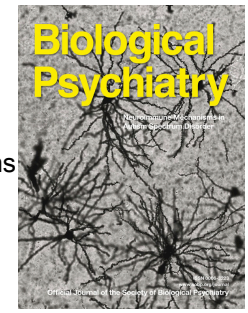

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PII: S0006-3223(24)01430-6

DOI: https://doi.org/10.1016/j.biopsych.2024.06.026

Reference: BPS 15534

To appear in: *Biological Psychiatry*

Received Date: 28 March 2024

Revised Date: 3 June 2024

Accepted Date: 26 June 2024

Please cite this article as: Fulford D., Marsch L.A. & Pratap A., Prescription digital therapeutics: An emerging treatment option for negative symptoms in schizophrenia *Biological Psychiatry* (2024), doi: https://doi.org/10.1016/j.biopsych.2024.06.026.

Prescription digital therapeutics: An emerging treatment option for negative symptoms in schizophrenia

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Invited Paper

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Submitted To: *Biological Psychiatry*, Special Issue: Drug Development for Schizophrenia

Keywords: digital health; mobile health; digital therapeutics; psychosocial treatments; schizophrenia; psychosis

Short title: *Digital Therapeutics in Schizophrenia*

Abstract

Digital therapeutics–web-based programs, smartphone applications, and wearable devices designed to prevent, treat, or manage clinical conditions through software-driven, evidence-based intervention–can provide accessible alternatives and/or may supplement standard care for patients with serious mental illnesses (SMI), including schizophrenia. In this paper we provide a targeted summary of the rapidly growing field of digital therapeutics for schizophrenia and related SMI. We first define digital therapeutics. We then provide a brief summary of the emerging evidence of efficacy of digital therapeutics for improving clinical outcomes, focusing on potential mechanisms of action for addressing some of the most challenging problems, including negative symptoms of psychosis. Our focus on these promising targets for digital therapeutics, including the latest in prescription models in the commercial space, highlights future directions for research and practice in this exciting field.

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Access to recommended psychosocial interventions for psychosis, including cognitive behavioral therapy (CBT) and social skills training, is low, with less than 30% of patients with schizophrenia in the US receiving psychotherapy and less than 7% in the UK receiving CBT (1–3). Furthermore, a severe shortage of psychiatrists in the US is predicted to continue through 2050s (4,5). There is a dire need to increase access to evidence-based therapeutic approaches for supporting patients with schizophrenia, particularly those that address the long-term impacts of negative symptoms on functioning. There are currently no US Food and Drug Administration (FDA)-approved pharmacological treatments specifically for the management of negative symptoms (6). In this review we describe the delivery of digital therapeutics, a promising approach to addressing this high need, with a particular focus on negative symptoms and functioning. We cover existing digital therapeutics and those emerging in the research and commercial landscapes—including those designed under Good Manufacturing Practices for prescription—and conclude with important considerations for implementation in service delivery.

Key Challenges in the Care of Schizophrenia

Although the efficacy of pharmacological treatments for reducing positive symptoms is well-established (7), addressing negative symptoms and associated distal improvements in social and occupational functioning typically requires evidence-based cognitive, behavioral, and supportive therapies to enhance skill development and coping (8,9). Psychosocial interventions, such as social skills training and cognitive behavioral therapy, are effective in enhancing these functioning outcomes (10,11). Yet they are time intensive and can require well-trained providers, limiting their accessibility to many patients.

Negative symptoms pose unique challenges given their significant impact on long-term functioning that is relatively resistant to existing treatments (12–14). Both expressive (e.g., flat affect and alogia) and experiential (e.g., amotivation and anhedonia) negative symptoms are present early on in the illness (15) and tend to persist (16). Negative symptoms directly interfere with the development of important social and occupational skills and sustained execution of goal-directed behavior, limiting effective interpersonal communication and stifling activity planning and completion (17). Over 90% of patients report negative symptoms at initial diagnosis of schizophrenia, and over 70% of patients experience negative symptoms before positive symptoms (18). Seventy-five percent of patients with schizophrenia and 78% of caregivers report that residual negative symptoms are an ongoing concern despite treatment with antipsychotics (19).

A key challenge in treating negative symptoms is that their etiology is often unclear–they can be either ‘primary’ (directly tied to the illness) or produced secondary to experiences related to the illness, like depression, or even resulting from medication side-effects (16). As such, primary and secondary negative symptoms are hard to reliably distinguish, even with standardized assessments (20,21), leading to difficulties in treatment planning and case conceptualization. Research shows negative symptoms have distinct pathophysiological mechanisms compared to depression (21,22). While the DSM-5 criteria for depression include

anhedonia (i.e., one of the negative symptoms), the additional symptoms of depression (e.g., depressed mood, sleep difficulties, suicidality) are not associated with negative symptoms (23). Therefore, antidepressants, which target the pathophysiology of depression, are not suitable for addressing the unmet need of negative symptoms.

Less than half of people with schizophrenia receive any treatment at all, and a small proportion of those receive evidence-based psychosocial intervention (24,25). Inadequate training in the healthcare workforce, few effective models for successful implementation, and limited leadership and financial support all contribute to a low likelihood that patients with schizophrenia access the interventions we know can help improve functioning, such as supported employment and social skills training (26). Furthermore, patient factors, such as low motivation for treatment and trust in providers, as well as cognitive impairments, interfere with engagement in treatment.

Digital Therapeutics: An Emerging Treatment Option

Digital or mobile intervention methods allow for the implementation of evidence-based treatments in naturalistic settings, often at the palm of one's hand. Digital therapeutics is a term used to describe web-based programs, smartphone applications, and wearable devices designed to prevent, treat, or manage clinical conditions through software-driven intervention (27). They are either delivered as stand-alone interventions, where content is designed to provide support without additional human involvement, or as hybrid approaches that incorporate provider or peer support. These methods have high potential to address ongoing challenges in the treatment of schizophrenia, and especially in addressing inadequate approaches to improving negative symptoms and functioning.

Digital therapeutics for mental health conditions are most often delivered through software that provides educational, supportive, or skills-based content that is tailored to the individual needs of the patient, including presenting symptoms, diagnosis, or functional goals. The most common formats for digital mental health interventions are smartphone applications that deliver elements of psychotherapy, including a combination of symptom monitoring, cognitive (e.g., thought challenging) and behavioral (e.g., exposure training) approaches, skill learning, and psychoeducation (i.e., knowledge about mental health conditions and associated triggers). These features are accessed through multimedia content in the mobile applications, often after prompting by 'push' notifications, text messages, or other indicators. Once in the application, users are typically guided through content and/or can elect to focus on specific areas of need, such as symptom reduction, socialization, or psychoeducation material. The period over which patients dedicate time and effort to a digital therapeutic will vary, but existing interventions are often modeled after time-limited psychotherapy approaches, ranging from several weeks to months, depending on the need and treatment goal. Different from traditional face-to-face care, however, is the accessibility of the digital therapeutic across time and location—i.e., there are typically no limits to when and where they can be used. Strategies can also be trained and practiced in these real-world settings, providing opportunities to reinforce skills in daily life. These are important ways in which digital therapeutics differ from other technology-supported treatments, such as telehealth, where clinicians treat conditions remotely but in an otherwise traditional approach.

Over the past 20 years, digital therapeutics have emerged as an innovative approach to addressing unmet needs in mental health care. The combination of increasing ubiquity in internet access and smartphone ownership, as well as increased awareness and acceptance of the importance of mental health care for all, have set the stage for the emergence of digital therapeutics as both an augment to existing approaches and, in milder cases, even an alternative to standard care.

The most common mental health needs addressed by digital therapeutics thus far have included depression, anxiety, insomnia, and substance use (28). They have been applied not only in traditional healthcare settings but also in places of employment and related sectors (e.g., schools). Although larger, well-controlled trials are still needed, the emerging evidence suggests that digital therapeutics are safe, accepted by patients, and effective in reducing symptoms and enhancing well-being (29). Furthermore, in the limited studies conducted to date, there is evidence of cost-effectiveness relative to standard care (30). These endpoints—safety (e.g., lack of adverse events), acceptability, efficacy, and cost-effectiveness—are most commonly used to evaluate the benefits of digital therapeutics relative to existing standards of care.

Prescription digital therapeutics are those that require a prescription and receive labeled claims by health authorities (e.g., the US FDA). These are developed under Good Manufacturing Practice, are rigorously evaluated for safety and effectiveness, and may be eligible for reimbursement by health insurance companies and regional health systems. As such, prescription digital therapeutics have the potential to increase access to evidence-based care for patients with existing insurance coverage and access to a licensed provider, though the extent to which they can increase accessibility remains an area of future work. Prescription digital therapeutics for substance use disorders, trauma-related disorders, attention-related disorders, and panic disorder have been cleared by the FDA (31).

Mechanisms of Action. An important question for all digital therapeutics concerns the mechanism of action–how do these interventions work? Because most digital therapeutics developed to address symptoms and functioning are built from the foundation of existing psychosocial interventions, such as skills training or CBT, it should not be surprising that treatment targets are often either psychological (e.g., changing thoughts, beliefs) or behavioral (e.g., supporting goal attainment) in nature. The common format of digital therapeutics, including interactive content delivered through smartphone applications, implies that improvements in treatment outcomes rely on active engagement from the patient. That is, patients are active players in the intervention itself, and thus mechanisms of action reside at the intersection between access to information (support, knowledge) and associated skill development, which support execution of suggested behavioral changes. For this reason, critical to the development of digital therapeutics is interactive co-design with patients, allowing for seamless integration into daily life.

Behavioral mechanisms of action in digital therapeutics might be influenced by cognitive changes, but they could also be targeted directly, including through basic improvements in physical activity supported by goal setting and scheduling. One example is behavioral activation, a common treatment for depression that has been adapted to address negative symptoms (32). Behavioral activation can enhance positive experiences (and mood) using activity monitoring, values and goals assessment, and scheduling/planning of goal-directed

activity. Psychological mechanisms could involve beliefs or attitudes, or even affect and emotions. Cognitive-behavioral therapies are designed to identify maladaptive thoughts that perpetuate styles of thinking that lead to self-doubt, depression, or experiences of suspiciousness/paranoia.

Neurocognitive mechanisms of action have been identified in digital therapeutics for various psychiatric conditions, including in substance use disorders. In one study, a computer-based cognitive-behavioral intervention led to reduced attention to drug-related cues in a behavioral task, suggesting a strengthening of cognitive control processes associated with substance use (33). Because of the clear impact of cognitive deficits on functional outcome among patients with schizophrenia, cognitive remediation (CR) is a treatment approach developed to directly target neurocognitive processes through both repeated practice and problem-solving support (34). CR has also been tested with remote delivery, typically on personal computers, making it a burgeoning digital therapeutic approach (35).

Biological mechanisms of action are yet to be examined directly in the context of digital therapeutics. However, some studies demonstrate impacts of psychological and cognitive interventions on neural activity, and given the overlap in intervention content, there is reason to believe these mechanisms are relevant for change in digital analogs (36). For example, CR may work by engaging neural targets relevant for cognitive control and executive function. Indeed, evidence suggests changes in these processes in the context of CR are associated with improvements in prefrontal cortical (PFC) efficiency (37). Recent studies have also shown changes in the neural correlates of anxiety and trauma disorders in the context of CBT (38,39). In one study following patients with schizophrenia after completion of 6 months of CBT for psychosis (CBTp), psychotic symptoms measured over several years were predicted by changes in PFC connections during a facial affective processing task (40). Greater increases in dorsolateral PFC-amygdala connectivity following CBTp were associated with better self-rated recovery at long-term follow-up. Of note, these studies included small samples, and changes in neural activity do not necessarily equate to associated changes in behavior, which are often most relevant for interventions designed to improve meaningful outcomes, such as functioning.

Digital Therapeutics in Schizophrenia

Given characteristic challenges with both access to evidence-based interventions and the unmet need for treatments that directly target negative symptoms and functional impairment, digital therapeutics have high potential to improve outcomes among patients with schizophrenia. Although differences in digital literacy are a valid concern (41), the majority of people with a serious mental illness (60-90%) report owning a smartphone and are willing to use it to help manage their mental healthcare (42,43). Furthermore, although engagement varies as a function of numerous factors, trials to date have demonstrated that patients with schizophrenia actively participate in digital therapeutics (44). There is also increasing attention being paid to directly supporting digital literacy and technology-based communication skills in schizophrenia (45,46). The confluence of increasing use of mobile technologies and translation of evidence-based approaches to digital formats has provided an opportunity to enhance the care of patients who are typically failed by traditional mental health care systems.

Over the past decade, several digital therapeutics have been developed and tested in schizophrenia. Although each intervention has unique elements in design and target outcomes, most involve some combination of behavioral and cognitive treatment approaches. The key symptom domains targeted are positive and negative symptoms, with a handful of therapeutics designed to enhance psychosocial functioning outcomes more directly. Most of these approaches have also been designed as hybrid interventions, tested along ongoing, standard care, including medication management and supportive psychotherapy.

Digital Therapeutics for the Positive Symptoms. Digital therapeutics that incorporate elements of CBT have been designed to address positive symptoms, including hallucinations and delusions. For example, the Coping with Voices web-based program was designed to provide patients the skills necessary to identify and challenge patterns of thinking that contribute to distress associated with auditory hallucinations, consistent with cognitive-behavioral models of psychosis. In an open label pilot trial, the program was successful in reducing auditory hallucinations and associated distress (47), and in a subsequent RCT, improvements in social functioning relative to usual care were evident (48).

Although there are other examples of web-based programs designed to reduce symptoms of psychosis, the majority of digital therapeutics developed to date are smartphone applications, with content delivered via push notifications in the context of daily life. Actissist is a smartphone application designed to address maladaptive cognitions in early psychosis. Rooted in the cognitive model of psychosis, application content is geared toward addressing auditory hallucinations, paranoia, and other related experiences (e.g., perceived criticism). The purported mechanism of action is the focus on identification of unhelpful appraisals of psychosis-related experiences, providing alternative coping strategies in daily life. In a small RCT, patients with early psychosis assigned to Actissist showed greater improvements in positive, negative, and general symptoms relative to a symptom monitoring group (49).

Another digital therapeutic, CBT2go, combined one in-person session of CBT with automated thought challenging/adaptive behavior delivered through smartphones. Intervention content includes real-time thought challenging that is individualized to the specific symptoms or defeatist beliefs that patients endorsed at the initial session. The purported mechanism of action of CBT2go was the generic cognitive model, which suggests that maladaptive thoughts can be challenged through behavioral experiments, examining evidence for these thoughts, and correcting mistakes in thinking. In a 12-week RCT, defeatist beliefs decreased more in the CBT2go condition relative to a self-monitoring control, though changes in psychosis symptoms were no different in these groups versus usual care (50).

Digital Therapeutics for the Negative Symptoms of Psychosis. Given the benefit of psychosocial interventions for addressing negative symptoms of psychosis, emerging digital therapeutics have been developed to target these symptoms directly using CBT and similar approaches. Early studies included text messaging interventions, such as Mobile Assessment and Treatment of Schizophrenia (MATS), which targeted defeatist attitudes using thought challenging (51). Of note, lower engagement with MATS was documented among patients with more severe negative symptoms. In CBT2go, mentioned above, patients with schizophrenia who had moderate to severe persistent experiential negative symptoms (i.e., anhedonia and

amotivation), defeatist attitudes and experiential negative symptoms decreased significantly over 18 weeks (52). Two other digital therapeutics were developed to address motivational impairment as a key negative symptom of psychosis. These interventions targeted deficits in the translation of anticipatory pleasure to effort-based decision-making and associated goal attainment. PRIME, a smartphone application for patients with early psychosis, demonstrated impact on self-reported motivation and pleasure deficits in a small randomized trial with a treatment as usual comparison group(53). Mobile Enhancement of Motivation in Schizophrenia (MEMS) was an intervention that used text messages to target effort-based decision-making and related mechanisms of impaired motivation in schizophrenia. In a controlled trial among patients with at least moderate motivation deficits, those in the MEMS condition demonstrated greater improvements in interviewer-rated motivation and anticipatory pleasure, and attained significantly more recovery-oriented goals at eight weeks, relative to controls(54).

In sum, several digital therapeutics designed to address negative symptoms of psychosis have demonstrated benefits in these impairments relative to control conditions. Of note, however, is that while participants in two of these trials were recruited based on their levels of experiential negative symptoms, and reductions in motivation deficits were shown, distinctions between patients with primary versus secondary negative symptoms were not documented. As such, it remains unclear whether these benefits are specific to one type of clinical presentation or generalize across negative symptom presentations.

Digital Therapeutics for Functioning in Schizophrenia. Some digital therapeutics have been designed to directly target functional outcomes. FOCUS is a smartphone application designed to address myriad facets associated with psychosis, including not only symptoms and associated distress, but also functioning (55). In comparison with an in-person, recovery-oriented intervention, FOCUS demonstrated comparable impacts on recovery and quality-of-life (56). The Motivation and Skills Support (MASS) smartphone application focuses on supporting social goal attainment via social skills and social motivation training (57). The development of MASS was grounded in models of social motivation(58), targeting impairments in the integration of anticipatory social pleasure with goal-directed behavior as a key mechanism of action. At an initial session, patients select among a list of social goals, including getting to know an acquaintance better, or improving communication with a family member. MASS content is then personalized to each patient's goal, whose completion is facilitated by social skills training content (video demonstrations and skill reminders), as well as statements of encouragement and validation, designed to increase social motivation. In an open pilot trial of MASS in patients with schizophrenia, significant improvements in self-reported social functioning were documented over the 60-day intervention period, though these improvements did not maintain at the 3-month follow-up (57).

Future directions

Digital Therapeutics in progress. Built from the foundation of emerging clinical research conducted in the university setting, there are some promising digital therapeutics for schizophrenia developed and tested in the commercial space. Pear Therapeutics developed PEAR-004, a digital therapeutic that includes cognitive restructuring, self-management, and

social skills training. In a RCT sponsored by Novartis Pharmaceuticals, 112 patients with schizophrenia were randomized to either PEAR-004 or a digital sham condition (59). Although both groups demonstrated small decreases in positive symptoms after 12 weeks, there was no benefit of PEAR-004 over the sham. The authors attributed lack of differential treatment response to unanticipated benefits of the sham control condition, which they state may have served to distract patients from distressing symptoms, as alluded to by patients in post-treatment interviews. It is possible that patients benefited less from the intervention than they could have due to limited understanding or active engagement with intervention content. It is also unclear what specific mechanisms of action were targeted with PEAR-004, limiting understanding of potential reasons for limited differential efficacy.

CT-155 is a new experimental digital therapeutic currently being developed by Click Therapeutics and Boehringer Ingelheim. CT-155 combines multiple neurobehavioral and psychotherapeutic techniques to target a validated, mechanistic 'psychosocial model of negative symptoms' in schizophrenia(60,61). Individual components of CT-155 were designed to incorporate principles of evidence-based, in-person psychosocial therapy to target experiential negative symptoms. The data from early clinical learning studies have demonstrated the feasibility and efficacy of this experimental treatment for negative symptoms (62). Patient feedback has been integral in the development and refinement of the CT-155 digital therapeutic. The efficacy and safety of two experimental digital therapeutics are currently being evaluated in a RCT (62).

Incorporating advanced technologies. Given the exponential growth of handheld technology (see Moore's Law), the opportunities to enhance delivery of mental health care through digital therapeutics are immense. One such approach receiving recent attention involves the use of passive sensing technology, such as smartphone-based location and movement detection, or application usage data (63,64). These passive streams of data provide opportunities to gather important contextual information on patients' daily lives, ultimately informing our understanding of how psychopathology manifests and enhancing measurement-based care. Artificial intelligence (AI) can also advance the content of digital therapeutics, for example through the use of natural language processing, an approach to automation of text data that can be used to predict clinical states (65,66). And generative AI may enable a dynamic, personalized interface to digital therapeutics that can be responsive to a given individual's needs in real time.

The proliferation of these technologies ultimately contributes to optimism regarding the promise of personalized medicine approaches, and in the case of digital therapeutics, the opportunity to deliver Just-in-Time Adaptive Interventions (JITAIs) (67). JITAIs are the future of digital therapeutics, capitalizing fully on the true potential of mobile technologies for supporting patients when they need it most.

Considerations for Implementation of Digital Therapeutics

Digital therapeutics may also enhance the scope and impact of mental health care systems. These tools may provide additional resources in mental health care systems to complement pharmacotherapies, potentially offering synergistic effects. And they can offer

important psychosocial interventions that are not routinely offered in systems of care and/or not offered in ways that reflect the most potent and personalized care. They can function as "clinician-extenders", offering patient-centered, evidence-based therapeutic support 24/7 in people's daily lives.

Understanding how to optimally deploy digital therapeutics to patients with schizophrenia to have the greatest reach and impact is an important and timely area for research (68). This includes how to best identify patients who may benefit from a digital therapeutic, how to best introduce these tools to patients as part of the clinical workflow, and how to support continued engagement. For example, once a digital therapeutic is prescribed, the care team will need to monitor ongoing use, help troubleshoot technical challenges, and ensure integration of therapeutic content with existing care. Given the multidisciplinary teams often engaged in systems of mental health care, these tasks could be championed by an occupational therapist, a case manager, a peer support specialist, or a digital health navigator, among others in the care team. In addition, understanding the extent to which digital therapeutics can be combined with existing pharmaceutical interventions, including standard and more novel compounds, is an important area of work to determine optimal outcomes.

Another key consideration is how to best engage persons with schizophrenia to use and derive value from digital therapeutics. Patients presenting with significant negative symptoms, in particular, may have difficulty engaging with a digital therapeutic that requires active participation and initiative, given reduced drive and motivation, as well as associated cognitive impairments (41). This may be particularly true when digital therapeutics are tested in more "real-world", less controlled treatment settings. At the same time, there may be benefits to digital therapeutics for these patients, given the ability to access them at all times and in virtually any setting, reducing the barriers associated with traditional treatments. Co-designing these tools with the target population to ensure value and direct relevance is key. And creating tools that embrace a navigational flow and functionality that is useful to and usable by end users, and is responsive to their motivational/cognitive challenges and digital health literacy (e.g., linear navigational flow; "push" notifications and micro-rewards provided within the software to prompt engagement), is critical (69).

A further consideration relates to what data should be collected and shared, and with whom. Data collected in digital therapeutics, such as patient tracking of symptoms and functioning, may be useful feedback to patients. For example, these data may provide novel behavioral insights about a given patient's clinical trajectory over time and guide a patient's use of therapeutic tools that may be most responsive to their needs. Some of these data may also provide actionable information to providers. It may be useful to evaluate flexible models of deployment in which patient preference can help drive how digital health data may be shared within their clinical support network.

Conclusions

Digital therapeutics provide a timely opportunity to increase access to evidence-based treatment approaches for patients with schizophrenia. Our brief summary included the emerging evidence of efficacy for improving negative symptoms and other hard to treat outcomes, with a focus on promising mechanisms of action that can be further explored in research and practice.

Future considerations, such as the expansion of mobile technologies and the challenges inherent in widespread implementation, will set forth a productive clinical research agenda that ultimately will serve to improve the lives of patients with schizophrenia.

Acknowledgement

DF is supported by NIH grants R01MH125426, R01MH127265, R21MH124095, R01MH122367, and P01AA029546. LAM is supported by NIH grants P30DA029926, UG1DA040309**,** U01DA047982, UG1DA013035-18S6, R21DA057535, UG1DA040316-S, and T32DA037202.

Financial Disclosures

DF reports consulting fees from Click Therapeutics and Boehringer Ingelheim.

LAM reports co-ownership of Square2 Systems, Inc. and consulting fees from Click Therapeutics and Boehringer Ingelheim. These relationships are extensively managed by LAM's employer, Dartmouth College.

AP is employee by Boehringer Ingelheim.

The authors did not receive consulting fees for the preparation of this manuscript.

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