

Prescription Digital Therapeutics: An Emerging Treatment Option for Negative Symptoms in Schizophrenia

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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, including schizophrenia. In this article, we provide a targeted summary of the rapidly growing field of digital therapeutics for schizophrenia and related serious mental illnesses. First, we define digital therapeutics. Then, we provide a brief summary of the emerging evidence of the 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 <30% of patients with schizophrenia in the United States receiving psychotherapy and <7% in the United Kingdom receiving CBT (1–3). Furthermore, a severe shortage of psychiatrists in the United States is predicted to continue through the 2050s (4,5). There is a dire need to increase access to evidence-based therapeutic approaches for supporting patients with schizophrenia, particularly approaches that address the long-term impacts of negative symptoms on functioning. There are currently no U.S. Food and Drug Administration–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 important 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 for prescription designed under Good Manufacturing Practices, 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 CBT, are

effective at enhancing these functioning outcomes (10,11). However, 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, which 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 during the course of 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, thereby limiting effective interpersonal communication and stifling activity planning and completion (17). Over 90% of patients report negative symptoms at the time of their 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 primary (directly tied to the illness), produced secondary to experiences related to the illness, such as depression, or even result from medication side effects (16). Therefore, primary and secondary negative symptoms are hard to distinguish reliably even with standardized assessments (20,21), which leads to difficulties in treatment planning and case conceptualization. Research shows that negative symptoms have pathophysiological mechanisms distinct from those of 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 health care workforce, few effective models for successful implementation, and limited leadership and financial support all contribute to a low likelihood that patients with schizophrenia will access the interventions that 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 great potential to address ongoing challenges in the treatment of schizophrenia, 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 skill-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 they have accessed 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. However, the accessibility of digital therapeutics across time and location is different from traditional face-to-face care, 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, which provides 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 using an otherwise traditional approach.

Over the past 20 years, digital therapeutics has emerged as an innovative approach to addressing unmet needs in mental health care. The combination of the increasing ubiquity of 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 a supplement meant to augment existing approaches and, in milder cases, even an alternative to standard care.

To date, the most common mental health needs that have been addressed by digital therapeutics have included depression, anxiety, insomnia, and substance use (28). They have been applied not only in traditional health care 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 at reducing symptoms and enhancing well-being (29). Furthermore, in the limited number of studies conducted to date, there is evidence of cost-effectiveness relative to standard care (30). These end points—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 U.S. Food and Drug Administration). These are developed under Good Manufacturing Practices, are rigorously evaluated for safety and effectiveness, and may be eligible for reimbursement by health insurance companies and regional health systems. Therefore, 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, although the extent to which they can increase accessibility remains an area for future work. Prescription digital therapeutics for substance use disorders, trauma-related disorders, attention-related disorders, and panic disorder have been cleared by the U.S. Food and Drug Administration (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 were 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 together support execution of suggested behavioral changes. For this reason, interactive co-design with patients is critical to the development of digital therapeutics, allowing for seamless integration into daily life.

Behavioral mechanisms of action in digital therapeutics may 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 of this 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. CBTs 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 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).

To date, biological mechanisms of action have not been examined directly in the context of digital therapeutics. However, some studies have demonstrated impacts of psychological and cognitive interventions on neural activity, and given the overlap in intervention content, there is reason to believe that 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. Evidence suggests that changes in these processes in the context of CR are associated with improvements in prefrontal cortical 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 that followed patients with schizophrenia after completion of 6 months of CBT for psychosis, psychotic symptoms measured over several years were predicted by changes in prefrontal cortical connections during a facial affective processing task (40). Greater increases in dorsolateral prefrontal cortex-amygdala connectivity following CBT for psychosis were associated with better self-rated recovery at long-term follow-up. Notably, 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 has great potential to improve outcomes among patients with schizophrenia. Although differences in digital literacy are a valid concern (41), most people with a serious mental illness (60%–90%) report owning a smartphone and are willing to use it to help manage their mental health care (42,43). Furthermore, although engagement varies as a function of numerous factors, trials reported 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 several therapeutics designed to enhance psychosocial functioning outcomes more directly. Most of these approaches have also been designed as hybrid interventions, tested alongside ongoing, standard care, including medication management and supportive psychotherapy.

Digital Therapeutics for 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 with 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 randomized controlled trial (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, most digital therapeutics developed to date are smartphone applications, with content being 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, the 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 and 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 than 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 is 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 than in a self-monitoring control condition, although changes in psychosis symptoms were no different in these groups versus usual care (50).

Digital Therapeutics for Negative Symptoms

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, which targeted defeatist attitudes using thought challenging (51). Notably, lower engagement with Mobile Assessment and Treatment of Schizophrenia was documented among patients with more severe negative symptoms. In CBT2go (mentioned above), defeatist attitudes and experiential negative symptoms decreased significantly over an 18-week period in patients with schizophrenia who had moderate to severe persistent experiential negative symptoms (i.e., anhedonia and amotivation) (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 an 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 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 Mobile Enhancement of Motivation in Schizophrenia condition demonstrated greater improvements in interviewer-rated motivation and anticipatory pleasure and attained significantly more recovery-oriented goals at 8 weeks than those in the control condition (54).

In sum, several digital therapeutics designed to address negative symptoms of psychosis have demonstrated benefits in these impairments relative to control conditions. It is notable, however, that while participants in 2 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. Therefore, it remains unclear whether these benefits are specific to one type

of clinical presentation or generalize across negative symptom presentations.

Digital Therapeutics for Functioning

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). Compared 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 from 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, the completion of which 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, although these improvements were not maintained 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 that have been 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 an 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 condition. The authors attributed the lack of differential treatment response to unanticipated benefits of the sham control condition, which they stated might have served to distract patients from distressing symptoms, as alluded to by patients in posttreatment 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 by PEAR-004, which limits 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 2 experimental digital therapeutics are currently being evaluated in an 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 that has received attention recently 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 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). In addition, generative artificial intelligence 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 (67). Just-in-time adaptive interventions 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. They can also 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 in people's daily lives 24 hours a day, 7 days a week.

Understanding how to optimally deploy digital therapeutics with patients with schizophrenia so as 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 has been 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 on 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 people with schizophrenia to use and derive value from digital therapeutics. Patients who present 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, which reduces some of the barriers associated with traditional treatments. Co-designing these tools with the target population to ensure value and direct relevance is key. Additionally, 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 microrewards provided within the software to prompt engagement) is critical (69).

A further consideration is related 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 for patients. For example, such 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 preferences 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. The current review included the emerging evidence of efficacy for improving negative symptoms and other difficult-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 will ultimately serve to improve the lives of patients with schizophrenia.

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Digital Therapeutics in Schizophrenia

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