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Digital health technologies and major depressive disorder

Roger S. McIntyre[1] , Walter Greenleaf[2], Grzegorz Bulaj[3], Steven T. Taylor[4,5], Georgia Mitsi[6], Dylan Saliu[6], Andy Czysz[7], Greg Silvesti[7], Manny Garcia[7] and Rakesh Jain[8]

[1]Department of Psychiatry and Pharmacology, University of Toronto, Toronto, ON, Canada, [2]Virtual Human Interaction Lab, Stanford University, San Francisco, CA, USA, [3]Department of Medicinal Chemistry, College of Pharmacy, University of Utah, Salt Lake City, UT, USA, [4]Department of Psychiatry, Harvard Medical School, Boston, MA, USA, [5]Department of Psychiatry, Massachusetts General Hospital, McLean Hospital, Boston, MA, USA, [6]Biogen, Cambridge, MA, USA, [7]Sage Therapeutics, Inc., Cambridge, MA, USA and [8]Department of Psychiatry, Texas Tech University School of Medicine, Lubbock, TX, USA

Abstract

There is an urgent need to improve the clinical management of major depressive disorder (MDD), which has become increasingly prevalent over the past two decades. Several gaps and challenges in the awareness, detection, treatment, and monitoring of MDD remain to be addressed. Digital health technologies have demonstrated utility in relation to various health conditions, including MDD. Factors related to the COVID-19 pandemic have accelerated the development of telemedicine, mobile medical apps, and virtual reality apps and have continued to introduce new possibilities across mental health care. Growing access to and acceptance of digital health technologies present opportunities to expand the scope of care and to close gaps in the management of MDD. Digital health technology is rapidly evolving the options for nonclinical support and clinical care for patients with MDD. Iterative efforts to validate and optimize such digital health technologies, including digital therapeutics and digital biomarkers, continue to improve access to and quality of personalized detection, treatment, and monitoring of MDD. The aim of this review is to highlight the existing gaps and challenges in depression management and discuss the current and future landscape of digital health technology as it applies to the challenges faced by patients with MDD and their healthcare providers.

Introduction

The global prevalence of depression has steadily increased from 1990 to 2019,[1] and approximately 1 in 5 adults in the US will experience major depressive disorder (MDD) at some point in their lifetime.[2] Depression was one of the top 10 causes of disability globally in 2019 and is associated with significant direct and indirect economic and societal burdens.[3,4] The COVID-19 pandemic exacerbated many risk factors for depression across countries of disparate economic status[5,6]; the prevalence of depressive symptoms in the US increased approximately threefold from 2017 to 2020,[7] along with increased associated economic burden[8] and rates of suicidal ideation.[9] Therefore, it is important to understand the challenges currently facing mental health practices (eg, geographical and health inequities may limit access and quality of care[10]) and the need to improve clinical management of depression.

Digital health technology is rapidly evolving the delivery of mental health care and holds promise for improving access to and quality of mental health care, thus improving the clinical management of depression.[10] Digital health technology includes categories such as digital therapeutics (eg, prescription or nonprescription digital therapeutics), digital interventions (eg, wellness apps), precision medicine (eg, digital biomarkers), and digital care (eg, telepsychiatry) (Figure 1).[11] Digital therapeutics provide software-based treatments that have been approved or cleared by the US Food and Drug Administration (FDA) ("Software as a Medical Device," or SaMD).[12] Digital biomarkers hold promise for enabling scalable, time-sensitive, and cost-effective assessment of depression[13,14] by providing real-time psychological, behavioral, and physiological data,[15] but further validation is required. Telepsychiatry, the use of electronic information and telecommunication technologies to provide mental health services, has been adopted in direct patient care, telepsychiatry-enhanced referral, and collaborative or integrated care models.[16] During the COVID-19 pandemic, telepsychiatry has transformed the mental health care landscape and may continue to help improve the clinical management of depression.[17] This review aims to highlight the current gaps in depression management and consider
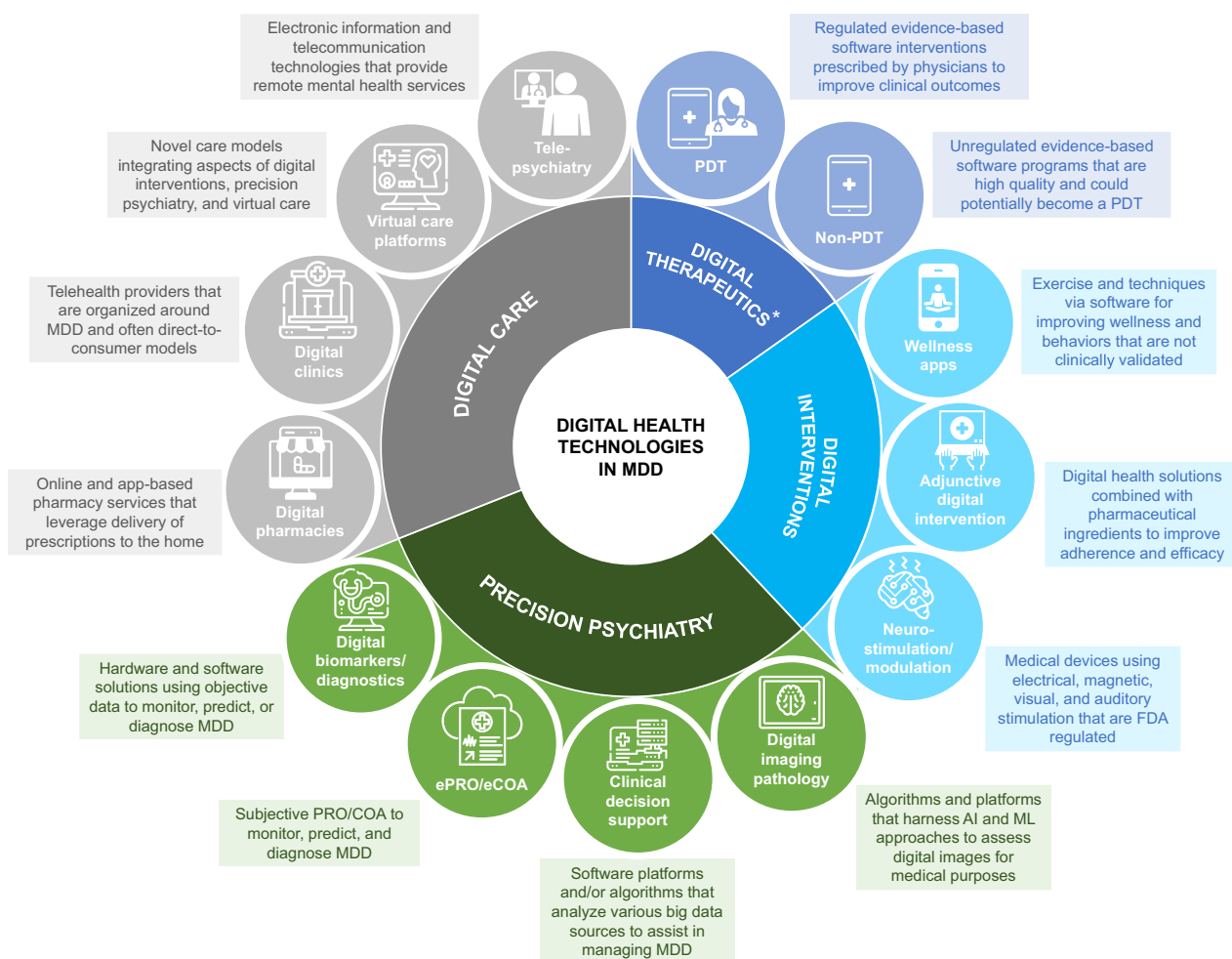
Figure 1. Different categories of digital health technologies. *Some apps are marketed as digital therapeutics under FDA enforcement discretion. Abbreviations: AI, artificial intelligence; eCOA, electronic clinical outcome assessment; ePRO, electronic patient-reported outcome; FDA, Food and Drug Administration; MDD, major depressive disorder; ML, machine learning; PDT, prescription digital therapeutics.

how digital health technologies can help address challenges faced by patients living with depression and providers managing depression.

Current challenges in the clinical management of depression

Gaps and challenges currently faced in the clinical management of depression include those related to disease awareness, screening and diagnosis, and treatment and monitoring (Figure 2).

Awareness

Poor mental health literacy, or the lack of knowledge and understanding of mental health disorders like depression, may prevent patients from recognizing depression symptoms early and seeking appropriate treatment.[18] Poor awareness of depression may also contribute to the stigma associated with the disorder that, in turn, diminishes treatment seeking and adherence to mental health services.[19] In a study involving more than 50 000 individuals across 21 countries, the vast majority of those affected by depression did not seek treatment due to stigma or lack of knowledge of the disorder.[20] For adolescents, many reported moderate to high levels of stigma associated with depression and low levels of

mental health literacy, which contributed to their early termination of treatment.[19] Men tend to experience higher levels of stigma regarding help-seeking and having depression than women,[21] which may result in higher rates of suicide.[22]

Screening and diagnosis

Over the last two decades, the US Preventive Services Task Force and Agency for Healthcare Research and Quality guidelines have recommended routine screening for depression in healthcare settings to address the under-recognition of depression.[23] However, the rates of depression screening remain low (1.4% of all primary care visits in the US in 2012),[24] and there have been few specific guidelines to support health system implementation of universal depression screening in primary care.[25] Barriers to depression screening and the lack of adequate follow-up in patients who screened positive for depression include lack of resources for treatment referrals, limited access to mental health services, and unequal geographical distribution of specialists.[26,27] Furthermore, health equity challenges and stigma associated with depression, including racialized framing on the part of the healthcare provider (HCP), may limit access and quality of care.[28,29] LGBTQ (lesbian, gay, bisexual, transgender, and queer) individuals may be at a higher risk for suicidal behavior and
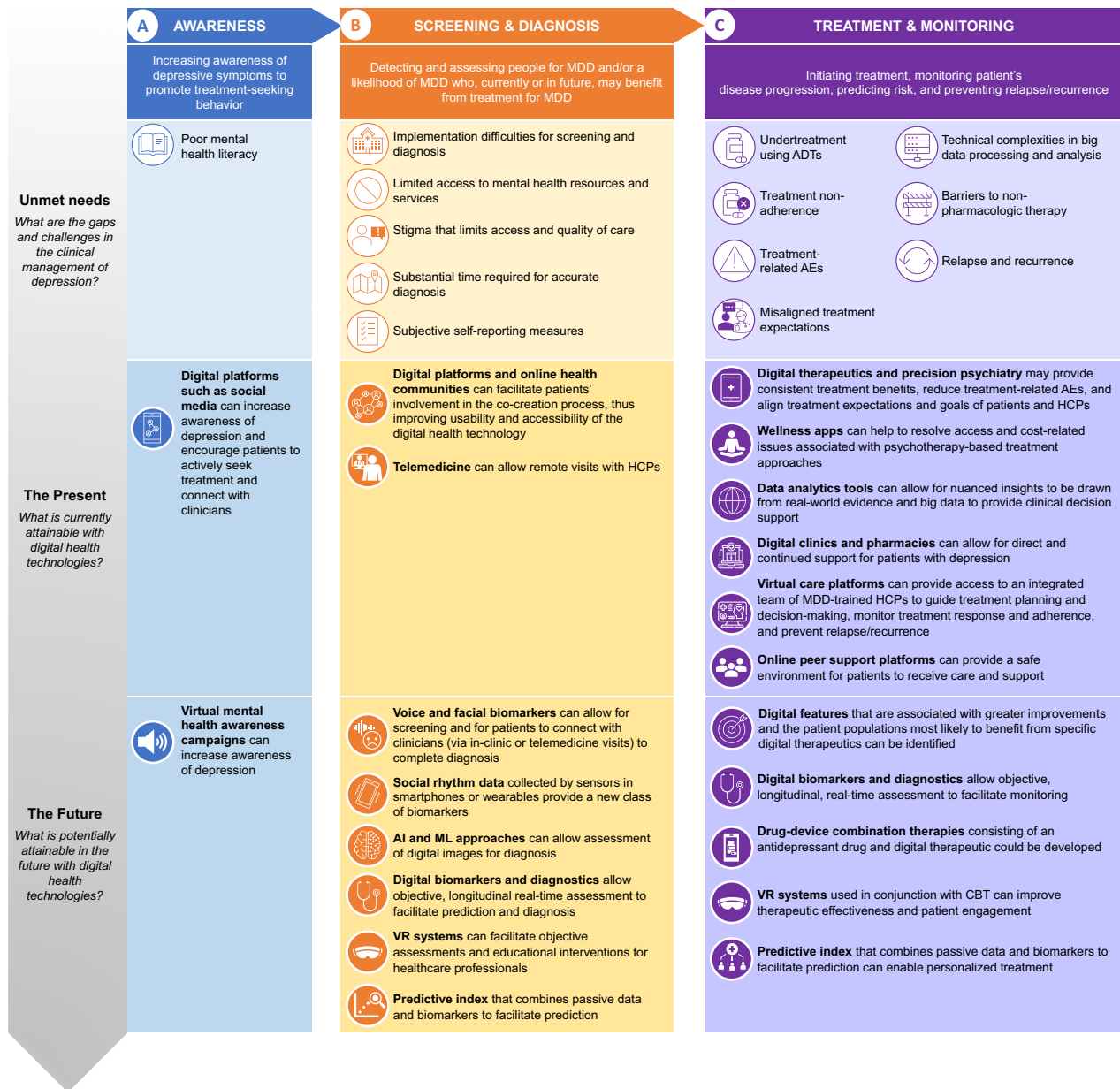
Figure 2. Major depressive disorder (MDD) patient journey—unmet needs in the clinical management of depression and the role of digital health technologies. Abbreviations: ADT, antidepressant therapy; AE, adverse event; AI, artificial intelligence; CBT, cognitive behavioural therapy; HCP, healthcare provider; MDD, major depressive disorder; ML, machine learning; VR, virtual reality.

discrimination in healthcare settings due to stigma compared with heterosexual individuals.[30,31]

Even with screening, diagnosis may be hampered by several challenges. Substantial time is required for an accurate diagnosis of depression, which is often observed alongside other physical and psychiatric comorbidities[32] that may obscure a diagnosis of depression. Additionally, the diagnostic workup involves self-reported measures that may be subjected to biases and may be challenging to implement in a clinical setting (eg, integration into clinic workflow and electronic health records [EHRs] and interpretation of self-reported outcomes by HCPs) and in certain populations (eg, children, individuals with organic or neurological deficits, individuals with developmental or communication disorders, and individuals with low mental health literacy).[33,34]

Treatment and monitoring

Patients with depression may be undertreated with antidepressant therapies (ADTs), as observed in a longitudinal study involving 789 primary care patients with depressive symptoms, in which 41% were undertreated (ie, did not receive ADTs even though an ADT was indicated).[35,36] Patients may discontinue chronic treatment due to lack of rapid and consistent treatment benefits,[37] treatment-related adverse events (AEs),[37-40] and expectations of treatment that are misaligned with the treatment goals of HCPs.[41,42] Non-adherence to ADTs is associated with increased severity of depressive symptoms, risk of relapse (ie, early return of symptoms within the expected duration of a current episode) and recurrence (ie, a new major depressive episode following a full-episode remission), and healthcare resource utilization, as well as significantly higher

medical costs, inpatient admissions, and visits to the emergency department.[43,44]

Both the American Psychiatric Association and the American Psychological Association practice guidelines recommend that HCPs consider appropriate treatments (including both pharmacologic and nonpharmacologic therapy options) for preventing relapse in patients with depression who have achieved remission.[45,46] Nonpharmacologic therapy refers to health interventions that are not based on medication (eg, psychotherapy, physical exercises, and transcranial magnetic therapy).[47] In a large sample of primary care patients, the majority of patients with depression (51%-58%) reported strong preferences for nonpharmacologic therapies,[48] but only about 20% of patients initiated such treatment,[49] and about 40% to 60% of those who initiated nonpharmacologic therapy did not complete the treatment,[50] suggesting that there are substantial barriers both to initiating and to adhering to nonpharmacologic therapy in the real-world practice.[51] These barriers may be structural (eg, transportation problems, time constraints, and cost) or emotional (eg, social stigma and discomfort talking about problems with a therapist).[52] There is also a lack of sufficient evidence for their effectiveness and cost-effectiveness in primary care settings.[53]

There is an increasing need for more personalized approaches to monitor and treat depression, but this is associated with several challenges.[54] It is difficult to integrate patient information in a clinically relevant manner due to technical complexities in processing and analyzing data generated from multidimensional data sets and/or using artificial intelligence (AI) modeling.[54] In addition, there are various ethical concerns, including privacy and security issues and risks of social discrimination.[54] The APA has published an app evaluation model that assesses access and background, privacy and safety, clinical foundation, usability, and therapeutic goal of a given app to attempt to address these concerns based on individual patients' needs.[55]

Rapid growth of digital health technologies

Digital health technologies have emerged over the past decade for the management of various diseases. In 2013, a mobile medical app (WellDoc's BlueStar Rx) was cleared by the FDA as a prescription digital therapeutic (PDT) to support the management of type 2 diabetes by analyzing patient data, formulating personalized guidance, and summarizing data analytics to the healthcare team for clinical decision support.[56] In 2017, the FDA cleared a PDT (Pear Therapeutic's reSET) that delivers a computerized version of cognitive behavioral therapy (CBT) and serves as an adjunct to clinician-supervised outpatient therapy programs in patients with substance use disorder.[57] Since then, the FDA has cleared more mobile medical apps, including those that help diagnose autism spectrum disorder: (a) Cognoa's Canvas Dx is a software that uses a machine learning (ML) algorithm to receive input from parents or caregivers, video analysts, and HCPs to help clinicians evaluate a patient's risk of the disorder, and (b) EarliTec's EarliPoint Evaluation is a device that uses AI to detect a patient's moment-by-moment looking behavior, serving as an objective measurement tool that helps clinicians diagnose and assess the disorder.[58,59] Recently, the FDA also issued marketing authorization for a virtual reality (VR)-based app, EaseVRx, as an adjunctive treatment for chronic low back pain.[60] Both the Digital Therapeutics Alliance[61] and the Digital Medicine Society[62] offer educational resources dedicated to the applications of digital health technologies.

During the COVID-19 pandemic, there was a rapid growth in access to and capabilities of digital health technologies worldwide.[63] A 2021 global survey involving 293 HCPs showed that various subsegments of digital health saw considerable growth (up to 36%) from 2020 to 2021,[64] with telehealth and telemedicine emerging as key digital approaches to disease management.[63] The majority of telehealth-related literature published during the COVID-19 pandemic (92.3%) reported provision of telehealth services for conditions not related to COVID-19,[65] with the most common being integrated clinical care (49.7%), including a combination of triage, diagnosis, treatment, follow-up, and rehabilitation services.[65] A 2020 survey of more than 3000 patients treated with telepsychiatry during the COVID-19 pandemic[66] and a separate survey of more than 100 mental health clinicians[67] during the COVID-19 pandemic revealed that both patients and clinicians were supportive of telepsychiatry, were satisfied with the quality of care, and would consider using this modality in the future.

The use of digital technologies for depression, including telehealth and telemedicine, also increased during the pandemic; patients with depression were three times more likely to use telehealth than those without.[68,69] The rapid growth in digital health technologies globally presents opportunities toward bridging the current gaps in the clinical management of depression. Besides therapeutic interventions, digital technologies may support clinical management of depression by: (a) capturing longitudinal, temporally dense, and multimodal mental health data for use in diagnosis and monitoring; (b) analyzing data using ML paradigms to generate personalized and clinically actionable insights and predictions; and (c) supporting integrated care by facilitating connections to clinical care, peer support, personalized resources, emergency care, and even novel therapies.[70] Several studies have demonstrated the potential of using digital biomarkers (based on sensor data from wearable devices or mobile apps) for the prediction and detection of depression.[71-73] There are also opportunities to develop online and mobile apps for the prevention of depression.[74] However, it should be noted that unlike conditions such as diabetes, where significant adoption of digital technologies has been observed, depression is more complex due to the unique challenges associated with the clinical management of the disorder (eg, poor mental health literacy, stigma, and the lack of objective tools for assessment and diagnosis). Further studies would be required to refine digital technologies for real-world implementation in depression management, which includes encouraging continued engagement with digital health technology beyond first-time use. It is worthwhile to examine lessons learned from other disease areas where high rates of engagement of digital technologies have been achieved.

The present: What is currently attainable with digital health technologies

Digital health technologies for depression gained broad public attention after the release of the SuperBetter app,[75] MoodHacker app,[76] and SPARX,[77] which are self-management tools to reduce depressive symptoms supported by randomized controlled trial data.

In a randomized controlled trial, participants using SuperBetter (n = 190) experienced a greater reduction in depressive symptoms than those placed on a waiting list (n = 93), as assessed by the Center for Epidemiological Studies Depression questionnaire

(CES-D) over the course of 6 weeks.[75] No significant difference in depressive symptoms was observed between a version of SuperBetter using CBT and positive psychotherapy (PPT) strategies and a general version of the app focused on self-esteem and acceptance.[75] This study was limited by a high rate of attrition and may not be generalizable due to recruitment from a self-help website, which may have captured a particularly motivated and/or hopeful segment of patients with depression.[75]

The MoodHacker app was assessed vs access to relevant depression websites in a randomized controlled trial of 300 employed adults with mild to moderate depression.[76] Participants using MoodHacker self-reported significant effects on symptoms of depression at the 6-week follow-up when compared with participants in the nontreatment arm.[76] However, a general attenuation of effects was observed at the 10-week follow-up.[76] Limitations of this study included the use of a convenience sample of interested individuals, the use of self-report surveys, and the use of compensation for completing assessments, which may reduce generalizability of results.[76]

The CBT-based intervention SPARX was assessed for noninferiority to treatment as usual in adolescents aged 12 to 19 years who were seeking help for depressive symptoms at primary care sites in a randomized controlled trial (n = 94 and n = 93, respectively).[77] SPARX was noninferior to treatment as usual following intervention and at the 3-month follow-up, as assessed by the observer-rated children's depression rating scale-revised.[77] The study was limited by the clinical service setting, wherein data on treatment adherence were limited, as well as by the heterogeneity of "treatment as usual," which primarily comprimised face-to-face counseling and varied based on primary care site.[77]

Despite limitations, these types of digital health technology are rapidly evolving the delivery of care for depression and hold promise for improving the clinical management of depression. There are several categories of digital health technologies for depression (Figure 2), and each of these categories may play a role in addressing the gaps and challenges in the clinical management of depression.

Currently available technologies aimed at addressing challenges in awareness and prevention

The use of social media platforms can help increase awareness of depression and encourage patients to actively seek treatment and connect with physicians.[18] Directly increasing patient and caregiver awareness of risk factors for depression can help promote proactive pursuit of treatment or incentivize visits to the clinic.[78] There are also efforts to use a multimodal framework to combine heterogeneous sets of features obtained from social media data, including inferences of demographic information (eg, age, sex, and race), that can be crucial for stratifying our understanding of population-level epidemiology of mental health disorders like depression and help develop demographic-aware interventions.[79,80]

Currently available technologies aimed at addressing challenges in screening and diagnosis

Digital health technologies may help address barriers to the implementation of depression screening and provide objective assessment to facilitate diagnosis. Telemedicine is already being implemented successfully to allow remote visits with HCPs, thus helping to overcome challenges associated with diagnosis (eg,

limited access to mental health resources/services and stigma associated with seeking diagnosis and treatment).[81]

Currently available technologies aimed at addressing challenges in treatment and monitoring

Digital technologies may also help guide treatment planning and medical decision-making and monitor or promote treatment adherence in patients with depression. Mobile apps such as MINDSTRONG are being evaluated for preemptive and early intervention of brain health care to improve clinical outcomes and reduce hospital visits.[82] VitalSign[6] software facilitates treatment selection, implementation, and revision for patients with depression.[23] The software can be augmented by other models of care (eg, mental health navigation and behavioral activation teletherapy) and offers the potential to add-on research and quality improvement projects.[23] Several studies have demonstrated the effectiveness of MoodGYM (a CBT-based intervention for depression that has been available since 2001 and used by over three-quarters of a million people)[83] in reducing depressive symptoms, but in some of these studies, adherence rates were low (10%-27%).[84,85] Free online access to this intervention can potentially benefit underserved patient populations.[85]

Although mobile apps targeting treatment adherence have been understudied, several recent examples have shown promise: AiCure uses a HIPAA-compliant and scalable AI platform to monitor treatment adherence[86,87]; Mango Health and Health Prize are incentive-based apps to improve access and adherence to prescribed treatments[88,89]; Medisafe is an app that provides reminders and alerts for users to take their prescriptions, thus improving treatment adherence[83,90]; and Innerworld is a social VR platform that can help patients with depression set and reach mental health goals and promote treatment adherence.[91] Some app-based digital therapeutics for depression use positive psychology approaches to promote app engagement, which may affect treatment adherence.[92]

Digital therapeutics have been approved by the FDA for the treatment of depression. One example is Otsuka Pharmaceutical's Abilify MyCite that combines pharmacologic therapy with a wearable sensor and a mobile app that help monitor treatment and enhance collaboration between patients and their providers.[93] Other digital therapeutics for the treatment of depression are available under FDA enforcement discretion and were intended as adjunctive digital interventions to reduce depressive symptoms: Deprexis (developed by Orexo and GAIA) is a software platform that uses CBT-based techniques and AI to personalize treatment and help patients with depression learn how to overcome negative thoughts and behavior patterns[94]; SparkRx (developed by Limbix) is a mobile app that uses CBT-based techniques to treat adolescent depression[95]; and Feel program (developed by Feel Therapeutics)[96,97] uses an emotion sensor (a wristband) combined with a mobile app to obtain real-time objective data of changes in emotional state and provide personalized interventions (eg, CBT program and virtual support from board-certified health coaches). The use of digital therapeutics may help provide consistent treatment benefits, reduce treatment-related AEs, and align the treatment expectations and goals of patients and HCPs; however, this may be a work in progress for some of the existing digital tools, including both PDT and non-PDT.[95-102]

Digital health technologies may help address privacy and security issues, as well as the structural or emotional barriers (including stigma) associated with personalized approaches to treating

depression.[23] For VitalSign,[6] data are stored securely, and access to the data is closely monitored to ensure the confidentiality of these records.[23] In addition, the remote patient assessment feature allows patients to complete the assessment at home using their own electronic devices; this potentially facilitates access to important and timely health data for resource-poor clinics that care for underserved and minority populations.[23] The Health Rhythms app uses AI to tailor interventions and enable personalized treatment,[103] whilst the Feel program provides real-time support and evidence-based interventions, CBT, and remote data-driven personalized coaching.[96,97]

Telemedicine or care coordination platforms can help provide remote care to rural areas or hard-to-reach communities, thereby enhancing patient-provider collaboration.[104] Services such as Valera Health,[105] BetterHelp,[106] Talkspace,[107] Silvercloud Health,[108] Ginger,[109] and Lyra Health[110] provide access to integrated teams of healthcare practitioners, specialists, and therapists trained in managing MDD. In nonclinical settings, online peer support groups and other resources[111-113] can provide a safe environment for patients with depression to receive care and support. While there is a paucity of high-quality studies examining the effectiveness of online peer support groups, they remain promising for depression management.

The future: What is potentially attainable with digital health technologies

Technologies under investigation aimed at addressing challenges in screening and diagnosis

Digital biomarkers hold promise in enabling objective detection of depression. Ellipsis Health is an ML-based mobile app that detects depression using speech analysis of smartphone audio, which can be easily recorded and transmitted, potentially allowing accessible screening and monitoring of depression.[114] Kintsugi is a passive vocal biomarker instrument that uses short clips of free-form speech for depression screening.[115,116] Kintsugi's technology can be integrated into enterprise call centers, telehealth platforms, and remote patient monitoring apps, potentially expanding access as well as standardizing the quality of screening in primary care settings. A multi-site fully remote e-clinical validation study that enrolled participants with MDD to evaluate the sensitivity and specificity of Kintsugi's technology's prediction has recently been completed.[115] Winterlight Labs has developed a tablet-based assessment that also uses speech analysis as a digital biomarker that can help identify depression and be used for long-term remote monitoring of behavioral health and treatment response.[117] There is an ongoing trial that uses this technology to examine changes in speech features over time in patients with psychiatric disorders (including depression).[118] Sonde Health is a voice-based technology that can be used as a digital biomarker for depression, with a sensitivity and specificity of 0.60 and 0.70, respectively.[119,120] This smartphone technology offers an accessible, objective, private, noninvasive, and cost-effective way to evaluate mental fitness.[120] Users have demonstrated high levels of engagement; the app keeps patients engaged when they are not seeing their HCP and allows the patient and their HCP to monitor measurements between appointments.[119,120] The app may also help HCPs evaluate treatment response.[120]

Digital technology may facilitate a more personalized, convenient, and cost-effective approach to assessment.[121] A recent study has shown that a mobile app-based version of the established Cognition Kit Digit Symbol Substitution Test (DSST) correlated with the paper-and-pencil version of the test in patients with MDD.[121] Furthermore, these patients reported that the Cognition Kit DSST app was user friendly, easy to navigate, and preferable over the paper-and-pencil version of the test.[121] Further studies are required in healthy individuals to validate the promising findings reported by patients with MDD.[121] VitalSign[6] is an EHR-integrated web-based iPad app designed for use in clinics that facilitates screening and diagnosis in patients with depression using the two-item version of the Patient Health Questionnaire (PHQ-2).[23] Patients screening positive are then prompted to complete a full PHQ-9 to aid HCPs in diagnosis and treatment planning. Follow-up assessments of symptoms, side effects, and adherence are recorded in an easy-to-search format that HCPs may use alongside clinical information recorded in the EHR.[23] The software has been optimized for integration and interoperability and frequently undergoes upgrades to improve efficiency, accuracy, and quality of care based on feedback from HCPs.[23] Screening efforts are focused on identifying patients with depression, and there are no additional screening assessments for those who screen negative on the PHQ-2; thus, patients with current suicidality who do not have significant depressive symptoms may be missed.[23]

Virtual reality environments can efficiently evoke and quantitatively score cognitive and emotional status and behavior in a reproducible, objective, standardized, dynamic, accurate, and culturally or contextually correct manner by using standardized and age-appropriate cognitive and emotional challenges in a computer-generated environment.[122] VR environment-based educational interventions can help mental HCPs update their skills and knowledge in a simulated environment, which in turn may improve the quality of health care and patients' satisfaction.[123]

Technologies under investigation aimed at addressing challenges in treatment and monitoring

Whilst there exists a wealth of mobile apps aimed at the treatment of depression, most are not backed by robust scientific evidence, and there are few ongoing studies evaluating the use of mobile apps as interventions for MDD, highlighting a need for further clinically oriented and systematic validation and testing of such mobile apps.[124]

CT-152 is a PDT developed by Otsuka Pharmaceutical and Click Therapeutics with the aim to be classified by the US FDA as a SaMD.[100,125] This mobile app delivers a digital cognitive-emotional training intervention (Emotional Face Memory Task) for the treatment of MDD; a pilot trial in 51 participants with MDD showed a greater reduction in the severity of depressive symptoms in patients who received the PDT compared with those who did not, although further studies are needed to elucidate its precise mechanism of action.[126,127] Pathway is another example of a mobile app for MDD management (tracking symptoms, medications, side effects, and treatment progress) that is under development. Based on a pilot feasibility randomized controlled trial, 18-week use of the Pathway app showed significant improvements in patient engagement and patient-provider communications compared with the usual care control group.[128]

Efforts to develop treatment strategies for MDD and other psychiatric indications by combining pharmacologic therapies (eg, ADTs) with digital therapeutics (eg, mobile medical apps, which are medical devices approved/cleared by the FDA or conformed with the Medical Device Regulation (MDR [EU]) 2017/745[129]) are ongoing,[130,131] and there are opportunities to

create integrated digital health ecosystems for the treatment of MDD.[132] Behavior theories such as the health belief model, the behavioral intervention technology model, and the just-in-time adaptive intervention (JITAI) model can help developers evaluate the feasibility of digital mental health services. For example, JITAI is an intervention design aiming to provide the right type/amount of support, at the right time, by adapting to an individual's changing internal and contextual state and impact on patient-reported outcomes (PROs).[133,134] The availability of increasingly powerful mobile and sensing technologies underpins the use of JITAIs to support health behavior, in which the state of the individual can change rapidly, unexpectedly, and outside of standard treatment settings.[133] However, the lack of publications investigating whether JITAI mechanisms lead to an increase in the effectiveness of the mobile apps highlights the need for further research, especially in real-world applications. There is a need to address the major gaps that exist between the growing technological capabilities for delivering JITAIs and research on the development and evaluation of these interventions.[133]

Digital technologies may soon facilitate long-term monitoring that in turn may help prevent the relapse and recurrence of depression. Remote measurement technologies can allow tracking of current depression status and identification of behavioral markers related to depression in a continuous and effortless manner for long-term passive monitoring.[135] Ecological momentary assessment can enable the collection and integration of multimodal data passively, continuously, and objectively and may be useful in assessing how depressive symptoms, including suicidal thoughts and behaviors, unfold in real-world contexts.[136-138] It is important that these technologies are validated for their sensitivity and specificity in detecting depressive symptoms. Multivariable prognostic models may aid in better prediction of relapse and remission of depression at the individual patient level, which in turn can support precision medicine and allow resources to be better targeted toward relapse prevention; such risk prediction tools are increasingly recommended by policymakers as they can be successfully incorporated into information technology systems in real-world practice.[139] Digital phenotyping offers a powerful approach for forecasting risk for suicidal ideation over time.[140]

The use of VR systems in conjunction with CBT programs addressing depression holds special promise for improving therapeutic effectiveness and patient engagement. A recent scoping review revealed that the use of CBT in a VR environment or the use of VR therapy in addition to CBT was an effective adjunct to the treatment of depression.[141] A review of 23 research studies showed that VR intervention was more effective in symptom management than the standard of care for depression.[142] Viewing positive scenes in a VR environment has been shown to significantly decrease self-reported anhedonia, depression, and negative affect in patients with clinically significant depression.[143] Whilst VR has been used for more than 3 decades in research laboratories and university clinics to facilitate CBT and other therapeutic approaches in behavioral medicine, its use in clinical care has yet to become commonplace. As VR systems now become more accessible and affordable, there is potential for large-scale implementation and a paradigm shift in the development and dissemination of VR in clinical practice.[144]

Limitations of digital health technologies in MDD and challenges to real-world implementation

Several challenges still need to be addressed for large-scale implementation of digital health technologies for the clinical management of depression. Whilst the application of big data to health care holds great promise, there are some hurdles to overcome. Firstly, symptoms related to depression, low mood, and tiredness may hinder the patient's engagement with digital technologies.[145] Patients' mistrust in data sharing due to privacy concerns and confidentiality breaches may reduce their acceptability of digital health technologies.[146]

Existing studies on monitoring users' well-being/depressive states via smartphones rely on correlation analysis to understand the association of well-being/depressive states with different aspects of context modalities and users' interactions with smartphones. A key challenge is to uncover the causal links between the depressive states and the smartphone interactions and context modalities. Understanding the causal effects between them would enable ubiquitous computing researchers as well as doctors to build more effective behavioral interventions.[147] In addition to limitations on generalizability and possible selection bias, user engagement challenges[148] and considerable dropout rates have presented challenges in clinical trials of smartphone apps.[149]

There are also high costs associated with implementation, training, and long-term maintenance.[110,150] Digital health technologies are not equally available to all social groups due to economic, geographical, social, or cultural inequalities.[146] This divide may hinder access for patient populations who could benefit most from these technologies.[151] Mental health apps that saw a surge in downloads during the COVID-19 pandemic (eg, Headspace, Calm, Talkspace, Teladoc's BetterHelp, and Noom) have since experienced declining downloads.[152] Whilst the rapid growth of digital health technologies during the pandemic was fuelled by the relaxation of regulations and increased insurance reimbursements, it remains unclear how much of this rapid expansion will be sustained and integrated across various countries given that many of the regulatory changes were temporary.[153] The pathways to market for digital health products are evolving, and there is a lack of structured processes around evaluation and commissioning of such products.[154] Many behavioral health apps are either unevaluated in clinical trials or claim evidential support by using an evidence-based foundation, such as CBT. Furthermore, expert-reviewed systematic frameworks for evaluating such apps have found inconsistent and/or contradictory results.[155] The FDA Software Precertification (Pre-Cert) Pilot Program findings reported that the speed of innovation may necessitate new statutory authority to foster innovation while continuing to provide reasonable assurance of safety and efficacy.[156]

Perspectives and needs of patients and caregivers

There is value in identifying the digital features that are associated with greater improvements and the patient populations most likely to benefit from specific mobile app interventions.[157] To improve usability and accessibility of digital health technologies, it would be beneficial to collaborate with patients throughout the entire process: from idea creation and design, to testing, and finally implementation.[158] The value of cocreation has been well studied in other sectors, but there are few examples of effective cocreation within the digital mental health landscape. The availability of digital health platforms and online health communities may facilitate cocreation by encouraging transparent communication with patients, improving health literacy (in patients and healthcare organizations), providing informational and social support to patients, and empowering patient self-management.[159]

Payors' perspectives

In the US, the Centers for Medicare and Medicaid Services has recently approved a new category of digital health services—Remote Therapeutic Monitoring—to complement the existing suite of Remote Physiological Monitoring codes covered under Medicare.[160] Whilst this was an important milestone, how payors in general would cover costs associated with digital health services could greatly impact the uptake of digital health technologies in mental health care.[161] In the EU, reimbursement processes for digital health technologies are beginning to take shape; Germany, Belgium, and France have standardized reimbursement processes in place or soon to be launched, while other EU countries have expressed interest in implementing standardized reimbursement processes for digital health technologies.[162]

Conclusions

Digital health technology has facilitated the clinical management of depression and will likely have future growth with continued expansion and integration in patient care. Ongoing efforts to optimize and validate the use of digital health technology should provide a personalized medicine approach in detecting, treating, and monitoring depression.

References

1. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry.* 2022;**9**(2):137–150.

2. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry.* 2018;**75**(4):336–346.

3. Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry.* 2015;**76**(2):155–162.

4. Greenberg PE, Fournier AA, Sisitsky T, et al. The economic burden of adults with major depressive disorder in the United States (2010 and 2018). *Pharmacoeconomics.* 2021;**39**(6):653–665.

5. Panchal N, Kamal R, Cox C, Garfield R. The implications of COVID-19 for mental health and substance use. https://www.kff.org/coronavirus-covid-19/issue-brief/the-implications-of-covid-19-for-mental-health-and-substance-use/. Published 2021. Accessed May 6, 2022.

6. Xiong J, Lipsitz O, Nasri F, et al. Impact of COVID-19 pandemic on mental health in the general population: a systematic review. *J Affect Disord.* 2020;**277**:55–64.

7. Ettman CK, Abdalla SM, Cohen GH, Sampson L, Vivier PM, Galea S. Prevalence of depression symptoms in US adults before and during the COVID-19 pandemic. *JAMA Netw Open.* 2020;**3**(9):e2019686.

8. Cutler DM, Summers LH. The COVID-19 pandemic and the $16 trillion virus. *JAMA.* 2020;**324**(15):1495–1496.

9. Czeisler M, Lane RI, Petrosky E, et al. Mental health, substance use, and suicidal ideation during the COVID-19 pandemic - United States, June 24–30, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;**69**(32):1049–1057.

10. Naslund JA, Aschbrenner KA, Araya R, et al. Digital technology for treating and preventing mental disorders in low-income and middle-income countries: a narrative review of the literature. *Lancet Psychiatry.* 2017;**4**(6):486–500.

11. US Food and Drug Administration. What is Digital Health? https://www.fda.gov/medical-devices/digital-health-center-excellence/what-digital-health. Published 2020. Accessed May 12, 2022.

12. Patel NA, Butte AJ. Characteristics and challenges of the clinical pipeline of digital therapeutics. *NPJ Digit Med.* 2020;**3**(1):159.

13. Jacobson NC, Weingarden H, Wilhelm S. Using digital phenotyping to accurately detect depression severity. *J Nerv Ment Dis.* 2019;**207**(10):893–896.

14. Jacobson NC, Weingarden H, Wilhelm S. Digital biomarkers of mood disorders and symptom change. *NPJ Digit Med.* 2019;**2**(1):3.

15. Marzano L, Bardill A, Fields B, et al. The application of mHealth to mental health: opportunities and challenges. *Lancet Psychiatry.* 2015;**2**(10):942–948.

16. Malhotra S, Chakrabarti S, Shah R. Telepsychiatry: promise, potential, and challenges. *Indian J Psychiatry.* 2013;**55**(1):3–11.

17. Duncan C, Serafica R, Williams D, Kuron M, Rogne A. Telepsychiatry during the COVID-19 pandemic. *Nurse Pract.* 2020;**45**(12):6–9.

18. Latha K, Meena KS, Pravitha MR, Dasgupta M, Chaturvedi SK. Effective use of social media platforms for promotion of mental health awareness. *J Educ Health Promot.* 2020;**9**:124.

19. Salerno JP. Effectiveness of universal school-based mental health awareness programs among youth in the United States: a systematic review. *J Sch Health.* 2016;**86**(12):922–931.

20. Thornicroft G, Chatterji S, Evans-Lacko S, et al. Undertreatment of people with major depressive disorder in 21 countries. *Br J Psychiatry.* 2017;**210**(2):119–124.

21. Staiger T, Stiawa M, Mueller-Stierlin AS, et al. Masculinity and help-seeking among men with depression: a qualitative study. *Front Psychiatry.* 2020;**11**:599039.

22. Stiawa M, Müller-Stierlin A, Staiger T, et al. Mental health professionals view about the impact of male gender for the treatment of men with depression - a qualitative study. *BMC Psychiatry.* 2020;**20**(1):276.

23. Trivedi MH, Jha MK, Kahalnik F, et al. VitalSign(6): a primary care first (PCP-first) model for universal screening and measurement-based care for depression. *Pharmaceuticals (Basel).* 2019;**12**(2):71.

24. U.S. National Ambulatory Medical Care Survey. The collaborative care model involves coordination between a primary care provider, a behavioral health care manager, and a psychiatrist. Published 2012. Accessed May 10, 2022.

25. Last BS, Buttenheim AM, Futterer AC, et al. A pilot study of participatory and rapid implementation approaches to increase depression screening in primary care. *BMC Fam Pract.* 2021;**22**(1):228.

26. Colligan EM, Cross-Barnet C, Lloyd JT, McNeely J. Barriers and facilitators to depression screening in older adults: a qualitative study. *Aging Ment Health.* 2020;**24**(2):341–348.

27. Andrilla CHA, Patterson DG, Garberson LA, Coulthard C, Larson EH. Geographic variation in the supply of selected behavioral health providers. *Am J Prev Med.* 2018;**54**(6 Suppl 3):S199–S207.

28. Knaak S, Mantler E, Szeto A. Mental illness-related stigma in healthcare: barriers to access and care and evidence-based solutions. *Healthc Manage Forum.* 2017;**30**(2):111–116.

29. Bailey RK, Mokonogho J, Kumar A. Racial and ethnic differences in depression: current perspectives. *Neuropsychiatr Dis Treat.* 2019;**15**:603–609.

30. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. *Psychol Bull.* 2003;**129**(5):674–697.

31. Kaniuka A, Pugh KC, Jordan M, et al. Stigma and suicide risk among the LGBTQ population: are anxiety and depression to blame and can connectedness to the LGBTQ community help? *J Gay Lesbian Ment Health.* 2019;**23**(2):205–220.

32. Lam RW, McIntosh D, Wang J, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 1. Disease burden and principles of care. *Can J Psychiatry.* 2016;**61**(9):510–523.

33. Richter T, Fishbain B, Richter-Levin G, Okon-Singer H. Machine learning-based behavioral diagnostic tools for depression: advances, challenges, and future directions. *J Pers Med.* 2021;**11**(10):957.

34. Finlay WM, Lyons E. Methodological issues in interviewing and using self-report questionnaires with people with mental retardation. *Psychol Assess.* 2001;**13**(3):319–335.

35. Davidson SK, Romaniuk H, Chondros P, et al. Antidepressant treatment for primary care patients with depressive symptoms: data from the diamond longitudinal cohort study. *Aust N Z J Psychiatry.* 2020;**54**(4):367–381.

36. Keyloun KR, Hansen RN, Hepp Z, Gillard P, Thase ME, Devine EB. Adherence and persistence across antidepressant therapeutic classes: a retrospective claims analysis among insured US patients with major depressive disorder (MDD). *CNS Drugs.* 2017;**31**(5):421–432.

37. Pompili M, Venturini P, Palermo M, et al. Mood disorders medications: predictors of nonadherence - review of the current literature. *Expert Rev Neurother.* 2013;**13**(7):809–825.

38. Braund TA, Tillman G, Palmer DM, Gordon E, Rush AJ, Harris AWF. Antidepressant side effects and their impact on treatment outcome in people with major depressive disorder: an iSPOT-D report. *Transl Psychiatry.* 2021;**11**(1):417.

39. Jacobsen PL, Thorley EM, Curran C. Real-world patient experience with sexual dysfunction and antidepressant use in patients with self-reported depression: a cross-sectional survey study. *Neurol Psychiatry Brain Res.* 2020;**36**:57–64.

40. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. *Prim Care Companion J Clin Psychiatry.* 2001;**3**(1):22–27.

41. Winter SE, Barber JP. Should treatment for depression be based more on patient preference? *Patient Prefer Adherence.* 2013;**7**:1047–1057.

42. Mercier A, Auger-Aubin I, Lebeau J-P, et al. Why do general practitioners prescribe antidepressants to their patients? A pilot study. *Biopsychosoc Med.* 2014;**8**:17–17.

43. Lewis G, Marston L, Duffy L, et al. Maintenance or discontinuation of antidepressants in primary care. *N Engl J Med.* 2021;**385**(14):1257–1267.

44. Ta JT, Sullivan SD, Tung A, Oliveri D, Gillard P, Devine B. Health care resource utilization and costs associated with nonadherence and nonpersistence to antidepressants in major depressive disorder. *J Manag Care Spec Pharm.* 2021;**27**(2):223–239.

45. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder, third edition. Published 2010. Accessed October 6, 2022.

46. American Psychological Association. APA clinical practice guideline for the treatment of depression across three age cohorts. https://www.apa.org/depression-guideline/guideline.pdf. Published 2019. Accessed May 9, 2022.

47. Gartlehner G, Wagner G, Matyas N, et al. Pharmacological and non-pharmacological treatments for major depressive disorder: review of systematic reviews. *BMJ Open.* 2017;**7**(6):e014912.

48. Dorow M, Löbner M, Pabst A, Stein J, Riedel-Heller SG. Preferences for depression treatment including internet-based interventions: results from a large sample of primary care patients. *Front Psychiatry.* 2018;**9**:181.

49. Waitzfelder B, Stewart C, Coleman KJ, et al. Treatment initiation for new episodes of depression in primary care settings. *J Gen Intern Med.* 2018;**33**(8):1283–1291.

50. Lazaratou H, Anagnostopoulos DC, Vlassopoulos M, Tzavara C, Zelios G. Treatment compliance and early termination of therapy: a comparative study. *Psychother Psychosom.* 2006;**75**(2):113–121.

51. Mental Health Taskforce. The five year forward view for mental health https://www.england.nhs.uk/wp-content/uploads/2016/02/Mental-Health-Taskforce-FYFV-final.pdf. Published 2016. Accessed April 18, 2022.

52. Mohr DC, Ho J, Duffecy J, et al. Perceived barriers to psychological treatments and their relationship to depression. *J Clin Psychol.* 2010;**66**(4):394–409.

53. National Institute for Health and Care Excellence. Depression in adults: treatment and management. Full guideline, Methods, evidence and recommendations. https://www.nice.org.uk/guidance/GID-CGWAVE0725/documents/draft-guideline. Published 2017. Accessed April 18, 2022.

54. Deif R, Salama M. Depression from a precision mental health perspective: utilizing personalized conceptualizations to guide personalized treatments. *Front Psychiatry.* 2021;**12**:650318.

55. American Psychiatric Association. APP Advisor: The App Evaluation Model. Accessed March 2, 2023.

56. Fleming GA, Petrie JR, Bergenstal RM, Holl RW, Peters AL, Heinemann L. Diabetes digital app technology: Benefits, challenges, and recommendations. A consensus report by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) Diabetes Technology Working Group. *Diabetes Care.* 2019;**43**(1):250–260.

57. US Food and Drug Administration. De novo classification request for reSET. https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160018.pdf. Published 2017. Accessed July 8, 2022.

58. US Food and Drug Administration. FDA Authorizes Marketing of Diagnostic Aid for Autism Spectrum Disorder. https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-diagnostic-aid-autism-spectrum-disorder. Published 2021. Accessed July 8, 2022.

59. Southwest Autism Research & Resource Center. First Tool to Diagnose Autism in Children as Young As 16 Months Receives FDA Clearance. https://www.autismcenter.org/first-tool-diagnose-autism-children-young-16-months-receives-fda-clearance. Published 2022. Accessed July 8, 2022.

60. Rubin R. Virtual reality device is authorized to relieve back pain. *JAMA.* 2021;**326**(23):2354.

61. Digital Therapeutics Alliance. https://dtxalliance.org/. Published 2022. Accessed November 3, 2022.

62. Digital Medicine Society. https://www.dimesociety.org/. Published 2022. Accessed November 3, 2022.

63. Omboni S, Padwal RS, Alessa T, et al. The worldwide impact of telemedicine during COVID-19: current evidence and recommendations for the future. *Connect Health.* 2022;**1**:7–35.

64. Research 2 Guidance. 2021 Global COVID-19 Survey: One year into the pandemic, how has the digital health industry changed? https://research2guidance.com/product/2021-global-covid-19-survey-one-year-into-the-pandemic-how-has-the-digital-health-industry-changed/. Accessed March 16, 2022.

65. Doraiswamy S, Abraham A, Mamtani R, Cheema S. Use of telehealth during the COVID-19 pandemic: scoping review. *J Med Internet Res.* 2020;**22**(12):e24087.

66. Guinart D, Marcy P, Hauser M, Dwyer M, Kane JM. Patient attitudes toward telepsychiatry during the COVID-19 pandemic: a nationwide, multisite survey. *JMIR Ment Health.* 2020;**7**(12):e24761.

67. Gentry MT, Puspitasari AJ, McKean AJ, et al. Clinician satisfaction with rapid adoption and implementation of telehealth services during the COVID-19 pandemic. *Telemed J E Health.* 2021;**27**(12): 1385–1392.

68. Andersen JA, Rowland B, Gloster E, McElfish PA. Telehealth utilization during COVID-19 among people with diagnosed mental health conditions. *Telemed J E Health.* 2022;**28**:743–746.

69. Arafat MY, Zaman S, Hawlader MDH. Telemedicine improves mental health in COVID-19 pandemic. *J Glob Health.* 2021;**11**:03004.

70. Torous J, Bucci S, Bell IH, et al. The growing field of digital psychiatry: current evidence and the future of apps, social media, chatbots, and virtual reality. *World Psychiatry.* 2021;**20**(3):318–335.

71. Opoku Asare K, Terhorst Y, Vega J, Peltonen E, Lagerspetz E, Ferreira D. Predicting depression from smartphone behavioral markers using machine learning methods, hyperparameter optimization, and feature importance analysis: exploratory study. *JMIR Mhealth Uhealth.* 2021;**9**(7):e26540.

72. Mandryk RL, Birk MV, Vedress S, et al. Remote assessment of depression using digital biomarkers from cognitive tasks. *Front Psychol.* 2021;**12**: 767507.

73. Rykov Y, Thach TQ, Bojic I, Christopoulos G, Car J. Digital biomarkers for depression screening with wearable devices: cross-sectional study with machine learning modeling. *JMIR Mhealth Uhealth.* 2021;**9**(10): e24872.

74. Sander LB, Paganini S, Terhorst Y, et al. Effectiveness of a guided web-based self-help intervention to prevent depression in patients with persistent back pain: the PROD-BP randomized clinical trial. *JAMA Psychiatry.* 2020;**77**(10):1001–1011.

75. Roepke AM, Jaffee SR, Riffle OM, McGonigal J, Broome R, Maxwell B. Randomized controlled trial of superbetter, a smartphone-based/internet-based self-help tool to reduce depressive symptoms. *Games Health J.* 2015; **4**(3):235–246.

76. Birney AJ, Gunn R, Russell JK, Ary DV. MoodHacker mobile web app with email for adults to self-manage mild-to-moderate depression: randomized controlled trial. *JMIR Mhealth Uhealth.* 2016;**4**(1):e8.

77. Merry SN, Stasiak K, Shepherd M, Frampton C, Fleming T, Lucassen MF. The effectiveness of SPARX, a computerised self help intervention for adolescents seeking help for depression: randomised controlled non-inferiority trial. *BMJ.* 2012;**344**:e2598.

78. Eigenhuis E, Waumans RC, Muntingh ADT, et al. Facilitating factors and barriers in help-seeking behaviour in adolescents and young adults with depressive symptoms: a qualitative study. *PLoS One.* 2021;**16**(3): e0247516.

79. Yazdavar AH, Mahdavinejad MS, Bajaj G, et al. Multimodal mental health analysis in social media. *PLoS One.* 2020;**15**(4):e0226248.

80. Cacheda F, Fernandez D, Novoa FJ, Carneiro V. Early detection of depression: social network analysis and random forest techniques. *J Med Internet Res.* 2019;**21**(6):e12554.

81. Barnett ML, Huskamp HA. Telemedicine for mental health in the United States: making progress, still a long way to go. *Psychiatr Serv.* 2020;**71**(2): 197–198.

82. Mazurek Melnyk B, Hoying J, Tan A. Effects of the MINDSTRONG© CBT-based program on depression, anxiety and healthy lifestyle behaviors in graduate health sciences students. *J Am Coll Health.* 2022;**70**(4): 1001–1009.

83. Medisafe. Adherence & Persistence https://www.medisafe.com/adherence-and-persistence/. Published 2022. Accessed May 27, 2022.

84. Christensen H, Griffiths KM, Korten A. Web-based cognitive behavior therapy: analysis of site usage and changes in depression and anxiety scores. *J Med Internet Res.* 2002;**4**(1):e3.

85. Twomey C, O'Reilly G. Effectiveness of a freely available computerised cognitive behavioural therapy programme (MoodGYM) for depression: Meta-analysis. *Aust N Z J Psychiatry.* 2017;**51**(3):260–269.

86. AiCure. https://aicure.com/. Published 2022. Accessed May 27, 2022.

87. Bain EE, Shafner L, Walling DP, et al. Use of a novel artificial intelligence platform on mobile devices to assess dosing compliance in a phase 2 clinical trial in subjects with schizophrenia. *JMIR mHealth uHealth.* 2017;**5**(2):e18.

88. Mango Health. https://www.mangohealth.com/. Published 2022. Accessed May 27, 2022.

89. Health Prize. https://healthprize.com/. Published 2022. Accessed May 27, 2022.

90. McGuiness CB, Michaeli J, Wang X, Wade RL. PMU106 evaluating the ability of a mobile medication app to improve adherence in a chronically non-adherent population in hypertension, diabetes and depression. *Value Health.* 2019;**22**:S268.

91. Innerworld. https://www.inner.world/. Published 2022. Accessed May 27, 2022.

92. Marshall JM, Dunstan DA, Bartik W. Apps with maps-anxiety and depression mobile apps with evidence-based frameworks: systematic search of major app stores. *JMIR Ment Health.* 2020;**7**(6):e16525.

93. Otsuka and Proteus Announce the First U.S. FDA Approval of a Digital Medicine System: ABILIFY MYCITE® (aripiprazole tablets with sensor). https://www.otsuka.co.jp/en/company/newsreleases/2017/20171114_1.html. Published 2017. Accessed August 16, 2022.

94. Twomey C, O'Reilly G, Bültmann O, Meyer B. Effectiveness of a tailored, integrative Internet intervention (deprexis) for depression: updated meta-analysis. *PLoS One.* 2020;**15**(1):e0228100.

95. ClinicalTrials.gov. A CBT-based Mobile Intervention as First Line Treatment for Adolescent Depression During COVID-19. https://clinicaltrials.gov/ct2/show/NCT04524598. Published 2022. Accessed May 30, 2022.

96. Feel Therapeutics. https://www.myfeel.co/. Published 2022. Accessed May 27, 2022.

97. Feel Therapeutics. Feel Therapeutics Launches Feel DTx, a DigitalTherapeutic for the Treatment of Depression and Anxiety. https://medium.com/feel-the-blog/introducing-feel-digital-therapeutic-feel-dtx-for-the-treatment-of-depression-anxiety-1198f0d30f3. Published 2022. Accessed May 27, 2022.

98. US Food and Drug Administration. Enforcement Policy for Digital Health Devices for Treating Psychiatric Disorders During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency. https://www.fda.gov/media/136939/download. Published 2020. Accessed May 26, 2022.

99. Parks AC, Williams AL, Tugade MM, Hokes KE, Honomichl RD, Zilca RD. Testing a scalable web and smartphone based intervention to improve depression, anxiety, and resilience: a randomized controlled trial. *Int J Wellbeing.* 2018;**8**(2):22–67.

100. ClinicalTrials.gov. Trial to Evaluate the Effectiveness of a Digital Therapeutics in Adults Diagnosed With Major Depressive Disorder (MIRAI). https://clinicaltrials.gov/ct2/show/NCT04770285. Published 2022. Accessed May 30, 2022.

101. Pear Therapeutics. Pear Therapeutics announces FDA submission for Somryst™, a prescription digital therapeutic for the treatment of adults with chronic insomnia and depression. https://peartherapeutics.com/pear-therapeutics-announces-fda-submission-for-somryst-a-prescription-digital-therapeutic-for-the-treatment-of-adults-with-chronic-insomnia-and-depression/. Published 2019. Accessed May 30, 2022.

102. Keefe RSE, Cañadas E, Farlow D, Etkin A. Digital intervention for cognitive deficits in major depression: a randomized controlled trial to assess efficacy and safety in adults. *Am J Psychiatry.* 2022;**179**(7):482–489.

103. Health Rhythms. https://www.healthrhythms.com/. Published 2022. Accessed May 27, 2022.

104. Falconer E, Kho D, Docherty JP. Use of technology for care coordination initiatives for patients with mental health issues: a systematic literature review. *Neuropsychiatr Dis Treat.* 2018;**14**:2337–2349.

105. Valera Health. How it works. https://www.valerahealth.com/how-it-works/. Published 2022. Accessed March 16, 2022.

106. BetterHelp. https://www.betterhelp.com/. Published 2022. Accessed May 27, 2022.

107. Talkspace. https://www.talkspace.com/. Published 2022. Accessed May 27, 2022.

108. SilverCloud Health. https://www.silvercloudhealth.com/. Published 2022. Accessed May 27, 2022.

109. Ginger. https://www.ginger.com/care. Published 2022. Accessed August 26, 2022.

110. Agrawal R, Prabakaran S. Big data in digital healthcare: lessons learnt and recommendations for general practice. *Heredity.* 2020;**124**(4):525–534.

111. Anxiety & Depression Association of America. https://adaa.org/find-help/support. Published 2022. Accessed May 9, 2022.

112. Depression and Bipolar Support Alliance. https://www.dbsalliance.org/support/chapters-and-support-groups/online-support-groups/. Published 2022. Accessed May 9, 2022.

113. 7 cups. https://www.7cups.com/. Published 2022. Accessed May 9, 2022.

114. Lin D, Nazreen T, Rutowski T, et al. Feasibility of a machine learning-based smartphone application in detecting depression and anxiety in a generally senior population. *Front Psychol.* 2022;**13**:811517.

115. ClinicalTrials.gov. Using Voice Biomarkers to Predict the Likelihood of Major Depressive Disorder. https://clinicaltrials.gov/ct2/show/NCT04874077. Published 2022. Accessed May 27, 2022.

116. Kintsugi. https://kintsugihello.com/. Published 2022. Accessed May 27, 2022.

117. Winterlight Labs. Monitoring cognitive impairment through speech. https://winterlightlabs.com/. Published 2022. Accessed May 27, 2022.

118. ClinicalTrials.gov. Speech-Based Digital Biomarker for Psychiatric Disease. https://clinicaltrials.gov/ct2/show/NCT04851912. Published 2022. Accessed May 27, 2022.

119. Sverdlov O, Curcic J, Hannesdottir K, et al. A study of novel exploratory tools, digital technologies, and central nervous system biomarkers to characterize unipolar depression. *Front Psychiatry.* 2021;**12**:640741.

120. Sonde Health. Vocal Biomarkers for Mental Fitness Scoring and Tracking. https://www.sondehealth.com/vocal-biomarkers-for-mental-fitness-scoring-and-tracking. Published 2021. Accessed May 27, 2022.

121. McIntyre RS, Lipsitz O, Rodrigues NB, et al. An app-based digit symbol substitution test for assessment of cognitive deficits in adults with major depressive disorder: evaluation study. *JMIR Ment Health.* 2022;**9**(10):e33871.

122. Bell IH, Nicholas J, Alvarez-Jimenez M, Thompson A, Valmaggia L. Virtual reality as a clinical tool in mental health research and practice. *Dialogues Clin Neurosci.* 2020;**22**(2):169–177.

123. Kyaw BM, Saxena N, Posadzki P, et al. Virtual reality for health professions education: systematic review and meta-analysis by the digital health education collaboration. *J Med Internet Res.* 2019;**21**(1):e12959.

124. Eis S, Solà-Morales O, Duarte-Díaz A, et al. Mobile applications in mood disorders and mental health: systematic search in apple app store and google play store and review of the literature. *Int J Environ Res Public Health.* 2022;**19**(4):2186.

125. Otsuka and Click Therapeutics Collaborate to Develop and Commercialize Digital Therapeutics for Patients with Major Depressive Disorder. https://www.otsuka-us.com/discover/otsuka-and-click-therapeutics-collaborate. Published 2018. Accessed November 4, 2022.

126. Iacoviello BM, Wu G, Alvarez E, et al. Cognitive-emotional training as an intervention for major depressive disorder. *Depress Anxiety.* 2014;**31**(8):699–706.

127. Iacoviello BM, Murrough JW, Hoch MM, et al. A randomized, controlled pilot trial of the emotional faces memory task: a digital therapeutic for depression. *NPJ Digit Med.* 2018;**1**(1):21.

128. McCue M, Blair C, Fehnert B, et al. Mobile app to enhance patient activation and patient-provider communication in major depressive disorder management: collaborative, randomized controlled pilot study [preprint]. *JMIR Form Res.* 2022;**6**(10):e34923.

129. Keutzer L, Simonsson US. Medical device apps: an introduction to regulatory affairs for developers. *JMIR Mhealth Uhealth.* 2020;**8**(6):e17567.

130. Sverdlov O, van Dam J, Hannesdottir K, Thornton-Wells T. Digital therapeutics: an integral component of digital innovation in drug development. *Clin Pharmacol Ther.* 2018;**104**(1):72–80.

131. Bulaj G. Combining non-pharmacological treatments with pharmacotherapies for neurological disorders: a unique interface of the brain, drug–device, and intellectual property. *Front Neurol.* 2014;**5**:126.

132. Spadaro B, Martin-Key NA, Bahn S. Building the digital mental health ecosystem: opportunities and challenges for mobile health innovators. *J Med Internet Res.* 2021;**23**(10):e27507.

133. Nahum-Shani I, Smith SN, Spring BJ, et al. Just-in-time adaptive interventions (JITAIs) in mobile health: key components and design principles for ongoing health behavior support. *Ann Behav Med.* 2018;**52**(6):446–462.

134. McIntyre RS, Ismail Z, Watling CP, et al. Patient-reported outcome measures for life engagement in mental health: a systematic review. *J Patient Rep Outcomes.* 2022;**6**(1):62.

135. Meyerhoff J, Liu T, Kording KP, et al. Evaluation of changes in depression, anxiety, and social anxiety using smartphone sensor features: longitudinal cohort study. *J Med Internet Res.* 2021;**23**(9):e22844.

136. McIntyre RS, Lee Y, Rong C, et al. Ecological momentary assessment of depressive symptoms using the mind.me application: convergence with the Patient Health Questionnaire-9 (PHQ-9). *J Psychiatr Res.* 2021;**135**:311–317.

137. Zhang H, Liao Y, Han X, et al. Screening depressive symptoms and incident major depressive disorder among Chinese community residents using a mobile app-based integrated mental health care model: cohort study. *J Med Internet Res.* 2022;**24**(5):e30907.

138. Kivelä L, van der Does WAJ, Riese H, Antypa N. Don't miss the moment: a systematic review of ecological momentary assessment in suicide research. *Front Digit Health.* 2022;**4**:876595.

139. Moriarty AS, Castleton J, Gilbody S, et al. Predicting and preventing relapse of depression in primary care. *Br J Gen Pract.* 2020;**70**(691):54.

140. Brown LA, Taylor DJ, Bryan C, et al. Digital phenotyping to improve prediction of suicidal urges in treatment: study protocol. *Aggress Violent Behav.* 2022;**66**:101733.

141. Baghaei N, Chitale V, Hlasnik A, Stemmet L, Liang HN, Porter R. Virtual reality for supporting the treatment of depression and anxiety: scoping review. *JMIR Ment Health.* 2021;**8**(9):e29681.

142. Ioannou A, Papastavrou E, Avraamides MN, Charalambous A. Virtual reality and symptoms management of anxiety, depression, fatigue, and pain: a systematic review. *SAGE Open Nurs.* 2020;**6**:2377960820936163.

143. Chen K, Barnes-Horowitz N, Treanor M, Sun M, Young KS, Craske MG. Virtual reality reward training for anhedonia: a pilot study. *Front Psychol.* 2020;**11**:613617.

144. Lindner P. Better, virtually: the past, present, and future of virtual reality cognitive behavior therapy. *Int J Cogn Ther.* 2021;**14**(1):23–46.

145. Borghouts J, Eikey E, Mark G, et al. Barriers to and facilitators of user engagement with digital mental health interventions: systematic review. *J Med Internet Res.* 2021;**23**(3):e24387.

146. Wies B, Landers C, Ienca M. Digital mental health for young people: a scoping review of ethical promises and challenges. *Front Digit Health.* 2021;**3**:697072.

147. Mehrotra A, Hendley R, Musolesi M. Towards multi-modal anticipatory monitoring of depressive states through the analysis of human-smartphone interaction. In: *Proceedings of the 2016 ACM International Joint Conference on Pervasive and Ubiquitous Computing: Adjunct; ; Heidelberg, Germany.* New York, NY: Association for Computing Machinery; 2016.

148. Koh J, Tng GYQ, Hartanto A. Potential and pitfalls of mobile mental health apps in traditional treatment: an umbrella review. *J Pers Med.* 2022;**12**(9):1376.

149. Torous J, Lipschitz J, Ng M, Firth J. Dropout rates in clinical trials of smartphone apps for depressive symptoms: a systematic review and meta-analysis. *J Affect Disord.* 2020;**263**:413–419.

150. Marwaha JS, Landman AB, Brat GA, Dunn T, Gordon WJ. Deploying digital health tools within large, complex health systems: key

considerations for adoption and implementation. *NPJ Digit Med.* 2022;
5(1):13.

151. Saeed SA, Masters RM. Disparities in health care and the digital divide.
Curr Psychiatry Rep. 2021;**23**(9):61–61.

152. Mental health app installs decline more than 30% since January 2021.
https://blog.apptopia.com/mental-health-app-installs-decline-more-
than-30-percent?utm_source=STAT+Newsletters&utm_campaign=
9db2a5462d-health_tech_COPY_01&utm_medium=email&utm_term=
0_8cab1d7961-9db2a5462d-154460636. Published 2022. Accessed May
30, 2022.

153. Kinoshita S, Cortright K, Crawford A, et al. Changes in telepsychiatry
regulations during the COVID-19 pandemic: 17 countries and regions'
approaches to an evolving healthcare landscape. *Psychol Med.* 2020;**52**:
1–8.

154. Williams MG, Stott R, Bromwich N, Oblak SK, Espie CA, Rose JB.
Determinants of and barriers to adoption of digital therapeutics for mental
health at scale in the NHS. *BMJ Innov.* 2020;**6**(3):92.

155. Carlo AD, Hosseini Ghomi R, Renn BN, Areán PA. By the numbers:
ratings and utilization of behavioral health mobile applications. *NPJ Digit
Med.* 2019;**2**(1):54.

156. US Food and Drug Administration. The Software Precertification (Pre-
Cert) Pilot Program: Tailored Total Product Lifecycle Approaches and
Key Findings. https://www.fda.gov/media/161815/download. Published
2022. Accessed March 6, 2023.

157. Serrano-Ripoll MJ, Zamanillo-Campos R, Fiol-DeRoque MA, Castro A,
Ricci-Cabello I. Impact of smartphone app-based psychological interven-
tions for reducing depressive symptoms in people with depression: sys-
tematic literature review and meta-analysis of randomized controlled
trials. *JMIR Mhealth Uhealth.* 2022;**10**(1):e29621.

158. Henni SH, Maurud S, Fuglerud KS, Moen A. The experiences, needs and
barriers of people with impairments related to usability and accessibility of
digital health solutions, levels of involvement in the design process and
strategies for participatory and universal design: a scoping review. *BMC
Public Health.* 2022;**22**(1):35.

159. Rezaei Aghdam A, Watson J, Cliff C, Miah SJ. Improving the theoretical
understanding toward patient-driven health care innovation through
online value cocreation: systematic review. *J Med Internet Res.* 2020;**22**
(4):e16324.

160. Centers for Medicare and Medicaid Services. Remote Therapeutic Moni-
toring/Treatment Management. https://public-inspection.federalregister.
gov/2021-23972.pdf. Published 2021. Accessed July 8, 2022.

161. Hayes CJ, Dawson L, McCoy H, et al. Utilization of remote patient
monitoring within the United States health care system: A scoping review.
Telemed J E Health. 2022;**29**:384–394.

162. Research 2 Guidance. Where is the money in digital health? The roadmap to
digital health app reimbursement in Europe. https://research2guidance.com/
where-is-the-money-in-digital-health-the-roadmap-to-digital-health-app-
reimbursement-in-europe/. Published 2022. Accessed December 22, 2022.