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REVIEW

Digital therapeutics in depression and bipolar disorder: a comprehensive systematic review

Laura ORSOLINI *, Giulio LONGO, Giuseppe L. NUZZO, Umberto VOLPE

Unit of Clinical Psychiatry, Department of Clinical Neurosciences (DIMSC), Polytechnic University of Marche, Ancona, Italy

*Corresponding author: Laura Orsolini, Unit of Clinical Psychiatry, Department of Clinical Neurosciences (DIMSC), Polytechnic University of Marche, 60126 Ancona, Italy. E-mail: l.orsolini@staff.univpm.it

ABSTRACT

INTRODUCTION: Digital therapeutics (DTx) represent a novel approach to treat mood disorders like major depressive disorder (MDD) and bipolar disorder (BD). Treatment can usually be based on interventions such as cognitive behavioral therapy (CBT) and psychoeducation, and they can be relatively inexpensive and more easily accessible. However, upscaling DTx in clinical practice is relatively slow due to regulatory barriers, lack of sufficient clinical evidence, and patient nonadherence.
EVIDENCE ACQUISITION: A systematic review following the PRISMA guidelines was carried out through MEDLINE/PubMed and Scopus. All studies exploring the use of DTx for MDD and BD were assessed. While excluding studies not presenting any clinical results or not aimed at DTx but instead at general digital mental health (DMH) interventions.
EVIDENCE SYNTHESIS: Initial search strategy produced 4598 papers, 24 of which have been selected and discussed. Most studies were conducted on MDD, rather than BD. Most frequently used approaches included CBT, psychoeducation and mindfulness. Most studies reported positive changes in mood symptoms, but only some of them provided information about the maintenance of these results in the long term. Among inhibitors in the acceptability of DTx were represented by limited real-world evidence, engagement issues and inconsistent regulatory environments.
CONCLUSIONS: Using DTx for mood disorders shows great promise. Effective interventions that are accessible and modeled are feasible. However, to structurally incorporate DTx into standard clinical practice, there is the need to develop clear regulatory channels, improve user's involvement and provide additional evidence of long-term efficacy.

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KEY WORDS: Therapeutics; Mood disorders; Psychiatry.

Introduction

The World Health Organization (WHO) estimated that one in eight people globally have a mental disorder, being mainly represented by mood and anxiety disorders. These conditions have been worsened by the pandemic of coronavirus disease 2019 (COVID-19)[1] In response, the WHO's Comprehensive Mental Health Action Plan 2013-2030 emphasizes the need to increase the focus on mental health promotion and prevention, the mental health information systems and the application of digital tools for mental health.[1] At the same time, the World Psychiatric Association (WPA)'s working Group on Digita-

lization in Mental Health and Care developed the Global Digitalization Action Plan 2023-2026, to support clinicians in the digitalization process of services.[2] Furthermore, the European Psychiatric Association published in the last years recommendations to help physicians using digital intervention and technology during their daily clinical life.[3] However, the shortage of doctors in the last few years has worsened the situation such that there are longer waiting lists and being able to offer quality services to the patients has been a challenge.[4-8] These gaps could be more likely be addressed by digital interventions that can provide an effective management and treatment of the patients.[9] Digital mental health (DMH) is able to provide different types of interventions for the prevention, treatment, and management of different conditions.[10] Specifically, many digitally-delivered interventions have been developed to offer effective and feasible treatments for mood disorders.[10]

Nonetheless, only a few DMH interventions, and in particular digital therapeutics (DTx), are well supported by robust scientific and clinical evidence. Joseph Kvedar was the first to introduce the concept of DTx in 1995 to encompass all software-based, evidence-driven therapeutic products to prevent, manage, or treat a medical condition or disease.[11] They can be delivered through different devices (applications, mobile devices, Internet of Things (IoT), mobile devices or wearable sensors) and can be administered together with psychotherapy or pharmacological treatment or on their own.[10, 11] DTx are classified as medical devices and have to fulfill strict development criteria, in terms of scientific robustness and validation through randomized controlled trials, as conventional pharmacological treatments.[11] The DTx are divided into two major categories: Software as a Medical Device (SaMD) and Software in a Medical Device (SiMD). SaMD is software that acts as a standalone medical device, while SiMD is incorporated into a physical device to support the management of a particular health issue.[12] When either SaMD or SiMD is applied through a smartphone, it is called a mobile medical app (MMA).[13] According to the definition, DTx are also supported by clinical evidence from real-world data and they need regulatory signing, such as from the U.S. Food and Drug Administration (FDA). These solutions are usually recommended by health care professionals, and in some countries, they may be reimbursed by public or private insurance.[14] Currently, Europe lacks a unified regulatory framework specifically addressing the evaluation, safety, and data integrity of DTx.[14] However, the European Medicines Agency (EMA) and the European Commission are beginning to explore the potential role of DTx in clinical care.[14] Only few countries in Europe have a specific framework in the evaluation and assessment of DTx (in particular Germany, France, the United Kingdom, Belgium, Finland and Sweden).[15]

Over the past few years, the list of recommended DTx by the National Institute for Health and Care Excellence (NICE) has increased, involving DTx for the treatment of depression, different anxiety disorders, obsessive compulsive disorder, post-traumatic stress disorder and psychotic disorders.[16-19] Meanwhile, the FDA in the United States has been operating a DTx precertification program since 2017.[20] Despite the potential of DTx in the treatment of mood disorders like major depression disorder (MDD) and bipolar disorder (BD), the number of actually approved solutions is limited. Hence there is a clear requirement to systematically review the current literature on real-world use and therapeutic efficacy of DTx in the management of mood spectrum disorders.

Evidence acquisition

Search strategy

A systematic review, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, was conducted with the aim of exploring the practical applications of DTx in mood disorders, including peripartum depression. The electronic database MEDLINE/PubMed and Scopus were used for the identification of the studies, using a combined search strategy of free text terms and exploded MESH headings for the topics of DTx and Mood Disorders as following: (((Digital Therapeutics [Title/Abstract]) OR (DTx [Title/Abstract])

AND ((Mood Disorder [Title/Abstract]) OR (Depression [Title/Abstract]) OR (Bipolar Disorder [Title/Abstract]))), without time restrictions, through March 18, 2025. In addition, other studies were retrieved from the reference list of relevant articles and from consultation with experts in the field or hand searching. We limited the search to only English-written studies only. The following exclusion criteria have been applied: 1) not human studies; 2) studies on DTx without data on its application in mood disorders; 3) studies on DMH but not specifically addressed to DTx; 4) studies on DTx applied in mood disorders in comorbidity with physical and/or other mental conditions; 5) studies discussing only protocols without clinical data; and 6) studies on already NICE recommended DTx for mood disorders. The identified studies were selected for eligibility independently by two authors (G.L. and G.L.N.) in a 2-step-based process; the first screening was based on the title and abstract and full texts were retrieved to perform the second screening. Disagreements by reviewers were ultimately reached by consensus at both stages. Data were extracted independently by two authors (G.L. and G.L.N.) and any disagreement was discussed and resolved by a third author (L.O.), and, in case of disagreement, further revised by a senior supervisor (U.V.), *via* an *ad-hoc* developed data extraction spreadsheet.

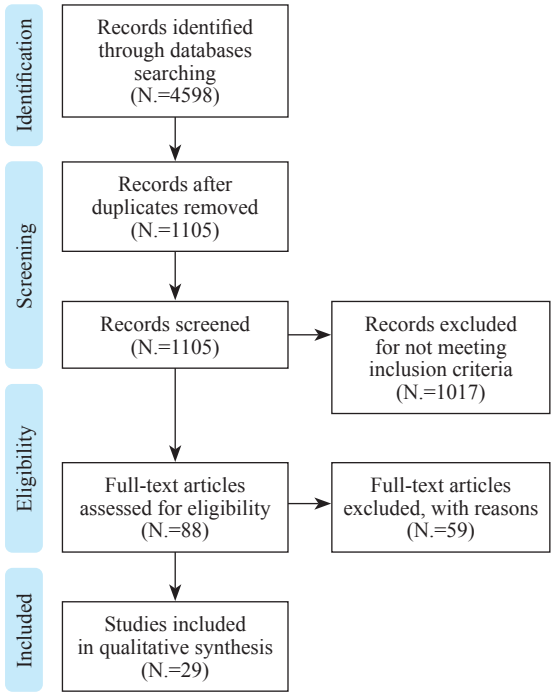

Figure 1.—Flow chart describing the process of study search and selection in accordance with PRISMA guidelines. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Evidence synthesis

The initial search using the keywords produced a total of 4598 results. After removing duplicates (N.=3493), further 1105 papers were excluded as they did not meet the inclusion criteria listed above. Amongst 88 remaining studies screened for eligibility depending on their abstract, 59 were not included because they were not pertinent to the topic of the present investigation. Finally, a total of 29 papers were included and accounted for in our analysis. Figure 1 presents the PRISMA flow diagram, illustrating the process of reviewing the articles identified through the source search. The selected studies are summarized in Supplementary Digital Material 1 (Supplementary Table I).[14, 21-48] Results have been reported based on interventional characteristics and on diagnostic groups (*i.e.*, papers focused on MDD, BD or on both together).

Depression

Iacoviello *et al*.[21] developed a cognitive-emotional training intervention for MDD, called the Emotional Faces Memory Task (EFMT), which consists of exposing patients to sequential photos of faces on a computer. Postintervention results showed significant improvement in emotional face recognition among patients and effective improvement in working memory.

Goldin *et al*.[22] implemented the "ascend program," composed of 8 module interventions, delivered *via* a mobile phone-based app in 8 weeks. This program includes CBT activities, behavioral activation therapy (BAT) and mindfulness. Modules were delivered with specific order: "introduction to mindfulness," "low mood and motivation," "self-compassion," "managing worry," "overcoming thinking traps," "rethinking your life values," "being aware of your relationships," and "relapse prevention." The objective was to

equip patients with useful tools to cope with depressive episodes. Findings demonstrated a significant long-term reduction of depressive symptoms over 4-weeks postintervention.

Bower *et al*.[23] created a digital intervention prototype, "Advisors," to support patients during the process of discontinuing antidepressant treatment. This intervention is intended to inform patients about their medication, focusing on side effects and discontinuation symptoms information. Such interventions can also enhance physicians' ability to detect and manage patients' health issues more effectively.

Venkatesan *et al*.[14] carried out a study on the effectiveness of the "Vida Health" app-based CBT program (Vida Health, San Francisco, CA, USA). The app allows users to talk with a therapist who provides weekly activities and goals according to the individual's therapeutic progress. Findings demonstrated a significant decrease in depressive symptoms, with stable improvements over time.

Gould *et al*.[24] studied the effectiveness of the "Meru Health" app for treating depressive symptoms in adults and older adults (Meru Health, San Mateo, CA, USA). The app provides daily CBT- and mindfulness-based therapy by trained psychotherapists through informational materials and videos. It also allows patients to request asynchronous conversations with the therapist and group discussions. The results showed good feasibility and a significant reduction in depressive and anxiety symptoms.

Tang *et al*.[25] developed the "MamaLift" app for *postpartum* depression (Curio Digital Therapeutics Inc., Princeton, NJ, USA). It consists of a self-guided digital intervention that can be administered with the support of a therapist or independently. Each day, a self-guided program based on CBT, Interpersonal Psychotherapy (IPT), dialectical behavioral therapy (DBT), and BAT is offered to the patient through video, audio, and text formats. The results found a high level of patient satisfaction, as well as high levels of feasibility and usability.

Kulikov *et al*.[26] developed the "Spark" app (Spark, Boston, MA, USA), a self-guided 5-weeks CBT with the aim of reducing depressive symptoms in a group of adolescents aged 13-21 patients. Findings suggested a high level of engagement and satisfaction by patients and a significant reduction in depressive symptoms. The same results were confirmed by a more recent study conducted by Peake *et al*.[27]

Gual-Montolio *et al*.[28] outlined the effects of the "My EMI" app (EMI Health, Murray, UT, USA), a tool to enhance emotional well-being in a group of adults affected by emotional disorders, including depressive symptomatology. The intervention was built based on Measurement-Based Care (MBC), consisting of regular monitoring of patients and periodic feedback to the therapist (or both therapist and patient), tailoring the intervention according to this feedback.

Chatbots are digital tools that simulate human conversation, allowing users to interact with digital devices as if they were interacting with a real person.[49] Fitzpatrick *et al*.[29] and Hoffman *et al*.[30] explored the effectiveness of the chatbot, "Woebot" (Woebot Health, San Francisco, CA, USA), in a group of young adult patients with depressive symptoms. Furthermore, using the same chatbot, Suharwardy *et al*.[31] evaluate its usefulness in the context of *postpartum* depression. This intervention provides patients with tools from CBT and IPT to manage mood and anxiety. These studies consistently demonstrated a significant reduction in depressive symptomatology, despite varying levels of engagements across patients. However, Suharwardy *et al*.[31] did not include only patients with an official diagnosis of *postpartum* depression.

Keefe *et al*.[32] and Stamatis *et al*.[33] used a Dtx (AKL-T03) targeting attentional control *via* a multitasking treatment game in patients affected by depression. The use of this resource improved cognitive metrics in measures of working memory, visuospatial attention, and processing speed, but was not correlated with variations in self-reported clinical outcomes.

Braun *et al*.[34] combined CBT therapy with the use of the app "Elona Therapy" (Elona Health GmbH, Düsseldorf, Germany) for addressing depressive and anxious symptoms in a group of university students. It provided psychoeducation and techniques and interventions related to behavior, thoughts, emotions, and relationships. It also included a specific module on relapse prevention. They found that DTx supplementing

face-to-face therapy sessions can be perceived as a useful tool for college students with mild to moderate symptoms of anxiety or depression in their daily lives.

Lv *et al*.[35] used a voice-based coach, "Lumen" (University of Illinois at Chicago, Chicago, IL, USA), delivering problem-solving treatment to patients affected by depression, anxiety or both. The app delivers an evidence-based problem solving treatment program, composed of 8 sessions (4 weekly sessions and then 4 biweekly sessions over 12 weeks). Results showed that it helped patients in reducing depressive and anxious symptoms.

Fundoiano-Hershcovitz *et al*.[36] using a mobile platform-based treatment called "Dario" (DarioHealth Corp., New York, NY, USA), explored the effect of this DTx on depressive and anxious symptoms in a group of patients. Each session is composed of conceptual videos, textual skills, breathing exercises, and progress monitoring tools. This study demonstrated an overall improvement followed by a period of stability in depression and anxiety symptoms associated with the digital intervention based on CBT.

Lawrence *et al*.[37] conducted a study to evaluate the effectiveness, usability, and user satisfaction of "PostpartumCare.ca," a web-enabled psychoeducational resource for patients affected by *postpartum* depression and anxiety. Two different groups were created, the control group and the intervention group that received the digital intervention. The intervention group showed greater improvements in depressive and anxiety symptoms compared to the control group, as well as a positive usability and satisfaction ratings for "PostpartumCare.ca."

Jeong *et al*.[38] developed a DTx CBT-based with a virtual agent, a zoomorphic agent design inspired by the Pembroke Welsh Corgi. They tested the app on a group of students affected by low mood. The intervention was composed of 24 CBT-focused sessions and 17 meditation modules. At the end, they described that the virtual agent improved the acceptability and usability of the app and that it lowered depressive symptoms in university students.

Vanderkruik *et al*.[39] investigated the effect of the mobile app "The Guardians" (MIT Media Lab, Cambridge, MA, USA), a behavioral activation gaming app, in women affected by depression during pregnancy. Findings of this study confirmed the feasibility of this digital intervention for patients affected by peripartum disorders, as well as good user acceptability. Retention and engagement levels were very high, and use of the app was associated with a significant reduction in depressive symptom scores over the 10-week trial. A subsequent study confirmed these findings, regardless of comorbidities (organic or psychiatric).[40]

Wilhelm *et al*.[41] described the feasibility, acceptability, and preliminary clinical effect of an app called "Mindset" to patients affected by depression (Koa Health, Melbourne, Australia). It is a deployment-ready 8-week smartphone-based CBT. Results showed that "Mindset" is a feasible and acceptable treatment option for patients with depression and that it reduces depressive symptoms, improving quality of life and functional impairments.

Fatouros *et al*.[42] developed a mobile app to deliver personalized CBT-based interventions for patients affected by depressive and generalized anxiety symptoms. Patients were randomized to the control group or the intervention group. Results showed that depressive and anxious symptoms were reduced significantly more in the experimental group rather than the control group.

Bipolar disorder (BD)

Depp *et al*.[43] carried out a study using "PRISM" (Seattle Children's Hospital, Seattle, WA, USA), a mobile intervention, that delivers to patients affected by BD information derived from psychoeducation for BP in a self-managed approach, without the involvement of a therapist. Using a series of questions about mood, the app also creates a mood chart, monitoring mood tendency and patterns. Findings showed a reduction in depressive symptoms, but not in manic symptoms.

Dodd *et al*.[44] and Lobban *et al*.[45] performed two studies using the "Enhanced Relapse Prevention" (ERPonline), targeted to BD patients. This is a web-based self-directed intervention that enables patients to build a model of their mood fluctuations, allowing them to identify and manage triggers for new episodes and developing new effective coping techniques. The inter-

vention has been considered by patients as relevant, accessible and user-friendly.

Jonathan *et al*.[46] and Dopke *et al*.[50] developed a self-management "LiveWell" app for BD patients (Northwestern University, Chicago, IL, USA). It delivers information about BD, teaching practical skills for managing emotional instability and preventing recurrence. Furthermore, it enables the creation of a Wellness plan, helping to reduce relapse risk and managing prodrome signs and symptoms in the initial phase of a recurrence. It also helps to monitor treatment adherence, sleep duration, and general wellness.[46, 47, 50]

Depression and bipolar disorder

Cho *et al*.[48] performed a study on patients suffering from MDD and BD that consisted of multiple digital interventions. They asked each patient to complete a daily eMood chart and use a wearable daily activity tracker. The "Circadian Rhythm for Mood" app (Korea University, Seoul, South Korea) collected all passive and active data, predicting mood patterns and identifying specific relapse factors. Findings showed that the app is useful in reducing significantly the number and duration of depressive and manic episodes, promoting also the development of healthy protective behaviors.

Discussion

There is a growing public health need for more scientifically solid and well-structured evidence-based, clinically applicable in the real-world settings, easily short-term implementable and long-term sustainable DTx for individuals affected by mood disorders. DTx can help increase access to mental health care, ideally reducing waiting lists, decreasing costs and the stigma associated with seeking mental health care and potentially improving the quality of diagnosis and treatment.[9, 51-53] However, the current evidence regarding DTx in mood disorders is relatively scant. Most of the published studies mainly investigated DTx in terms of their feasibility and acceptability, failing to provide an investigation and verification of their clinical effectiveness in real-world settings.[20]

Overall, the current existing research is more oriented towards MDD than other mood disorders; furthermore, many of these studies included participants with symptoms of depression but not meeting the criteria for a MDD (Supplementary Table I). Most of the studies enrolled adults, four studies targeted specific age groups, three with young adults,[29, 34, 38] two with adolescents[26, 27] and the other with older adults.[24] Furthermore, five papers were specifically addressed to women at risk for postpartum depression (PPD)[25, 31, 37, 39, 40] The vast majority of MDD-related DTx studies were conducted in the United States, they were mainly conducted in single research sites and recruited a relatively small sample size (less than 100 subjects). Most of these interventions were CBT-based[14, 22, 24, 26-30, 34, 36, 38, 41, 42] with some interventions based on emotion-focused mindfulness therapy (EFMT),[21] problem solving therapy (PST)[35] and/or psychoeducational approach.[23] Studies on PPD all included CBT interventions,[31, 37, 39, 40] with only one providing an additional IPT-based and dialectical behavior therapy (DBT)-based approach.[25]

Regarding BD, only five published studies were found, which had a relatively small number of participants.[43-47, 50] Also in this case, studies on BD mainly focused on feasibility and/or acceptability as main outcomes, failing again in assessing clinical effectiveness in real-world settings. These interventions were mostly developed according to a psychoeducational approach. Moreover, DTx on BD were mainly conducted in the United States or the United Kingdom, with adult participants. A rare exception was a study from Korea which included both MDD and BD patients and compared efficacy and effectiveness outcomes.[48] Overall, all the studies that measured symptoms, before and after the interventions, found a post-treatment improvement.[14, 21, 22, 24, 26-28, 29-33, 35-43, 48] However, only one of the studies included a follow-up assessment that provided a long-term longitudinal monitoring of symptomatology improvement.[32]

Limitations of the study

The systematic review has several limitations, mainly due to the relatively limited amount of literature published so far. Firstly, most of the studies enrolled relatively small and heterogeneous

samples (in terms of sex and age distribution), which could limit a larger generalizability of the findings. In particular, the lack of DTx assessing the intervention in terms of efficacy and effectiveness across all ages could significantly limit the clinical considerations regarding the findings here provided. Further studies on DTx should definitely provide the intervention by using a sex-based but also an age-sensitive personalized approach, in order to evaluate which are the best targeted population to be addressed by using a DTx tool. Secondly, most studies used heterogeneous inclusion criteria and not comparable assessment tools, which could significantly limit the comparability of all interventions. Thirdly, the main outcome investigated in most of the studies addresses feasibility and acceptability, rather than clinical outcomes. Therefore, we could hypothesize that the current literature on DTx more specifically assessed the level of acceptability of the intervention by clinical population, within a context of improving the attrition and retention rate following a DTx tool. These outcomes are relevant at the beginning of the development of new DMH instruments but do not provide relevant clinical implications useful for establishing whether DTx could be effective in real-world settings. Therefore, the next level of studies on DTx should include more cost-effective as well as long-term sustainable measures by investigating the improvement (if any) that can be achieved from a symptomatological perspective. Fourthly, studies rarely reported the attrition rates ("nonattrition bias"), and most were conducted in a single-site research in the United States or United Kingdom. These criteria could definitely limit the generalizability of DTx interventions across other countries, with different legislations and regulamentations on DTx implementation in routine psychiatric clinical practice, but also lacking a cultural/ethnic-sensitive approach. Fifthly, very few studies provided follow-up assessments to verify the persistence of DTx therapeutic benefits. Finally, methodology used in the included studies appears too heterogeneous, making it difficult in comparing the effects and use DTx in clinical practice. Therefore, future studies should be carried out by recruiting larger samples, involving more age groups, with a sex- and ethnic-sensitive methodology. At the same time, DTx should be tested in real-world settings, evaluating the actual usefulness, feasibility and acceptability of digital interventions in everyday life. Another limitation, that prevents from the generalization of results, is that many studies included subjects with depressive symptoms, meanwhile there are only few studies on the population of patients with an official diagnosis of MDD. Also, literature on the BD population should be increased, developing DTx, based on CBT, IPT, and interpersonal and social rhythm therapy (IPSRT), for these patients. In addition, other driving factors such as affective temperaments[54] or personality traits[55] may play a significant role, along with individual variables,[56] in determining both optimal treatment outcomes and greater engagement in digital tools. However, the current literature still provides only limited coverage of these topics, and further research is needed to address the issue systematically.[56, 57] Finally, there are no publications addressing individuals affected by other mood disorders, such as cyclothymic mood disorder or individuals with other comorbid psychiatric and/or internal conditions, including substance and/or alcohol use disorders.

Conclusions

In conclusion, DTx represents a promising tool for the prevention, treatment and management of mood disorders, in particular for MDD and BD. Despite their potential, the use of DTx, for definition, must be supported by adequate regulatory frameworks and standardized clinical trials, increasing their access, applicability and spread across all countries. First published studies, despite their evident limitations, seem encouraging, demonstrating their potential to decrease depressive symptoms and enhance emotional well-being as well as cognitive function in some patients. Further studies are fundamental to establish these clinical regulations and train specialists to use them in their daily clinical practice.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Laura Orsolini and Umberto Volpe have given substantial contributions to the study conception and design; Giulio Longo and Giuseppe L. Nuzzo contributed to the data acquisition; Laura Orsolini, Giulio Longo, Giuseppe L. Nuzzo, and Umberto Volpe contributed to the manuscript draft, Umberto Volpe revised it critically. All authors read and approved the final version of the manuscript.

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