






The Promise of Digital Health Interventions for Addressing Loneliness in Serious Mental Illness

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Abstract

Purpose of review People living with serious mental illness (SMI) experience high rates of loneliness, though few evidence-based psychosocial treatments directly target this experience. Mobile and web-based digital health interventions offer unique opportunities to translate psychosocial treatments to address loneliness in daily life.

Recent findings In this paper, we review the common types of psychosocial treatments aimed at addressing loneliness in the general population (social skills training, social prescribing, and cognitive-based therapies), their efficacy, and their ability to address the specific concerns of those living with SMI. We highlight three recent cognitive-based digital interventions (Nod, Connect+, and Horyzons) that show promise for addressing loneliness in people with SMI.

Summary We argue for the adaptation of cognitive therapeutic approaches for addressing loneliness and discuss future innovations that can capitalize on the promise of mobile technologies for addressing loneliness in SMI. Furthermore, we discuss how these digital innovations will allow us to create more individualized therapies.

Introduction

Loneliness—the subjective experience of social disconnection—is a pervasive difficulty for people living with serious mental illness (SMI) [1•]. People with SMI are twice as likely to experience loneliness compared to the general population and often cite improved social relationships as a top treatment goal [1•, 2, 3]. Given that loneliness is a significant contributor to cardiometabolic disease and early mortality [4], and people with SMI die on average 15–20 years younger than the general population, addressing loneliness is a top priority for improving both the quality and quantity of life for those living with these conditions [5].

Despite the clear need for interventions to address loneliness in people with SMI, evidence on the efficacy of these interventions in this population is limited [1•]. One half of people with SMI in the USA do not receive evidence-based mental health treatment [6, 7]. Lack of clinician training, diminished resources, and avoidance of treatment due to stigma surrounding both mental health issues and loneliness limit people with SMI from accessing treatment. There is also substantial heterogeneity in the contributors to loneliness among people living with SMI, including other social difficulties such as paranoia or social skills deficits, that may influence a person's social experiences. Outside of psychiatric presentation, one's sociocultural environment (e.g., urban or rural) and context (e.g., living alone or married) can have a large influence on potential treatment targets. Thus, adequately tailoring interventions for loneliness in people with SMI presents unique challenges. It is critical to target the myriad risk factors, triggers, and socioenvironmental characteristics unique to people living with SMI.

Digital innovations in mobile health (mHealth) and web-based treatments offer promise in providing personalized approaches to address loneliness for people with SMI. Digital mental health interventions (or digital therapeutics) are generally acceptable, scalable, and can provide personalized means to address psychosocial functioning

and community engagement among people living with SMI [8, 9]. Indeed, rates of smartphone usage by people with SMI are similar to those of the general population, with one study showing that approximately 86% of people with SMI own a smartphone [10]. Ownership of smartphones with internet connectivity is more variable (e.g., 20–80%) [11, 12], reflecting differences in access based on age and socioeconomic status [13]. Nonetheless, sufficient rates of use suggest opportunities for increased access to evidence-based supports.

For example, our team developed the Motivation and Skills Support (MASS) smartphone app to improve social goal attainment and social skills for people with schizophrenia [14, 15••]. Over a 60-day open pilot, participants showed low attrition, high engagement, and improved social functioning from baseline to treatment termination [15••]. Another recent example of a digital therapeutic for social functioning in SMI is the Schizophrenia Mobile Assessment and RealTime Feedback App (SMARTapp). In a pre-post open trial of the app over 21 days, participants demonstrated high adherence, consistent completion of surveys, and reported that the app was easy to use and appealing [16]. Despite these promising outcomes for addressing social functioning broadly in SMI using digital therapeutics, loneliness was not directly assessed. As research on digital interventions for people living with SMI continues to grow, we argue for the importance of including loneliness as a primary intervention target. In this paper, we briefly summarize the literature on evidence-based psychosocial treatments for addressing loneliness in the general population, discuss specific types of loneliness interventions that can be tailored to digital platforms, and highlight three examples of promising digital health interventions for addressing loneliness in people with SMI. We will conclude with future directions for researchers to consider in adapting loneliness interventions to the digital medium for people living with SMI.

Evidence-based psychosocial interventions for loneliness

The most consistently studied types of interventions that address loneliness in the general population include (a) social skills training (SST), (b) social prescribing (e.g., “befriending”), and (c) cognitive-based therapy. SST focuses

on building conversation skills (e.g., active listening, appropriate eye contact) and reading of nonverbal social cues (e.g., affective expression, vocal tone). The goal of SST is to improve one's social skills to the extent that one can feel more confident and capable at making and maintaining social relationships, thus addressing loneliness through promoting more frequent and satisfying social interactions. Social prescribing aims to facilitate opportunities for social engagement through befriending (i.e., an individual is matched with someone else in the community who is meant to provide social support) or shared experiences (e.g., group programs where people engage in new activities together). Again, it is thought that through promoting more opportunities for positive social experiences and decreasing social isolation, participants will feel less lonely. Cognitive-based interventions typically follow principles of traditional cognitive-behavioral therapy (CBT) (e.g., cognitive restructuring, behavioral testing) to target negative social beliefs. Cognitive interventions can help address negative biases about the self (e.g., "I am too boring for anyone to like me") and others (e.g., "People probably just want to make fun of me"), which are often theorized as mechanisms through which loneliness occurs and maintains itself [17, 18]. Cognitive interventions may also include mindfulness-based practices and/or principles of positive psychology, where participants practice skills meant to promote positive affect, including engaging in pleasant social experiences [19].

Recent reviews of randomized controlled trials (RCTs) of loneliness interventions in the general population show low to moderate effects, though there is substantial heterogeneity in the types of interventions studied. Masi and colleagues conducted a meta-analysis to examine the efficacy of loneliness interventions across single group pre-post designs, non-randomized group comparison designs, and RCTs [20]. Within RCTs, they found a small yet significant effect size for psychosocial interventions in reducing loneliness (20 studies, Hedge's $g=0.20$) [20]. This meta-analysis was the only one that directly compared cognitive-based interventions, social prescribing, and SST interventions. Although there were no differences in intervention type across the non-randomized designs, the researchers found within RCTs that cognitive interventions (4 studies; Hedge's $g=0.60$) produced a significantly larger effect size compared to social prescribing interventions—including studies they identified as those meant to "enhance social support" (12 studies, Hedge's $g=0.16$) or improve opportunities for social interactions (2 studies, Hedge's $g=0.06$)—or SST interventions (2 studies, Hedge's $g=0.02$) [20].

Two other meta-analyses found moderate effect sizes of psychosocial interventions for loneliness. Hickin and colleagues found a moderate effect of a broad array of psychotherapies to address loneliness across 28 RCTs (Hedge's $g=0.43$) [21], including CBT (9 studies), integrative therapy (6 studies), mindfulness-based therapy (3 studies), SST (3 studies), and a handful of additional interventions (e.g., interpersonal therapy, social identity intervention, reminiscence-based therapy) [21]. They did not find any differences in efficacy across therapy types. Eccles and Qualter examined 25 RCTs of loneliness interventions for young people and also found a moderate effect size (Hedge's $g=0.32$) [22]. In this analysis, cognitive therapy was not differentiated from other types of therapy: studies were identified as those focused

on social skills (5 studies), social and emotional support (7 studies), just social support (4 studies), psychological therapy (8 studies), and learning a new hobby (2 studies) [22]. There were no differences in intervention type in addressing loneliness.

SST, social prescribing, and cognitive interventions have also been examined in people with SMI to target psychosocial functioning. Social prescribing treatments, including befriending, peer-support, and social activity programs, consistently show less efficacy than SST and cognitive therapies in improving functioning [23, 24]. RCTs of SST in people with schizophrenia show moderate improvement in psychosocial functioning and performance-based measures of social and living skills [25], and more effectively reduces general psychopathology and negative symptoms, compared to control conditions (e.g., treatment as usual) [25]. Similarly, cognitive interventions such as CBT for psychosis effectively improve psychosocial functioning, positive and negative symptoms, mood, and social anxiety in people with schizophrenia [26]. Overall, all three intervention types show some efficacy in addressing psychosocial functioning and symptoms for people with SMI. While there have been recent promising open pilots that directly address loneliness through other intervention types (e.g., group choral singing) [25], loneliness is rarely (if ever) assessed in SST, social prescribing, and cognitive-based interventions for people with SMI.

Overall, psychosocial interventions in the general population show moderate efficacy in reducing loneliness. It is difficult to directly compare different types of interventions given the limited number of studies of each approach; however, when directly compared, cognitive-based interventions appear to show increased efficacy compared to other intervention types. Theoretically, cognitive approaches may be one of the only types of interventions that directly address the potential maintaining mechanisms of loneliness—namely, the subjective experience of social connection. While SST and social prescribing focus on increasing opportunities for social interactions, which may help reduce isolation, cognitive interventions directly target experiences such as negatively biased interpretations of social interactions, which may more effectively target loneliness. The primary approaches to addressing loneliness in the general population—SST, social prescribing, and cognitive interventions—are effective at improving psychosocial functioning broadly in SMI, but effects on loneliness specifically have not been examined.

Adapting evidence-based interventions to address loneliness in SMI

Cognitive interventions appear to show the most promise for addressing loneliness in SMI. These interventions may more directly target loneliness through their focus on subjective experience of social disconnection, when compared to SST and social prescribing interventions [20]. CBT, for example, can help identify and replace negative social beliefs through strategies such as cognitive restructuring, which may in turn help reduce loneliness.

Additionally, positive psychology interventions can help generate pleasant emotions related to one's thoughts of other people without needing to be in the physical presence of others. In SMI, CBT is effective in addressing loneliness-adjacent psychiatric concerns, including social anxiety and negative symptoms [20]. Loneliness has robust associations with negative beliefs common for people living with SMI, including defeatist attitudes (i.e., overly generalized negative thoughts about our own abilities), self-stigma, paranoia, and social anxiety, all concerns that have been addressed through cognitive therapy [29–31]. Finally, cognitive-based treatments have already been leveraged to address other concerns in psychosis, suggesting the feasibility to tailor such interventions to directly address loneliness in this population [32].

Digital interventions for addressing loneliness: promising applications for SMI

Only recently have digital interventions been developed to address loneliness. Here, we briefly summarize three recent mHealth interventions that illustrate the advantages of cognitive-based interventions to address loneliness (see Table 1). We focus on preliminary outcomes of these interventions and discuss their promise for addressing loneliness among those with SMI.

Nod is a mobile app that was designed to target loneliness in nonclinical college students through integrating positive psychology and CBT principles [33••]. Participants are provided “social challenges” through the app, where they are encouraged to engage in behaviors meant to help initiate and strengthen the quality of their social connections (e.g., “Invite someone to have lunch with you in the dining hall”). Following these prescribed social activities, Nod assesses the student's current emotion and uses this report to choose a relevant reflection exercise. For example, if a student reports negative emotion, Nod will guide the student through an exercise to reappraise their negative beliefs. Alternatively, if the student reports a positive emotion, Nod will guide the student through a savoring exercise to help maintain positive thoughts about the experience. One-hundred participants assigned to use Nod did not differ in loneliness from 121 wait-list control participants after 4 weeks. However, greater depression at baseline was associated with higher loneliness in control participants at treatment termination; there was no relationship in the Nod group, suggesting the interventions may have protected against higher loneliness for those with greater baseline depression.

Nod demonstrates the benefits of several features that can easily be adapted for people living with SMI. The social challenges were contextually relevant to participants' surroundings (i.e., a college campus). Such challenges could easily be tailored to different environments (e.g., a residential home, an apartment complex), or populations (e.g., following a first episode of psychosis, students returning to college after an psychiatric hospitalization). Treatment components could also be broken down into smaller steps for people with SMI, who may experience other barriers to completing the challenges (e.g., motivational or cognitive difficulties). For example, though

Table 1. Digital therapeutics for loneliness

Name	Intervention content	Target population	Key findings
Nod	<ul style="list-style-type: none"> - Social challenges - Cognitive-based reflection exercises 	First year college students	<ul style="list-style-type: none"> - Loneliness outcomes did not differ from waitlist control participants after 4 weeks - Higher baseline depression associated with greater loneliness at termination in controls, but not in the intervention group
+Connect	<ul style="list-style-type: none"> - Text- and video-delivered content - Practice exercises - Gamified true/false questions 	Young people with first-episode psychosis	<ul style="list-style-type: none"> - High rates of enjoyability, acceptability, satisfaction, and usability after 6 weeks - Reductions in loneliness at post-intervention (6 weeks) and 3-month follow-up
Horyzons	<ul style="list-style-type: none"> - Online monitoring by clinician moderators - Goal-setting - Personalized messages - Psychoeducation - Online community 	Young people with first-episode psychosis	<ul style="list-style-type: none"> - Reductions in loneliness from baseline to mid-treatment (after 6 weeks) - No differences post-treatment

our team was not directly targeting loneliness, our MASS app for people with schizophrenia included person-specific social goals (e.g., make a new friend by going to events that interest you) and broke those goals down into smaller, more achievable steps (e.g., identify an event that interests you, remind yourself about the event), which users found helpful [14, 15••]. Additionally, Nod's options for cognitive-based reflection exercises that depended on the student's reported affect and behavior offered a dynamic, yet simple means of personalizing content. Drawing from the student's momentary state allowed Nod to optimize the treatment in-the-moment. People with SMI can also engage in similar automated reflection exercises. If necessary, some participants may also benefit from a clinician guiding them through the exercise virtually, and/or the app could be tailored to send a message to the participant's clinician regarding the exercises the participant was assigned in a given week.

+ Connect is a mobile app designed with and for people living with psychosis to address loneliness [34••]. + Connect delivers content emphasizing positive psychology concepts such as identifying personal strengths, performing acts of kindness, and expressing gratitude. Importantly, + Connect focuses on improving the quality of existing relationships, as opposed to just creating new ones. App content was delivered through videos and written content posts. Videos included shared experience videos featuring young people with lived experience of psychosis, expert videos from academics, and actor videos where actors modeled a range of behaviors. Following delivery of the content, users were prompted to engage in an exercise to practice app content (e.g., "Name three good things"). An additional feature of + Connect was true/false questions related to video content. This feature was gamified through points, challenges, and badges to encourage sustained engagement. In an open trial of 12 young adults with a psychotic disorder, participants reported high rates of enjoyability, acceptability, satisfaction, and usability after using the app for 6 weeks. Self-reported loneliness was lower at both post-intervention (after 6 weeks) and 3-month follow-up. Additionally, 8 of the 12 participants continued to use the app 3 months post-intervention.

+ Connect has many strengths for addressing loneliness in people with SMI. Importantly, the app underwent 2 years of trial testing where young people with and without mental illness provided input through focus groups. By co-designing interventions with people living with SMI, researchers can more readily address potential barriers (e.g., cognitive difficulties) early in development that may be unique to their specific population. Co-design also allows users to be active participants in their treatment, providing agency to a group that has frequently been marginalized in and out of health care settings ("Nothing about us without us"). In line with this, the use of lived-experience videos may minimize stigma related to having a mental illness or being lonely.

Self-stigma (e.g., internalization of negative stereotypes) and social stigma (i.e., negative attitudes from the general public) are critical to address in loneliness treatments for people with SMI because they often prevent people from disclosing their experiences or seeking help [35]. Self-stigma can lead to social withdrawal among people with SMI, further limiting opportunities for social engagement and worsening loneliness [35]. Although the researchers did not assess stigma, participants using + Connect perceived the

shared experience and actor videos to be the most useful and enjoyable of the video types. Participants also viewed the shared experience videos as “motivational examples” of how people like them can apply skills they were learning. Finally, the researchers reported that users responded consistently well to the gamification of the app. Gamification may be a particularly useful method for maintaining motivation and adherence to digital health interventions for people with SMI.

Horyzons is a web-based, social media-like platform designed to address loneliness in people with a first episode of psychosis [36••]. Within Horyzons, participants can post online content and comment on other users’ content, track personal goals (social and nonsocial), and access psychoeducational content based on CBT, positive psychology (e.g., self-compassion), and mindfulness-based principles (e.g., mindful walking). In contrast to the previously discussed apps, Horyzons included interactions and ongoing monitoring by a clinician (a “moderator”) who would tailor content to each specific participant, send personalized messages with suggestions about activities the participant might enjoy, and follow-up with participants to discuss potential treatment engagement barriers. The level and type of moderator interaction depended on the participant’s own needs (e.g., inactive participants were contacted at least weekly). Twenty-six young adults with a psychotic disorder participated in a 12-week open trial of Horyzons. Participants reported significant improvements in negative emotions, depression symptoms, and positive symptoms from baseline to post-treatment. Importantly, participants reported significant reductions in loneliness from baseline to mid-treatment (after 6 weeks), though these differences did not remain at post-treatment. While initial improvements in loneliness speak to the benefit of online social platforms, loneliness was not a primary focus of this treatment; indeed, Horyzons incorporated both social and non-social interventions (e.g., mindfulness, social and non-social goal-setting). Thus, the initial reductions in loneliness may have tapered over time due to the fact that the intervention itself was not specifically targeting loneliness as its main treatment outcome. In examining different types of platform engagement and reductions in loneliness, commenting on others’ posts more frequently was associated with a larger decrease in loneliness in participants throughout the intervention.

Horyzons illustrates the potential benefit of a web-based platform with clinician-provided support. The same “moderator” communicated with the same participants consistently throughout the intervention, allowing them to build rapport and provide guidance specific to each person’s strengths and goals. Importantly, frequency and method of communication depended on the participants’ levels of engagement, with some receiving messages solely through the platform while others received more frequent emails/texts from their moderator. This flexible approach is ideal for people living with SMI, who may feel more comfortable engaging with a web-based platform that one can access on a computer or talking to their moderator through texts. Furthermore, Horyzons illustrates that digital health apps do not need to be stand-alone treatments, but may be used in conjunction with in-person treatment to help users generalize therapeutic skills into everyday life and receive personalized real-time feedback on their goal progress.

These three mHealth interventions reflect exciting opportunities for advances in the treatment of loneliness using cognitive-based principles. They used a combination of approaches (e.g., Horyzons combined CBT, positive psychology, and mindfulness exercises) and tailored their content to meet the specific needs of their users (e.g., Nod was specific to students living on a college campus). Furthermore, they demonstrate different ways to facilitate engagement, including gamification (+ Connect), co-design (+ Connect), and continuous check-ins with clinicians (Horyzons). + Connect benefited from including people living with SMI as part of the development process as well as having video examples of people with mental health concerns succeeding at the very skills that the app was promoting to users. The benefit of combining approaches from a diversity of perspectives speaks to the flexibility of digital interventions for more precise, individualized treatment options, as opposed to the traditional one-size-fits-all approach.

Addressing loneliness “just-in-time”

In addition to the strategies used by the interventions outlined above, there are other digital-specific methods that can be leveraged to better address loneliness for people living with SMI. Just-in-time adaptive interventions (JITAI) use self-report (active) and sensor-based (passive) data to predict optimal times for a treatment component to be delivered [37]. Ecological momentary assessments (EMA) can be delivered frequently through mobile devices, prompting users to report their current state (e.g., stress, affect, loneliness), environment, and context as they go about their daily lives. Passive data capture, on the other hand, leverages readily available sensing metrics (e.g., GPS, activity trackers, accelerometers) as potential markers of specific activity types. When assessed together, actively and passively collected data allow JITAI to adaptively respond to a user’s actions or states. By doing so, JITAI can predict which intervention components should be delivered, when and where they are most needed. For example, if a person tends to report elevated loneliness in the morning, an app may prompt the user with a social activity suggestion or cognitive reappraisal exercise earlier in the day. Alternatively, a positive psychology exercise such as savoring a previous positive experience may only be useful after the user has engaged in a social activity that they report as pleasant (versus anxiety-provoking). Further, different prompts can vary based on the person’s activity level or geolocation. For example, if a person has been stationary for a given period of time, then a social activity prompt that involves physical activity (e.g., go on a walk and call a friend) may be more beneficial than a different type of prompt (e.g., text a friend). See Fig. 1 for examples.

JITAI are particularly useful for people with SMI because treatment delivery can be automated and delivered in short bursts. Most common mobile interventions occur through a “pull” approach, where a user decides when to access certain treatment components (e.g., a user decides to watch a social

skills video). However, the predictive nature of JITAIs enables mobile devices to “push” notifications when optimal (e.g., an app suggests an activity based on user feedback). For people with SMI, the push approach is especially advantageous because pull interventions require some degree of awareness and motivation, while push notifications automate these decisions, and lessen the burden on users. Furthermore, push notifications may enhance long-term engagement with mental health apps for people with SMI because they deliver treatment at a higher frequency and shorter duration than other types of interventions, either digital or face-to-face. Indeed, those with and without SMI report preferences for discrete app features (daily motivational quotes, brief breathing exercises) and show higher engagement with apps requiring short bursts of interactions, rather than full intervention protocols [38]. This cadence of treatment delivery is especially useful for those with SMI as it may reduce the cognitive load required for treatment engagement, which is a known barrier for this population.

To create a JITAI for the treatment of loneliness, it is critical to collect and evaluate the reliability and validity of active and passive data for identifying indicators for loneliness and social connection, and to identify the contexts in which loneliness may fluctuate. Though limited, existing studies have identified mobility (i.e., as measured using GPS geolocation) [39] and ambulatory videos of facial affect expression [40] as potential indicators of social activity in daily life, including links with loneliness. For JITAIs to be functional, it is important we establish the efficacy of treatment components (i.e., active ingredients) individually, rather than as packages. Furthermore, we must examine these individual components alongside passively collected

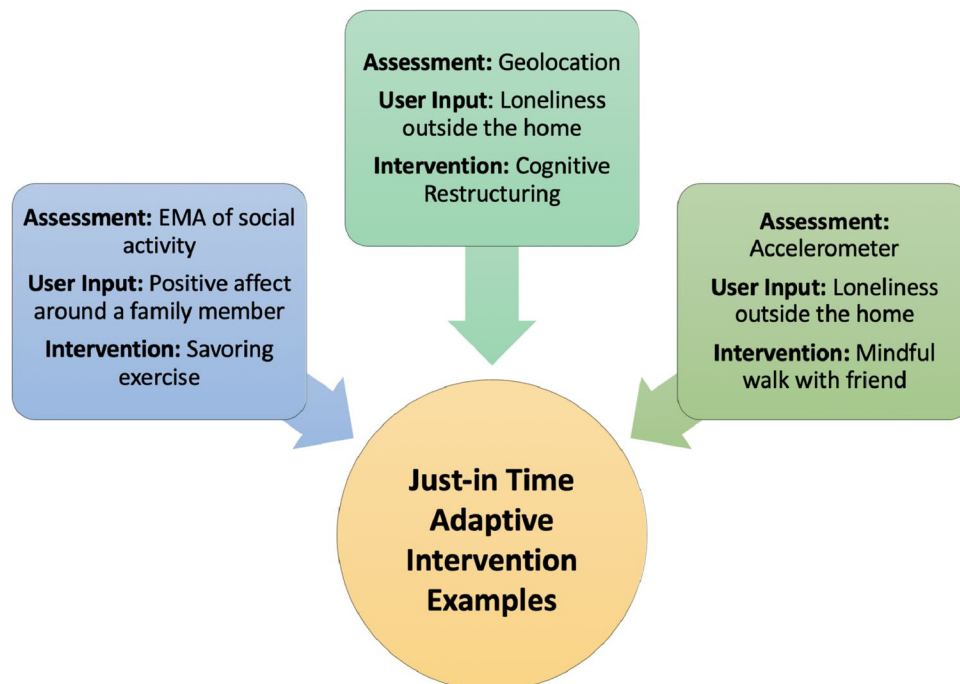


Fig. 1 Applications for just-in-time adaptive interventions (JITAI) for loneliness

data to optimize when, and under what conditions certain components are most effective. Lastly, involving people with lived experience in the development of digital treatments will ensure that these treatments are conducive to the skills, knowledge, and strengths of people with SMI.

Other considerations for digital health interventions that address loneliness in SMI

As we consider digital innovations to treatments, it is also critical to address limitations of treatments in both the digital and non-digital space. Existing treatments in people with and without SMI primarily target ways to create new relationships, but often ignore skills relevant for maintaining or improving existing relationships. People with SMI often report strained relationships with family members and have a lower likelihood of being in a romantic relationship [41]. High quality, existing relationships are critical as they may reduce the risk of loneliness by offering more readily accessible emotional support. Additionally, mechanisms driving loneliness may also operate differently in regard to existing intimate relationships. For example, a person with schizophrenia who feels lonely partially because of their paranoia in relation to a family member (e.g., unfounded fear that one's sibling wishes them harm) most likely requires a different intervention target than a person who feels lonely because a family member does not want a relationship with them.

The ability to tailor digital interventions to an individual's specific needs allows researchers to incorporate skills relevant to both initiating new and fostering existing relationships. +Connect is an example of an mHealth intervention that provided psychoeducation material on addressing existing relationships for young adults with psychosis. A strength of JITAIs includes the opportunity to assess whether a person feels loneliness depending on the type of social interactions they have. For example, if a person consistently reports elevated levels of loneliness when they are with a parent, an app could suggest interventions to improve their relationship with that parent (e.g., communication skills, cognitive restructuring exercise). Future digital interventions could be designed to incorporate responses from more than one user to promote healthy relationships. For example, an app could be developed for spouses to use individually to help foster intimacy and communication. The app could also be tailored depending on if one spouse or both live with SMI and may be incorporated into in-person treatment (e.g., couples counseling).

While we have focused on the specific strengths of tailoring cognitive-based treatments to the digital space, social skills and social prescribing interventions may also benefit from such adaptations. The difficulties in comparison across intervention types may illustrate the challenges we face when interventions are not tailored to meet individual needs. For example, some may experience loneliness due to a lack of social opportunities, where a social prescribing intervention may be most effective, while others may experience loneliness primarily due to social skill deficits, where social skills training may be the most appropriate. More research is necessary to not only understand which intervention type may show the most evidence for addressing loneliness for people living with SMI, but also when and why specific interventions may work better for some than

others. Adapting these intervention types to the digital space, possibly all within the same app, could help address these and other questions.

Conclusions

Innovations in digital therapeutics offer exciting opportunities to better address loneliness for people living with SMI. Cognitive approaches show the most promise compared to other intervention modalities, given the central role of subjective perceptions of social connection in the onset and maintenance of loneliness. Nonetheless, this area of work remains nascent and requires continuous assessment and adaptations to best optimize these approaches. Digital therapeutics offer an ideal tool for addressing loneliness because they are accessible in the environments and contexts in which social interactions naturally occur, and can be tailored to meet an individual's unique needs. Modifications to meet the cognitive, emotional, and structural needs of people living with SMI are crucial as we continue to adapt these tools. In addition to simply measuring loneliness as a key outcome in psychosocial interventions, we can continue to tailor digital therapeutics for the specific needs of people with SMI and capitalize on the strengths of the digital medium.

Declarations

Conflict of Interest

The authors declare no competing interests.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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