clinical trial with 162 adolescents.[7] Therapy action uses proprietary algorithms continuously increasing or decreasing the difficulty level according to the performance of the person

receiving therapy to target frontoparietal networks associated with dopamine/norepinephrine dysregulation pathway which plays a role in ADHD.

Randomized controlled trial studies have shown that objective improvements in attention (measured by Test of Variables of Attention) have been found, with a mean improvement of 0.93 compared with 0.03 (P=0.006) in the measured groups (with approximately 0.5 SD effect size improvement). Across a wider age range of children (0–18), and adolescents (18–19) and adults (>19 years), there were significant benefits in TOVA-ACS among children (P=0.014), adolescents (P=0.007) and adults (P<0.001).[8] Excellent levels of treatment engagement are evident from compliance rates, with 83-96% completion rates across trials.[9]

More importantly, there is evidence from randomized controlled trials that there is additional efficacy with the addition of an adjunctive medication. In one study, the digital therapeutic mobile intervention for 30 children with ADHD, Korean ADHD Rating Scale total scores were significantly decreased with the treatment of digital therapeutic mobile intervention and medication (P<0.001), and the scores of attention deficit subscale were also significantly decreased (P=0.001) when compared with medication alone.[10] In the secondary outcome measures using Korean-Child Behavior Checklist, the digital therapeutics adjunctive group showed significant reductions in total behavioral problems (P=0.001), internalizing disorders (P=0.001), and externalizing disorders (P=0.001).[11]

An adverse event profile is indicative of excellent tolerability. The EndeavorRx trials reported no serious adverse events and fewer than 5 percent of participants reported treatment-related adverse events, which were mostly frustration and occasional headache. Most studies of pediatric digital therapeutics report adverse event rates < 10% and no long-term safety concerns are reported from short-term studies available to date.[12] Long-term safety data, however, are limited and long-term cumulative digital exposure effects are especially important on developing neurocognitive systems.[7]

3.2 Autism spectrum disorder: social skills training and behavioral intervention

Specific potential areas for the use of digital therapeutics for autism spectrum disorder include social skills training and enhanced communication skills using gamification and personalisation techniques. Small to moderate effect sizes have been reported in children with ASD for digital interventions focusing on social-emotional skills in systematic reviews and meta-analyses of RCTs.[6] Superpower Glass is another innovative application involving the

use of artificial intelligence based wearable technology that allows real-time facial engagement, emotion recognition with superior performance compared to other classifiers, with 51% improvement.[13]

The data from wearable digital intervention studies show encouraging gains in socialization measures, including large effect sizes on standardized measures of social engagement and adaptive functioning as measured in RCTs.[14] Virtual reality (VR) social cognition training programs have been demonstrated to have positive effects on emotion recognition, conversational skills, and measures of social engagement, but most published literature to date comes from studies with young adults and not children.[15]

3.3 Anxiety disorders and Mood Disturbances: digital cognitive-behavioral therapy

Meta-analyses across a wide range of anxiety disorders in children show medium to large effect sizes for digital cognitive-behavioral therapy interventions, and those studies that include therapeutic guidance, show efficacy. All digital CBT interventions show better results than unguided interventions, with the therapeutic alliance and engagement of the clinician emphasized, even with digital delivery. For adolescents and young adults suffering from depressive symptoms, SparkRx was given emergency use authorization for the COVID-19 pandemic to incorporate cognitive-behavioral, and behavioral activation (CB/BAT), techniques. Digital interventions to prevent experimentation with substances show small, but significant, decreases in alcohol, tobacco and cannabis use among youth populations.[14]

3.4 Chronic disease management: diabetes, asthma, and post intensive care rehabilitation

If look at the clinical effects of type 1 diabetes closed-loop systems, they have been seen to provide a significant benefit. They can enhance time in range by 12% and improve nighttime blood sugar control by 26% over the standard care. Average time in range of 74% was found when evaluating the real-world data of more than 3200 pediatric patients with advanced hybrid closed-loop systems, which is higher than clinical consensus guidelines.[17] However, there are inconsistent data to support the reductions in visits to the emergency department (ED) associated with improved medication adherence provided by a smart inhaler platform for asthma management. Overall, the use of a smart inhaler platform for asthma management has shown improved medication adherence with variance in the reduction of emergency department visits (data inconsistent).

Luminopia One is important landmark innovation for treatment of amblyopia, approved in October 2021 in children ages 4-7 years with FDA clearance expanded to ages 4-12 based on real world evidence in April 2025. In the age group 8-12, the VIEWS clinical trial showed a 62% response rate compared to the control group response rate of 33% (first FDA clearance in this age range in more than 20 years).[18]

4. REGULATORY FRAMEWORK AND FDA-APPROVED DIGITAL THERAPEUTICS LANDSCAPE

In the past, there has been a significant evolution of the regulatory roadmap for digital therapeutics, with precedent set through key FDA approvals. The game-based digital therapeutics device classification was developed by EndeavorRx to require new special controls and clinical data proving safety and effectiveness. This regulatory precedent was the precursor to future 510(k) submissions in other therapeutic areas.[7]

Approval from the FDA, Luminopia signals a changing philosophy with regard to the collection of post-market data and a willingness to give due consideration to real-world evidence for expanding labels. There are several regulatory pathways for approval of digital therapeutics: De Novo classification for novel devices that have little or no predicate, 510(k) pathway for devices that are substantially similar to predicate devices and Post-Market Approval for more high-risk devices.[18] International regulation frameworks show different approaches: In Germany, the Digital Health Applications formulary shows reimbursement pathways for DHAs, however, this does not include specific pathways for those that are intended for paediatrics.

5. CHALLENGES IN IMPLEMENTATION AND BARRIERS IN HEALTH CARE SYSTEM

5.1 Socio-economic inequalities in digital literacy

Implementing digital therapeutics is met with fundamental barriers to access, such as the availability of the technology, including devices and internet connection, as well as digital literacy, especially among disadvantaged groups.[20] COPPA and its requirements for children under 13, not only require verifiable parental consent, but also seek to strike the right balance between parental control and parental rights. The legal requirements generate an administrative burden that is limiting implementation for children.[21]

5.2 Challenge for healthcare provider adoption & integration

Conditions that hinder provider adoption are digital literacy, the lack of obvious paths to integrate digital therapeutics into current clinical workflows, and the lack of a standard protocol for e-prescribing digital therapeutics. Healthcare professionals are excited about digital interventions, although some are still reluctant about placement in conjunction with in-person therapy. Workflow disruption has significant setup, monitoring, and patient care time commitments, a lack of integration with electronic health records, and not clearly defined clinical decision support processes. The successful implementation is supported by training programmes or employing digital champions in healthcare organisations. Technical infrastructure to support a seamless digital therapeutics integration is often not available within healthcare systems and major investment and complete staff training is required.[20]

5.3 Coverage barriers of fragmented reimbursement landscape

Reimbursement is one of the most important hurdles for clinical uptake and use by patients. Payment systems are disjointed, meaning there is no one-size-fits all coverage and access for state Medicaid programs and commercial payers. There is no consensus on adequate evidence thresholds for coverage decisions, and payers differ greatly in their requirements for evidence. Current health economic evaluation methods fail to account for the capability of iterative improvement of digital interventions, requiring new methods of measuring outcomes and a new model for value for money. A few U.S. state Medicaid programs started pilot initiatives to assess feasibility and cost-effectiveness of coverage of digital platforms for ADHD. Several European countries such as Germany and the United Kingdom have initiated the development of digital health formularies with reimbursement pathways, with the inclusion of pediatric products being limited.[19]

6. SAFETY MONITORING AND ADVERSE EVENT SURVEILLANCE

Digital therapeutics have good safety profiles relative to pharmacologic treatments, as they are non-invasive and thus eliminate pharmaceutical side-effects. A detailed evaluation of safety, however, is still necessary during the entire period of intervention. The CT-155 digital therapeutic for schizophrenia negative symptoms has a comprehensive safety monitoring system, such as hospital admission surveillance, crisis support referral tracking and suicidal ideation assessment.[22]

Specific safety issues for children involve developmental appropriateness assessment, monitoring screen time and improving post-market surveillance. Because medications are

still in development and may present long-term, undefined risks or benefits, FDA requires more safety information in children. Worry also goes beyond issues related to adverse events to concerns about the potential neurodevelopmental effects of prolonged digital exposure, data privacy questions for minors, and risk of over-reliance on screen-based interventions. Personalization integration with the use of artificial intelligence still poses ethical implications around algorithmic transparency, bias, and the use and vulnerability of children as user groups. The solutions to these problems involve the cooperation of several parties: regulators, doctors and physicians' ethicists, and patient families.[7]

7. FUTURISTIC INNOVATIONS AND EMERGING TECHNOLOGIES

7.1 Artificial Intelligence-powered personalization

AI integration can facilitate prompt therapeutic adjustments to meet patient needs and developmental level.[13] These algorithms can perform predictive modelling for treatment outcomes, allowing for more flexible choices for treatment intervention and treatment dose optimisation. A multi-modal AI system that merges visual, auditory and behavioural inputs will offer improvements in therapeutic precision. But personalization problems have to do with the fact that people of different ethnicities and socioeconomic backgrounds might not be well represented in the algorithms if they are not generalizable. Using NLP, patients are able to engage in a complex AI dialogue, with sentiment analysis influencing treatment strategies in real time.[23]

7.2 Virtual and augmented reality applications

Virtual reality has great potential in a diverse range of paediatric applications, such as mental health, neurodevelopment and procedural support. Pilot RCTs demonstrate substantial anxiety reduction and tolerance. For those with ASD, there have been improvements in emotion recognition and conversational skills shown through virtual reality social cognition training.[16]

Virtual environments allow for systematic exposure and skills practice, with no consequences in the real world, and especially useful for anxiety-based disorders. Haptic feedback systems can give advanced haptic feedback to the user, which can improve the learning and retention of concepts.[24]

7.3 Continuous health monitoring using wearable devices integration

The advanced development of the biosensors includes surface electromyographic devices for children with movement disorders that are now capable of communicating wirelessly with other equipment, cardiac monitoring integration and developing smart clothing containing sensors. Wearable integration with gaming platforms provides further engagement with games and passive monitoring of activity, sleep and physiological parameters.[24]

Yet, there remain concerns about data privacy arrangements within the purview of children, such as risks of data leakage and regulatory issues surrounding general data protection regulation and children's online privacy protection act. By facilitating digital therapeutic integration, biofeedback and adaptive therapeutic responses are possible in real time through physiological state.[25]

8. IMPLEMENTING EVIDENCE IN REAL-WORLD HEALTH SYSTEMS: IMPLEMENTATION SCIENCE AND EFFECTIVENESS

While the effects of RCTs are good, the reality of clinical outcomes is very different. Implementation science focuses on integration instead of the use of digital therapeutics as a standalone element in complex care pathways. While there was evidence that partnerships occur within schools, there is limited evidence of school integration.[20]

Sustainability is a long-term goal, which needs to be addressed with systematic strategies, overcoming implementation barriers. The value-based care models work well with digital therapeutics implementation, as interventions enable ongoing monitoring and outcomes tracking and facilitate risk-sharing between payers and providers.[19]

9. PSYCHIATRIC APPLICATIONS: DIGITAL THERAPEUTICS FOR SCHIZOPHRENIA NEGATIVE SYMPTOMS

Schizophrenia is one of the most important diseases with unmet treatment needs, especially for the negative symptoms that are unresponsive to existing treatments. Substantial functional impact and burden of negative symptoms, no FDA-approved pharmacotherapy specific for negative symptoms. Negative symptoms are conceptualized as having an affective flattening (flattening of reactions) and/or an experiential (social withdrawal, aminitive, anhedonia) dimension.[26]

In the present antipsychotics, they show some efficacy on the positive symptoms, but have a very modest effect on the negative symptoms leaving many patients with little or no benefit if any at all.[27] Negative symptoms are addressed by psychosocial interventions that focus on altering negative dysfunctional beliefs and defeatist performance attitude.[28] But psychosocial interventions are still time consuming, expensive, and need special clinicians which are not easily available.[27]

Digital therapeutics is a form of nonpharmacologic treatment for schizophrenia that can be delivered via smartphone, is cost effective, supports treatment while waiting for drug approvals and offers anonymity that decreases the stigma associated with seeking treatment.[29] CT-155/BI 3972080 is a digital therapeutic delivered via smartphone that can be used in conjunction with the treatment of antipsychotic medications for psychosocial intervention techniques. In December, 2023, the FDA granted CT-155 breakthrough device designation.[30]

CONVOKE is largest phase 3 RCT study of digital therapeutics for schizophrenia which included a digital control arm compared to CT-155 and was conducted over 16 weeks. Study design is used to minimize placebo effects by using the clinical assessment interview for negative symptoms as a primary outcome, which is measured by centrally trained raters. This is the first digital therapeutics study in schizophrenia negative symptoms using digital control group.

10. PEDIATRIC CONSIDERATIONS AND FAMILY CENTERED APPROACHES

Unlike adult use, pediatric DT implementation must be developmentally sensitive and involve families. Specific design needs are addressed to different age groups, based on differences in motor skills, attention spans, literacy and cultural differences in the design of the audience. Greater levels of safety supervision refer to more dynamic monitoring, straightforward escalation guidelines, and the different rules of professional care and supervision depending on the age and condition of the child. Childhood is a developmental period and the concept of appropriateness should be continually analysed as the child develops and tastes change.[4]

The family dynamics and caregiver involvement also contribute to the complexity of implementation; treatment success often requires parent/guardian involvement and technological skills. Family values and communication styles are significant factors in

treatment acceptance and adherence, making cultural sensitivity an important consideration.[21]

11. ROLE OF HEALTH EQUITY, SOCIOECONOMIC AND GLOBAL IMPLEMENTATION

While digital therapeutics offer a potential way to reach underserved populations and in low-resource settings, they also have the potential to further widen any existing inequalities through technological barriers. The higher concentrations of devices, broadband, and implementation digital literacy are found among high-income populations. The current digital therapeutics literature shows geographic bias with a majority of the studies conducted in the United States, which may not be broadly applicable to low-resource areas where internet access and cultural relevance of game design to digital therapeutics may be a barrier. Ethical issues such as data privacy for minors, and overmedicalisation related to the diagnosis of conditions as cognitive deficits have not been adequately studied.

12. CONSIDERATIONS OF FUTURE RESEARCH

The long-term effectiveness beyond 6-month treatments is not defined, and the current evidence has a short-term randomized controlled trial design. Emerging issues of academic and social functioning need to be measured via cohort studies that are followed over time. Critical research priority is the expansion to understudied populations such as adolescents, adults and people with comorbidities.

Embedding these mechanistic effects on neural circuitry by using neuroimaging approaches, such as functional magnetic resonance imaging, would support the validity of the digital therapeutics through gameplay mechanisms and neurocognitive outcomes. Independent studies outside of industry studies mitigate concerns about commercial bias.

Message sent by the Developer and Clinician should follow a framework of Neurodiversity Affirming Communications which highlights strengths and acknowledge impairments, also ensure that Digital therapeutics have no stigmatisation.

13. CONCLUSION

Digital therapeutics are a game-changer in therapeutic delivery with proof-based therapies that fill in some of the gaps in accessing healthcare and clinical outcomes. There is strong clinical evidence of efficacy in neurodevelopmental, psychiatric and chronic disease

conditions, and FDA-approved treatments like EndeavorRx and Luminopia have set a precedent for FDA regulatory clearance and provided technology proof-of-concept as a valid therapeutic approach. Positive safety and excellent treatment adherence make implementation beneficial as an additional treatment component within a full treatment plan. But significant barriers hinder broad adoption, such as a disjointed reimbursement structure, limited adoption of providers, health equity gaps, and a lack of long-term safety data. Virtual reality, wearable technology and artificial intelligence are poised for massive growth in the applications of digital therapeutics, offering more personalisation and scalability. The transformative potential of digital therapeutics can only be realised with integrated implementation solutions that tackle the barriers within health care systems, patient-centred design strategies that integrate the insights of lived experience, strategies to address the digital divide, and comprehensive post-market surveillance systems. Future research directions include combination treatments combining pharmacologic and digital interventions, long-term efficacy trials of real-world implementation, extending to under-researched populations and conditions, and regulatory reform to foster innovation and ensure safety and security. Finally, adopting the methodologies of co-design, involving many stakeholders in digital therapeutic development, and collecting continuous evidence on clinical effectiveness and the accessibility of digital therapeutics for different groups of people will lead digital therapeutics to become a key part of the precision medicine approach to personalised care.

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