Digital Mental Health

A Practitioner's Guide

Ives Cavalcante Passos
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Foreword

The dawn of the digital age has utterly transformed multiple domains of life. Health is no different, and mental health is being transformed in the digital age. Digital approaches offer promise in diverse domains of health care from assessment to diagnosis to treatment, and across a diversity of different disorders. This book captures the cutting edge of an emerging discipline and provides a contemporaneous overview of the field of digital mental health to guide clinicians, practitioners, and researchers.

Several secular trends have accelerated the drive to digital mental health assessment and interventions. Firstly, there has been a global increase in mental health help-seeking behaviour which in even first world countries has exceeded the capacity of the existing mental health system. This has been greatly accelerated by the COVID pandemic particularly amongst youth. While this is a welcome consequence of decades of work on health literacy and de-stigmatisation, it has led to demand for care that is often unable to be met within already stretched resources. Unsurprisingly this has catalysed interest in models of care that are a scale unlimited and modest in cost, with digital interventions at the forefront. Secondly, over the past several decades the scope of mental health help-seeking and care has expanded from serious mental illness to incorporate much milder but much more common phenotypes. These generally require more psychosocially orientated therapies than serious mental illness which generally requires more somatic approaches to care. The move towards community care thirdly has put an unintended burden on caregivers, and existing face-to-face models of care are not resourced for, and generally unable to meet the needs of supporting caregivers. This is a domain ideally suited to digital interventions. Lastly in almost all disorders, the benefits of psychological therapies are recognised and increasingly supported by an abundant evidence base. The problem is that even in first world countries, there will never likely be the workforce to deliver such therapies at scale and this is unequivocally true at a global level. The ability to deliver interventions at scale and at low cost makes the Internet extremely attractive.

Health however is complex. The healthcare system is fragmented and poorly integrated in most countries. Consequently, it is economically, politically, and bureaucratically complex to embed digital systems into routine clinical care. Most interventions are not embedded into routine care and, like nutraceuticals, are accessed by consumers in a way that is often disengaged from structured care. There are now a blizzard of interventions and apps for diverse conditions. As a likely over-simplification, many commercially available and actively marketed apps and interventions are not well validated and supported by evidence, and conversely, many apps and interventions that are validated in academic practice do not have a business plan or translational strategy to embed them into clinical care.

Psychotherapy itself is complicated with many competing models, but the one common active element to existing psychotherapeutic models is the therapeutic alliance. This remains a significant challenge for the development and implementation of digital interventions. Many digital interventions were initially developed as standalone, but this understanding has led to a shift from stand-alone digital to hybrid or digitally supported models of care. Across digital interventions, time on site is often low, and much lower than in face-to-face psychotherapeutic interventions, corresponding to a low dose of the active ingredient. At the level of research methodology, there are many complexities in designing studies that control for non-specific operative variables. Blinding is a particular problem. Equally control groups are complicated, with many widely used choices such as treatment as usual or wait list risking exaggerated effect sizes; there is good evidence that the aforementioned are nocebo conditions and risk providing spurious evidence of efficacy. Consequently, study quality and the consequent evidence base are often suboptimal.

Nevertheless, digital interventions offer huge promise. Most of the work to date has gone into adapting face-to-face psychotherapeutic models to digital delivery. As the most mature element in the digital healthcare space, this is the most widely evidence-based and the most widely used application. Digital devices are also increasingly used for tracking and monitoring. This includes digital diary-based mood monitoring for example, but automated actigraphy-based monitoring is increasingly being explored for its clinical validity. Assessment is also possible using more sophisticated techniques; for example, linguistic text and speech-based digital assessments honed by artificial intelligence techniques are being explored to calibrate mood. The large scale of data available through digital mining lends itself to artificial intelligence analytic techniques; these have shown promise in areas like suicide risk detection.

The various chapters in this book take the reader through several applications of digital approaches from diagnosis to assessment, from apps to websites, chatbots and to artificial intelligence, and across several of the high prevalence and burdensome conditions. The book navigates the balance between presenting the promise,

potential, and evidence around digital interventions while being mindful of the early state and tentative nature of much of the science. But in aggregate it provides an essential overview of a digital healthcare future in which we will all be living.

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Preface

This is the first book to describe how mental health will change with the arrival of new digital technologies, such as smartphone applications, chatbots, wearable devices, telepsychiatry, and artificial intelligence.

Smartphones are ubiquitous, and they will enable information to be gathered and processed in real time, thereby providing us with objective measures and digital phenotypes, which could potentially help us to better understand illness trajectory at an individual level. For instance, variations in symptoms and behaviour are common between medical appointments in patients with mental disorders. However, when a patient or a caregiver is asked about symptoms, she/he tends to rely on the current symptoms and extrapolate this perspective to the whole period between the two appointments. It is impossible for a professional to constantly assess a patient's condition to obtain better measures because of the costs involved, both in logistic and financial terms. Computers, however, have no such problem, and in fact there is potential for the development of continuous real-time monitoring, where the clinician will have access to this information in graph format on his or her computer. Indeed, from the active collection of data through digital scales to the passive collection of data regarding the amount of time a patient spends on his or her smartphone and how she/he interacts with social media, all could become digital biomarkers, which can be used by a clinician to assess a patient's behaviour.

Digital devices also pave the way for patients' empowerment. Many researchers have pointed to the smartphone as a great instrument to empower patients to manage their own health daily. People who the health system cannot reach would most certainly benefit from a cheap, secure, and fast approach to obtaining clinical insights. This puts patients first and democratises health. Additionally, chatbots, devices based on natural language, have been increasingly used for mental health promotion and care, and telepsychiatry became popular in the context of the COVID-19 pandemic due to the unavailability of face-to-face consultations. In fact, nowadays telepsychiatry is already recognised among several cultures as a substitute for face-to-face consultations. Studies have shown that telepsychiatry has been successful in terms of patient and clinical satisfaction, decreasing no-show rates and reducing logistic barriers. It is important to note that these digital strategies would not

remove the clinician from a patient's treatment, but rather would enable the patient to follow their health more closely and leave more complex decision making to the clinician.

Besides monitoring and providing insights to patients regarding his or her own health, another interesting angle of the digital mental health landscape is the use of smartphone-based treatments. Recently, the United States Food and Drug Administration (FDA) approved apps to treat insomnia and substance use disorders, beginning the new era of digital prescriptions. Additionally, an increasing number of scientific studies, including meta-analyses, showed the efficacy and limitations of these kinds of interventions for other mental disorders, such as anxiety, depressive, and bipolar disorders. These apps use mainly strategies based on psychoeducation, cognitive behaviour therapy, dialectical behaviour therapy, among other types of structured psychotherapy.

Digital mental health also includes artificial intelligence techniques, such as machine learning algorithms to build risk calculator to predict clinical outcomes in mental disorders, such as suicide attempts or psychosis. An elusive goal in modern psychiatry is the prediction of the propensity for developing mental disorders and potentially preventable poor outcomes. It is important to consider whether the very way we currently think about causality in psychiatry is preventing us from achieving more accurate predictions. The linear association between risk factors and clinical outcomes is important to understand the course of chronic disorders. However, linear patterns do not accurately stratify what patient will have a specific disease or, if a patient already has it, what will be his or her prognosis. By theoretically being able to model any function, machines can find complex nonlinear patterns relating predictors to outcomes. In the present book, we also describe how big data, machine learning techniques, sensors, and other devices started to play a role in unravelling the abovementioned clinical dilemmas.

This volume has a total of 15 chapters, which are structured as follows: Chap. 1 introduces the concept of digital psychiatry and provides theoretical perspective of how patient-clinician relationship will work in the digital clinic. Chapters 2 and 3 explore how passive collection of data will generate digital biomarkers to help clinicians. Chapter 4 describes the psychometric properties of some instruments assessing depression, anxiety, post-traumatic stress, drug abuse, panic disorder, and general mental health in digital formats. Chapter 5 provides a systematic review of smartphone-based treatment in psychiatry, while Chapters 6 and 7 propose a deeper look at these interventions in the fields of insomnia and bipolar disorder respectively. Chapter 8 presents an overview of the use of chatbots in mental health care, highlighting its potential contributions to clinical practice. Chapter 9 addresses an important pragmatic question: how to evaluate a mobile app and advise our patients about it? Chapter 10 discusses how telepsychiatry and telepsychology facilitate the access of patients to the mental health clinicians and can also assist general practitioners in remote areas to better evaluate and treat patients with mental disorders. Chapters 11, 12, 13, and 14 explore predictive models, including the ones using artificial intelligence, to address several outcomes in mental disorders. In addition to describing the potential beneficial effects, all abovementioned chapters describe

limitations and ethical concerns, such as data security and privacy, related to these digital strategies. Lastly, Chapter 15 identifies the harm related to the immersive and rewarding experience of gaming and the problematic use of social media.

The present book focuses on potential, limitations, and recommendations for the digital mental health landscape. Invited authors are true leaders of this emerging field and synthesised existing literature on the validity of digital health technologies.

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Contents

Chapter 1
The Dawn of Digital Psychiatry

Aline Zimerman, Bruno Braga Montezano, Giancarlo Franceschi Dalla Vecchia, Flavio Kapczinski, and Ives Cavalcante Passos

Introduction

The digital world has been growing exponentially for decades now [1]. More and more people join the World Wide Web each year, smartphone numbers have already surpassed the six billion milestone, social media is an ingrained part of life for most of the population [2], and the amount of digital data produced as of 2020 would fill almost six trillion 8 GB flash drives [3]. Such staggering growth comes with new challenges, but it also opens up unique opportunities in various fields, like in the mental healthcare department, that must be seized in order to improve patients' quality of life [4].

Moore's Law states that the number of transistors in an integrated circuit doubles every 2 years, getting ever so small [5]. For example, the Intel Pentium processor had 3.1 million transistors in 1993; by 1995, the same processor had 5.5 million transistors; and by 2003, that same piece of technology, updated through the years,

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had 55 million transistors in it. Nowadays, processors have around 50 billion transistors per chip [6]. This directly correlates with faster processing speed and larger storage units, especially for smaller devices: with transistors nearing the size of atoms, we can fit a world of knowledge in a smartphone, which is able to reach a significant part of the population that would not benefit from such information otherwise [7].

However, fair distribution across the board has not been reached yet. For example, less than half of the people with depression have access to mental healthcare worldwide [8]. Smartphones and gadgets could lead to a revolution in the democratization of access to those pieces of information regarding their anguishes and needs, especially through apps specifically designed to help people in such situations. Notoriously, Dr. Eric Topol compares mental healthcare apps to Gutenberg's printing press [9], which introduced the notion of books to the general population; in a similar way, smartphones and digital mental healthcare apps will make it so the laymen population can access and act upon their own healthcare situation.

But it is not just hardware evolution that has exploded in the last decades: data is being created by everyone and about everything. The era of Big Data is defined by the "Five V's": volume, velocity, variety, veracity, and value [10]. Volume refers to the almost infinite amount of data that is collected; velocity refers to the increasing speed in which we collect such data; variety refers to the diverse nature of the data, which relates to sociodemographic, molecular, genetics, clinical information, etc; veracity refers to the importance of the data reflecting the true state of things; value refers to the intrinsic value generated towards the community and patients through the usage of the data. Aside from that, machine learning (ML) is another defining characteristic of the era of Big Data: ML is the method used to analyze big data through pattern recognition among variables, in order to make sense of an unending amount of information that could not be looked over manually [11].

The advances made in the technological field in the past decades have undoubtedly shaped our world and the way we experience it. New technology is sure to arise in the next few years and that too will have to be analyzed and incorporated into the mental healthcare field. For example, it could be argued that the newest hype from the industry as of now is the Metaverse, a digital counterpart to our physical world, where people can interact in a virtual reality space [12]. We do not know how that will impact people, but we do have to be prepared to deal with it. Most importantly, we must utilize such technology in our favor, the same way we must utilize smartphones, digital mental health apps, and big data to better treat patients.

Digital Mental Health

Due to the progress of technological resources, some utilities within the field of digital mental health have emerged. Mobile interventions to deliver psychoeducation and psychotherapies have already been developed, along with tools to assess patient's current condition through digital monitoring. Digital phenotyping can also

allow better screening of mental disorders at the population level by taking into account health conditions outside the clinical context [13], especially when capturing real-time data that could potentially be used by the mental health professional.

Chatbots are another technology that could possibly help mental health professionals manage patients' symptoms [14]. They consist of digital systems that can interact with people in their natural language. Despite being at the beginning of its development in the field of mental health, it is a promise to democratize access to psychotherapeutic care. Perhaps, the main problem today with these conversational agents is still the lack of standardization in studies on the topic [15]. These approaches, however, do not rule out the presence of mental health professionals and curators who will work on translating the insights provided by each of these technologies to other professionals and patients. Considering that data findings sometimes require specific technical knowledge to fully understand the information, these skilled curators can devise more accessible ways of visualizing, managing, and applying the findings.

When it comes to psychotherapy and psychiatric visits, these mental health interventions in the virtual environment, also called telepsychiatry and telepsychology, became popular in the context of the COVID-19 pandemic due to the unavailability of in-person consultations. Today, the practice is already recognized among several countries as a substitute for face-to-face consultations [16]. Studies have shown that the practice has been successful in terms of patient and clinical satisfaction, diagnostic reliability, professional guidance [17], as well as decreasing no-show rates and reducing logistic barriers that could allow higher volume of patients in treatment [18].

In 2019, the United States Food and Drug Administration (FDA) released a document guiding for regulation of mobile medical applications due to the increase of smartphone usage in the medical field, aiming to avoid harm to patients and ensure proper functionality [19]. In addition, during the COVID-19 pandemic, the FDA released new guidelines on the use of digital health devices for treating psychiatric disorders, as many people were suffering from mental-related symptoms during that period [20].

Currently, there are mental health digital tools that were approved by the FDA. One of them is Somryst, a software-based medical device that, through a mobile application, aims to treat chronic insomnia using cognitive behavioral therapy for insomnia (CBT-I). The FDA approval was based on two clinical trials using a web-based CBT-I platform [21]. Another approved tool is Reset, a software-based medical solution for complementary substance use disorders (SUD) treatment. Although the application has not been suitable to treat opioids dependence, or solely alcohol dependence, data from a 12-week clinical trial showed significant increase in adherence to abstinence in alcohol, cannabis, cocaine, and stimulant SUD on patients that used Reset compared to the patients who did not [22].

In the year 2018, the FDA started a new innovation challenge named "Devices to Prevent and Treat Opioid Use Disorder" to improve treatment devices for opioid use disorder, since there is a profound public health crisis because of this disorder in the USA. The program selected eight developer teams of the candidate devices to work

together with FDA's Center for Devices and Radiological Health (CDRH) to accelerate the development of these solutions [23]. Given this scenario, we can expect more and more digital tools helping psychiatry and psychology professionals in the diagnosis, care, and follow-up in the clinic. These technologies, however, despite being very promising, often need a clinician giving meaning to their outputs, support in their interventions, and a human and empathetic look at their own patients.

Digital Clinic

The patient-clinician relationship as we know it is expected to change in the Digital Clinic, with the integration of new technologies in the clinical setting (Fig. 1.1). Until now, clinicians mainly rely on symptoms patients remember to address, and symptoms from the period between two appointments suffer from biases, in which many are forgotten. In addition, providers diagnose and treat based on their own subjective judgment over these biased information. Continuous patient self-monitoring can give clinicians more data on their patient's real condition, and both self-monitoring and mobile interventions can empower patients in their own treatment [24].

One of the changes that is expected in the Digital Clinic is the inclusion of real-time monitoring of symptoms, using smartphones and other sensors. This can be done both in an active manner, with the patient filling out questionnaires or reporting changes in symptomatology through an app, and passive, through heart rhythm,

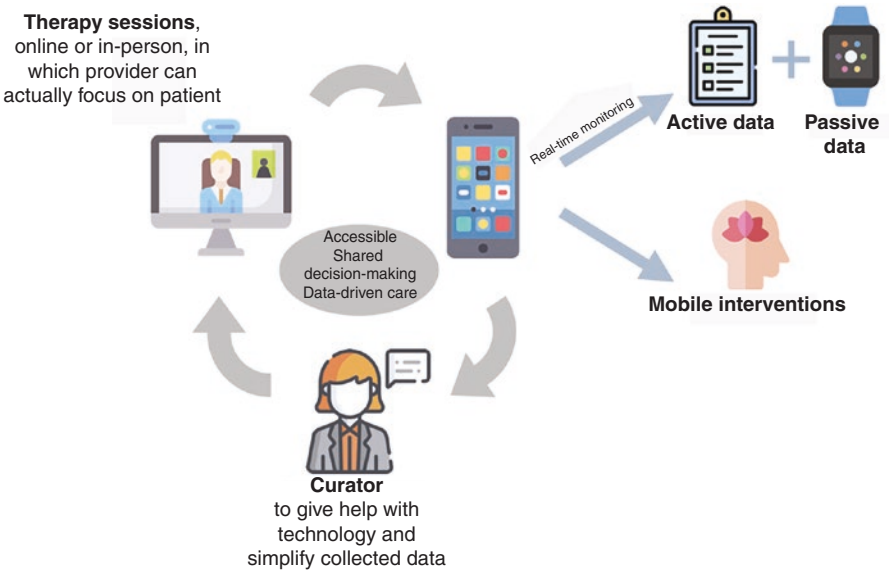

Fig. 1.1 Digital clinic flowchart

microphone, or number of steps registered [25]. This way, not only do clinicians have access to more reliable information on their patients, but also have access to clinical calculators, so that their decisions are more data-driven [26].

For a more intuitive view of the data collected, the presence of curators mediating the patient-clinician relationship is expected. Curators are mainly scientists and engineers with big data, health sciences, predictive modeling and analytic skills, who have access to data collected by patients' devices outside of sessions and create graphs with the data for clearer interpretation, leading to more clinical insights. The easier interpretation of data will allow providers both to propose treatment modifications in a more effective way, and also to discuss treatment history and perspective more directly with the patients, as the curated data is also designed for laypeople [27].

In addition, mobile interventions can allow patients to work on themselves even outside of the office. These interventions, such as symptom monitoring, meditation, and psychoeducation, have been proven to improve outcomes, mainly in mood disorders [24, 28]. In the treatment of bipolar disorder and major depression, mobile applications can be used in order to improve self-management of the disease, improving the patient's ability to self-monitor symptoms through reminders and providing early identification of depressive or manic episodes [24]. A recent study by Faurholt-Jepsen shows that voice features from phone calls, used as supplementary markers, can both distinguish bipolar patients from healthy controls and also provide state classification within bipolars [29].

With access to curated data, self-monitoring, and mobile interventions, patients gain more power over their own treatment, as they can understand their condition and symptoms better and work on themselves outside of the office. With more data and curators facilitating the patient-clinician relationship, not only will interventions in the office be more effective and data-driven, but also providers will be able to have a stronger connection with patients, since their time and energy towards treatment decisions may diminish, leaving more time to actually focus on the patients themselves. With all of these changes, it is expected that patients can gain insights on their own conditions, and maybe in the future AI can even alert them, based on certain patterns or changes of behavior, when it is time self-monitoring is not enough and they should go see a provider [30].

Regulation of Mobile Apps

The regulation of mobile health apps is of utmost importance because of the sensitive data they collect and utilize, the clinical nature of the information provided, which has to be reliable for the patient's sake, and the efficacy and risks attached to the treatment provided by such apps.

The first question regarding the regulation of mobile mental health apps that should be addressed is why these apps should be assessed and rated in the first place. As the interest in mobile mental health apps rises, a plethora of new apps are

developed and released in app stores across all platforms, targeting different psychiatric illnesses and with various therapeutic objectives in mind. However, regulation is still lacking [31], leaving the user to distinguish between a good and a bad app based on a frail system of non-verifiable reviews. This can harm patients and the general healthcare community if, for example, the app offers incorrect or misleading information, or the app is not secure and manages sensitive data improperly. Thus, a systematic method for rating mental health apps was put in place, allowing users to better assess the apps they desire to utilize [32].

The second question regarding the regulation of the apps is how to evaluate them and create an objective ranking method for assessing different apps. The American Psychiatric Association (APA) has developed an evaluation model to do such assessment based on "accessibility, privacy and security, clinical foundation, engagement, and interoperability" [33]. The model is supposed to be used by the patient and the health professional so that they, together, make an informed decision on which app better suits the patient's needs. The comprehensive model has five steps (namely Access and Background, Privacy and Security, Clinical Foundation, Usability, and Data Integration towards Therapeutic Goal), and it is comprised of 37 questions, such as "Has the app been updated in the last 180 days?" or "What are the relevant sources or references supporting the app use cases?". It is important to note that this model does not generate a hard, static rating, but a case-dependent ranking that is supposed to make the subjective process of choosing an app as objective as possible.

Besides the need to assess and rate mental health apps, there are also legal obligations that must be followed in order for an app to be considered viable. Laws regarding the use of sensitive data vary from country to country, but there is one piece of legislation that effectively rules above or in the absence of national statutes: the European Union's General Data Protection Regulation (GDPR). The GDPR is the ruler for digital data handling across the globe because of the so-called Brussels effect, which refers to the unilateral power the EU has to regulate global markets [34]. For example, the GDPR does not directly apply to US-based businesses; however, if that business tracks and analyzes any EU citizen's data, the provisions of the GDPR must be observed for them [35]. That way, any business that aspires to having European customers must follow the European rules—and since they will have to put in place such a rigid protocol for certain users, it just makes sense to apply those same rules for every customer of theirs. That way, indirectly, the GDPR is legally binding to businesses all over the world.

The GDPR personal data principles revolve around six axes: data must be secure, specifically collected for legitimate purposes, adequate and limited to what is necessary, accurate and up-to-date, identifiable only for as long as necessary, and transparently processed. In that sense, one would expect mental health apps to follow GDPR guidelines when dealing with patients' sensitive data, such as providing clear privacy notices explaining how the user's data is handled, capturing the user's consent before tracking them, encrypting data, and allowing users to withdraw their consent and delete data related to them at any point in time [36]. Nevertheless, the majority of mental health apps do not abide by GDPR rules, and security measures must be implemented in order to ensure that users' sensitive data are being correctly handled [37].

Artificial Intelligence

Over the years, artificial intelligence within the medical space has only grown [38]. By dealing specifically with use of machine learning in the context of mental health, the implementation of classification models for prediction of psychiatry-related outcomes and elaboration of risk calculators show themselves with an important role in clinician assistance.

These classification models use supervised machine learning to predict a categorical response (Fig. 1.2). The technique consists in receiving existing data to generate a model that can be used to make predictions about the future of an outcome (e.g. suicide attempt, psychiatric diagnosis, treatment response) [39], and consequently creating risk calculators—in addition to the use of unsupervised models for cluster analysis and dimensionality reduction [40]. One advantage about more complex machine learning models when compared to classic statistical learning methods is the capability of capturing various nonlinear relationships between the variables in a given dataset [41].

In recent years, several studies have been published reporting models able to predict mental health outcomes with good performance. Considering a few examples, using a representative sample of the US population with sociodemographic, psychiatric disorders' diagnosis, and stressful events data, Machado et al. developed a model capable of predicting suicide attempts in the general population with great accuracy (82%) [42].

Another good example was reported by Berni et al., where a text classification model was created to identify patterns in Virginia Woolf writing that could characterize her suicide behavior. The model was capable of identifying the period of 2 months preceding her suicide with 80% of accuracy [43]. Regarding the psychiatric diagnosis, recent studies demonstrate attempts to identify such disorders through artificial intelligence. Historically, these diagnoses have been carried out based only on the clinical perception of the health care professional without the aid of computational techniques. In this perspective, the study of Dean et al. reported the use of a support vector machine model with 28 biomarkers to diagnose warzone-related

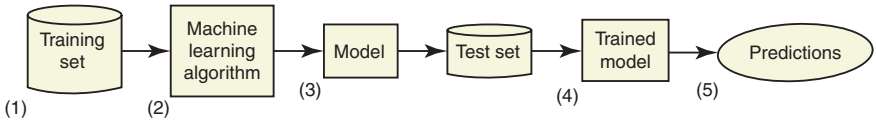

Fig. 1.2 Machine learning model flowchart. The following steps can be adopted to achieve a standard machine learning approach: (1) Data are split into training and test sets. (2) A machine learning algorithm (e.g. linear regression, decision tree, support vector machines) is chosen to be applied into the training dataset. (3) A model is fitted to the training data. At this point, hyperparameters could be tuned through a data resampling method in order to accomplish better model performance. (4) After the final model fit, the test set (unseen data) is brought to have the model applied to it. (5) The model generates predictions based on test data. These predictions should be based on the outcome: continuous values in regression problems, and probabilities or classes in classification problems

post-traumatic stress disorder with an accuracy of 81% [44]. Focusing on mood disorders, a meta-analysis published in 2020 aimed to verify the evidence in identifying BD through structural magnetic resonance imaging (MRI) with ML methods using data from 13 cohort studies. Regardless of large sample size, the study reported an area below the receiver operator characteristic (ROC) curve of 71%, a result that indicates progress but also need for improvement in ML approaches for such complex outcomes such as BD [45].

Concerning the treatment response, we can point out a study from Nunes et al. that aimed to train a random forest model that classifies lithium response in patients with BD using 180 clinical predictors. The model presented an ROC curve of 80% accompanied by a low false-positive rate, showing itself as a promising tool in clinical practice [46].

As anything, machine learning is not always a bed of roses. In general, one of the problems being pointed out within the validation of machine learning models published in the literature is the lack of testing in independent samples. Often, there are models that present great performance in the original study test data, but are never tested in real life datasets with different patients, cultures, and contexts. This phenomenon may end up masking bad statistical models because of a bias of the data themselves. A good practice that can lead to better results and more robust models in the long-term is the creation of standard pipelines for ML use in mental health, with a uniform step-by-step that can ensure good computational, clinical, and methodological routines [47].

Therefore, in the case of artificial intelligence in mental health, we must understand its potentialities, which are many, and also its limitations. Nowadays, artificial intelligence already helps a lot, diagnoses can already be observed being aided through risk calculators, treatments being evaluated through statistical learning models, cognitive performance being predicted by MRI, patients being helped by chatbots, among other capabilities. However, some models can become complex when capturing nonlinear signals, outputting results less and less human-friendly, causing an interpretability problem. So the improvement of these ML models should be focused on predictive power but also on interpretability, in view of not losing the ability to be an assistant that walks alongside the clinician and losing its initial purpose.

Future

With new technologies, the Digital Clinic is expected to change and to expand, adding more people and tools to the equation, for a more effective and human approach. Apps tend to bring several advantages for diagnosis and treatment, such as accessibility, affordability, easier access to information to both clinicians and patients, engagement, and lack of stigma.

However, the rise of digital psychiatry must also be seen through the lens of its limitations. One of the main concerns lies on ethical issues that may arise with the

huge amount of data and information being processed. Questions about data security, privacy, and anonymity of the researched population are extremely relevant issues that must be discussed to enable a healthy evolution of these technologies.

Users of these new technologies must have the autonomy to decide whether to have their data collected and used, their prognosis predicted by machine learning models, or their participation in any other intervention that may affect them directly or indirectly. In addition, regulations must continue to be held to guarantee any intervention or data collection is effective and worthwhile.

Considering these precautions, the addition of artificial intelligence to the world of psychiatry may take mental healthcare inside our homes, with tools such as our smartphones or even Alexa detecting behavior change and warning a patient to go see a doctor. Possibilities are limitless and, although no one is sure of what it will look like in the future, the promise is of a world with much more data, information closer and clearer than ever and focus on who really matters, in a patient-clinician relationship with much more humanity involved.

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Chapter 2
Digital Biomarkers and Passive Digital Indicators of Generalized Anxiety Disorder

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Introduction

Consider John, a fictional 29-year-old man with undiagnosed generalized anxiety disorder (GAD). John has a 2-year history of uncontrollable worry and anxiety about work, school, and family. It interferes with his relationships, and he finds himself so focused on his worries that he is significantly distracted from important activities. He has associated sleep problems, fatigue (taking frequent naps during the day), and generalized muscle aches.

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John uses social media (Instagram and Twitter) regularly. He has a smartwatch that connects to his Android phone. He sees a local primary care physician (though never with the complaint of anxiety) who keeps an electronic health record (EHR). (How) can we use this information to best support John's mental health care?

Let us first imagine the wealth of information that we could learn about John, and likely his anxiety, by triaging these data sources (i.e., medical record, mobile and wearable devices, and social media, summarized in Fig. 2.1). We might learn about dysfunctional sleep patterns considering movement, light, and sound collected by his wearable/mobile device; we could infer changes in his physical arousal, considering heart rate and data derived from this (like heart rate variability [1]); we might be able to get a glimpse into real-time anxious thoughts considering content from social media posts and text messages; we might even gain insight into nonspecific physical complaints like muscle tension and restlessness. Since these data types are longitudinal and often collected in real-time, albeit frequently existing below our threshold of awareness, curating and analyzing this information grants us access to a descriptive mosaic of time courses and symptom fluctuations, which are otherwise

Fig. 2.1 The figure shows an overview of types of passively collected data, including medical record data, social media data, and mobile and wearable data

unavailable. If we collected passive data from a large group of people with GAD like John, we might also find novel variables from the EHR, mobile sensors, or social media that could inform GAD assessment.

The focus of this chapter is on improving and personalizing the assessment of generalized anxiety disorder (GAD) with the use of passively collected data.

In this chapter, we define **passively collected data** to include data generated as individuals go about their daily lives, not requiring additional effort on their part. Sources of such data which we will discuss in this chapter include electronic health records (EHR), mobile and wearable device sensors, and social media activity. All of these contain rich information, which may be used to inform assessment of GAD. We will discuss current research which does this, as well as investigate the theoretical basis for understanding GAD through passively collected data. We will begin with overviews of (1) GAD, (2) how GAD is assessed currently, and (3) potential areas where passively collected data may complement current assessment.

GAD as a Diagnostic Category

GAD is defined by prolonged (>6 months), excessive worry and anxiety about multiple events or activities, leading to functional impairment and/or a significant degree of distress. The worry is difficult to control and is associated with a combination of sleep problems, easy fatigability, concentration difficulties, irritability, muscle tension, and restlessness [2]. The prevalence of GAD among adults in the USA is estimated at 3% annually and 9% over a lifetime [2].

GAD is associated with significant burden for individuals and society, including an estimated 4–8 days lost to disability per person per month [3] and significant impairments in role functioning and quality of life, comparable to those associated with major depressive disorder [4]. It is associated with significant treatment delays, in excess of 7 years and is misdiagnosed, estimated as high as 71% of cases in primary care [5]. Measures such as the GAD-7 [6] and GAD-Q [7] may be completed by patients or embedded in clinical interviews to guide screening and assessment of GAD. Instruments like the Structured Clinical Interview for the DSM-5 (SCID-5) [8] may also be used to guide the diagnosis of GAD.

Current GAD Assessment

The Diagnostic and Statistical Manual of Mental Disorders (DSM), now in its fifth edition, has enabled advancements in clinical and research domains of mental health. For GAD, as well as other mental illnesses it has allowed for (1) identifying prevalence rates to guide mental health services, (2) identifying patient cohorts for translational and basic science research, and (3) documenting public health statistics, like morbidity and mortality [2]. DSM constructs for GAD are embedded in measures like the GAD-7 and the GAD-Q IV, which have been well validated [6, 9,

10] and widely used for illness screening and diagnosis. While the GAD classification has made possible standardization of diagnosis for guiding treatment and prognosis, current assessments have limitations worth discussing.

Reliance on Retrospective Self-Report

Screening and diagnosis in GAD heavily rely on retrospective self-report known to be limited by recall bias [11–16]. In addition, self-report measures require patient time and effort in recalling past symptomatology. In the case of the GAD-Q IV, for instance, patients must recall symptoms varying across metacognitive (e.g., controlling worry), behavioral (e.g., sleep, restlessness), and physiologic (muscle tension, fatigue) domains over the previous 6 months [7]. For the GAD-7, patients must recall similar features over a 2-week span [6].

Limitation in Accounting for Contextual and Time-Dependent Factors

GAD is known to be chronic and fluctuating [17]. Assessment measures, like the GAD-7 and GAD-Q have limited capacity to account for the time course of GAD and naturalistic environmental, behavioral, and physiologic co-occurrences [6, 18]. Consider the anxious patient, John, completing the GAD-Q IV prior to his visit with his primary care provider (PCP). He must attempt to recall what his sleep has been like over the last 6 months and then (even if recalled accurately) reduce this rich longitudinal data to a single "yes" or "no." He must repeat this for other factors, like muscle tension, "uncontrollable worries," and restlessness, reducing each to a binary "yes" or "no."

Heterogeneity in GAD

GAD presentation is heterogeneous with wide individual variability and significant symptom overlap with other mood disorders [19]. This is complicated by the lack of observed features that are sufficiently specific for reliable diagnosis with most empirical findings or symptoms—employed by most diagnostic algorithms—yielding an area under the curve less than 0.7 in a receiver operating characteristic curve [19]. This is despite the robust sensitivity of diagnostic platforms to detect characteristic symptoms of GAD such as intolerance of uncertainty, excessive worry among others [20]. Additionally, these symptoms lack the specificity to adequately discriminate GAD from other anxiety disorders [21]. These collectively present a diagnostic challenge for specifically confirming GAD and highlight the need for novel symptomatic associations to optimize this diagnostic pipeline.

This unique challenge in the diagnosis and assessment of GAD prompted us to spotlight this prevalent mental condition as the theme of this investigation. Insofar as GAD presents in an amorphous—often in a highly individualized—fashion, designing better detection strategies for GAD will lay the foundations to improve our abilities to spot other, more specific anxiety disorders, let alone other mental health conditions.

Potential for Improvements with the Use of Passively Collected Data

Self-report screening and assessment (including such measures as the GAD-7, the GAD-Q IV, and the structured clinical interview) may be complemented with objective, passively collected data. Herein, we explore data collected from the electronic health record (EHR), personal mobile devices, and social media to inform clinical assessment. Such data have the potential to complement subjective self-report by capturing real-time, highly dimensional behavioral, physiologic, and environmental data. Importantly, these data are captured, naturalistically, as an individual goes about his daily life.

Machine Learning Models Applied to Passive Data

Fundamentally, a machine learning model is a mathematical expression that takes one or more inputs, changes them in some way, and produces one or more outputs. In psychological and behavioral sciences, such models can represent (potentially complex) relationships in human-driven data generating processes, like those that result in heart rate, sleep, and activity. With a sufficiently large and broad dataset, such a model learns to generalize (i.e., making predictions with new data). A machine learning model *learns* implicitly from data, without explicit programming by humans. With powerful computers, such models can handle multi-dimensional datasets like those from mobile passive sensors and EHRs. Table 2.1 exemplifies

Table 2.1 This table displays a hypothetical dataset with sleep (hours), time spent at home (hours), and presence of GAD (yes or no) for each subject in rows

Sleep (h)	Time spent at home (h)	GAD diagnosis
5	20	Yes
4	18	Yes
8	14	No
6		No
:	:	:
9		Yes
8	23	Yes
7	19	Yes

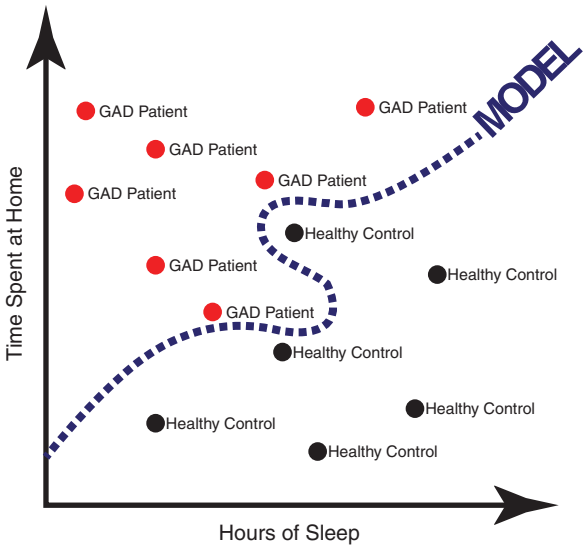

Fig. 2.2 The figure shows a graphical display of the hypothetical data presented in Table 2.1. The data are plotted in 2 dimensional space with sleep (h) on the horizontal axis and time spent at home (h) on the vertical axis. A simple classification model is represented by the dashed line, separating GAD subjects from non-GAD subjects

such a (hypothetical) dataset that includes individuals with and without GAD. For each individual, we know sleep (in hours, determined by passive sensors on a wearable device), time spent at home (in hours, determined by GPS location on a mobile phone), and GAD diagnosis ("yes" or "no"). We might train a model to learn relationships in the data, which can be visualized in Fig. 2.2. The model is essentially a nonlinear equation, which—in our case—sorts GAD patients from healthy controls. Such a model illuminates and associates sleep and time spent at home with GAD. We might also use the model to predict GAD in a new patient for whom we know sleep and time spent at home.

Greater computing power allows for the use of larger datasets with more variables and subjects. Models trained from large datasets can be used to predict outcomes in new data, complementing cross-sectional self-report. Such models offer epidemiologic benefits by identifying novel risk factors, behaviors, environmental factors, and physiologic factors associated with GAD. These could ultimately be used to shape clinical guidelines for GAD. For the individual, deep learning offers a digital GAD "fingerprint" or a personalized representation of GAD.

The following sections will provide the framework for a deep learning approach to GAD, as well as provide an overview of the studies which have investigated this domain. Figure 2.3 shows some of the connections between passively collected data (including that from mobile and wearables, social media, and EHR) and the current understanding of GAD.

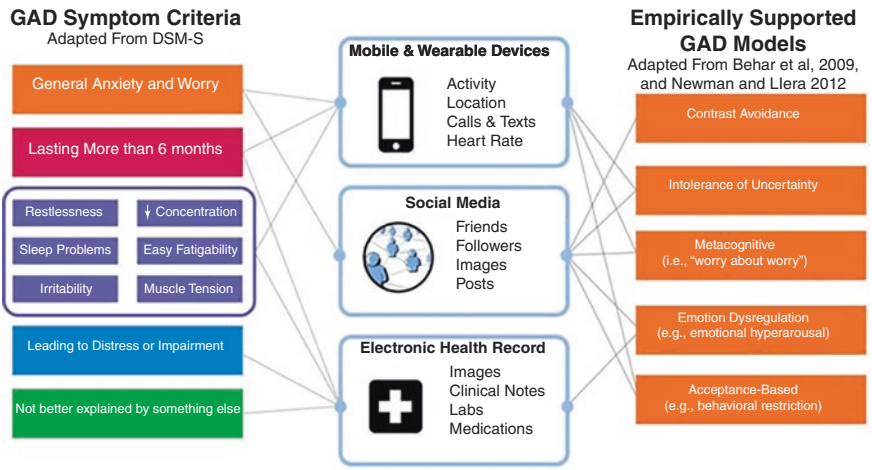

Fig. 2.3 The figure above displays DSM-5 GAD criteria (left), domains of passively collected data (middle), and empirically supported GAD models (right). The connecting lines display ways of indexing various GAD features (DSM-5 features + features from empirically derived GAD models) using passively collected data

Passive Sensing of GAD with Data from the Electronic Medical Record

Electronic health records (EHRs) are oceans of data (see Table 2.2 for examples of data types in the EHR) with vast potentials to facilitate the passive sensing of GAD, let alone a multitude of mental health conditions. With 85.8% of providers using EHRs (recorded in 2017) [22] and each patient generating 80 megabytes of data in the EHR annually [23], the pressure to optimize EHRs as diagnostic platforms is larger than ever. Despite these potentials, few studies have explored data embedded in EHRs as a source for detecting GAD via passive sensing. This is in spite of the rich literature that details the heterogeneous topology through which GAD can manifest. To stay true to the use of EHRs as a platform for facilitating passive sensing, we focused primarily on investigations that involved data extracted from EHRs.

Diversity and depth of data are key strengths of an EHR that can facilitate passive sensing of GAD. EHRs are centralized data repositories that support an organizational architecture for efficiently browsing and classifying information. Assuming consistency in data curation, EHRs also serve as a nexus where diverse content, ranging from qualitative notes to objective measures such as laboratory tests and

Table 2.2 Data types in EHR

Data collection type	What is measured?	Structured or unstructured format
Patient notes	Patient subjective experience (filtered through clinician)	Unstructured
Laboratory results	Chemicals in bodily fluids	Structured
Imaging	Anatomy	Unstructured
Electrophysiology	Electrical/physiological recordings	Unstructured
Demographics	Age, gender, and others	Structured
Medications	Patients' documented medication history	Structured
Problem list and diagnoses	Patient's past medical problems	Structured

imaging results converge. Such an organizational advantage is observed in the increased sensitivity towards detecting GAD in family medicine practices following the comprehensive consideration of clinical data facilitated via EHRs [24]. While these improved recognition rates were understandably accompanied by higher false positive rates, the evidence suggests—with high ecological validity—that EHRs support and streamline clinical decision making permitting the recruitment of all relevant data [24]. This includes data that were collected for reasons unrelated to a formal evaluation of GAD, directly representative of passive sensing. Insofar as the purpose of screening is detecting concerns for GAD, the higher false positive rates observed above are tolerable outcomes given the screening benefits that EHR usage accommodates. Accordingly, the capacity for passively sensing GAD via charting documentation in EHRs opens opportunities to detect and monitor mental health outcomes in populations with high vulnerabilities or barriers to adequate or equitable health care access. For instance, incorporation of EHRs into transgender care has identified higher than normal prevalences—and therefore risks—of GAD within this population, signaling the need to practice greater vigilance in screening and monitoring GAD among this specialized and potentially vulnerable population [25]. Unique—often non-conventional—presentations of GAD, or other mental health conditions, observed in specific subpopulations are appropriate opportunities for passive sensing to identify diagnostic trends that will aid clinicians to spot, assess, and serve the needs of these individuals. Thus, the impressive content and breadth of data stored in EHRs provide opportunities to telescope between broad and specific populations in the diagnosis and management of GAD.

Passive sensing GAD through the dense data present in EHRs requires efficient data handling, This will involve both deductive (top-down) and inductive (bottom-up) computations. The former supports rapid browsing of GAD symptoms based on clinical guidelines as well as the literature. The latter involves establishing new patterns and associations via inputs collected for reasons unrelated to formal evaluation for GAD. Thus, this modality is arguably more insightful and relevant to appreciate the promise and scope of passive sensing within EHRs. Nemesure et al. [26] pioneered and experimented with various machine learning modalities in a multi-tiered learning and classification algorithm, trained on EHR data from over 4000

individuals to identify features that predicted GAD. This algorithm robustly predicted GAD (AUC = 0.73, sensitivity = 0.66, specificity = 0.7) [26]; this even matches the diagnostic success of GAD by physicians in a primary care setting where GAD is most frequently encountered [24, 27, 28]. Notably, while diagnostic acumen employed by clinicians is deductive and is designed to identify only symptoms previously documented in clinical guidelines, inductive approaches offer opportunities to form new associations to facilitate diagnostic pattern recognition. Indeed, Nemesure et al. [26] used Shapley additive explanation (SHAP) values to infer, evaluate, and vectorize features—and their relative contributions—that are associated with a clinical diagnosis of GAD. This metric boosts the explainability of the model and provides a key source for identifying novel connections in the pathological landscape for GAD. Surprisingly, this revealed (in)completion of recommended vaccination, marijuana use, and the need for follow-up examination as the top three features—in consecutive order—that best predicted GAD [26]. Notably, none of these items relates to criteria for formally diagnosing GAD. This, therefore, exemplifies the promise of passive sensing as a modality for identifying new and useful diagnostic insights from EHRs, even among data collected for completely independent reasons.

Though the future is promising for passive sensing via EHRs, notable obstacles delay its integration into the clinic. First, insofar as most EHRs are designed to facilitate billing and scheduling clinical services rather than supporting clinical evaluation, assessment, or planning [29, 30], the data architecture is inherently not conducive to streamline diagnoses and management. This is exemplified by the organization of clinical records based on encounters rather than content, which presents a logistical challenge in extracting relevant data. This is further compounded by the provider-to-provider (even institution-to-institution) diversity of documentation formats and styles. Understandably, this has resulted in the poor documentation of heterogeneously presenting conditions such as GAD [31] with high provider variability and confusion due to duplications [32]. Unsurprisingly, these challenges even result in delays in detection and treatment for GAD [33]. While recent efforts are experimenting with algorithmic strategies that recruit advanced techniques such as natural language processing to streamline data extraction and curation [34, 35], significant challenges still persist in optimizing—and preserving—the integrity of stored information and its relevance.

Improving the accuracy and precision of passively sensing GAD through EHRs requires developments in data quality and volume. In addition to reinforcing high standards during clinical interviews, high quality data necessitates efficient and reliable curation and maintenance. This issue is brought to the forefront with increased transparency of EHRs, now granting patients direct access to their health data [36]. Despite concerns that this may discourage providers from registering sensitive information in clinical documentation, patient participation can offer a valuable layer to audit data logged into EHRs, ultimately improving the integrity and accuracy of the data [37], which is essential to ensure the validity of subsequent algorithmic outputs.

Data Science Pearl: Structured vs Unstructured Data

Most data types can be classified into two categories: structured and unstructured. **Structured data** is so named because it can be stored and represented in a *structured* format. Many demographic features (e.g., age, gender, race, ethnicity) fit into this category. Structured data generally requires little preprocessing prior to modeling, and it lends itself well to tabular format. **Unstructured data**, in contrast, lacks consistent structure and generally requires significant preprocessing prior to modeling. Examples of such data include free-text clinical narratives and images. These data types can only be used in machine learning models after meaningful features are extracted. **Sentiment analysis**, discussed in the Social Section is an example of feature extraction from an unstructured data source.

Passive Sensing of GAD with Data from Mobile and Wearable Devices

Passively collected data from wearables and mobile devices (see Table 2.3 for some examples of data types from mobile devices) is widely available due to the ubiquity of such devices. It is estimated that 85% of people in the USA own a smartphone [38] and 21% regularly use some type of activity tracking wearable device [39]. The increased adoption of such devices in recent years provides a method for unobtrusive monitoring of passively collected information (see Table 2.3). This information can be leveraged to investigate mental health disorders, such as GAD. The current section considers the capacity of an individual's passively collected data to detect or enhance the detection of GAD.

Table 2.3 Data types obtainable from mobile and wearable devices

Data collection type	What is measured?	Structured or unstructured format
Accelerometer	Linear acceleration	Structured
Gyroscope	Rotational acceleration	Structured
Proximity sensor	Phone's distance from an object (often used to darken)	Structured
Incoming/outgoing texts or calls	Volume	Structured
Incoming/outgoing texts or calls	Content	Unstructured
Wi-Fi network connection status		Structured
Time		Structured
Global positioning system (GPS)		Structured

Overview and Basis

Historically, GAD has been poorly defined and thus subject to change as a result of low diagnostic reliability with standard criteria [40]. The lack of consistent, operationalized criteria for GAD diagnoses has resulted in a comparatively poor understanding of GAD compared to other anxiety disorders [41–43]. However, recent efforts have sought to better characterize GAD, marking uncontrollable, excessive worry as its distinguishing symptom [44, 45]. This has been coupled with increased consideration for the influence of somatic/autonomic (e.g., heart rate variability, autonomic inflexibility) and behavioral (e.g., behavioral avoidance, excessive worry) symptoms, of which their relative influence on GAD has been previously inconsistent or scarcely considered [40, 46]. For example, although Chalmers et al. found that broadly anxiety disorders have shown reduced heart rate variability (HRV) [47], other studies have not consistently validated this finding for GAD [48, 49]. Similarly, a limited body of research exists for behavior models of GAD, despite consideration for the role of behavioral avoidance in other anxiety disorders, such as social anxiety disorder (SAD) [50, 51]. Given both the inconsistent internal outcomes of GAD research and the inconsistent outcomes compared to other anxiety disorders, the incorporation of passively collected data from mobile and wearable devices may complement and improve traditional self-report assessment methods. Further, as an unobtrusive data collection method that allows for participant observation in a naturalistic setting, passively collected data is uniquely positioned to avoid the potential for recall or interviewer biases.

Recent efforts within mental health research have highlighted the promise of using passively collected data to detect anxiety disorders and anxiety disorder-related symptoms [52–54]. However, as the incorporation of passively collected data to research GAD remains in its infancy, the efficacy of leveraging such data for GAD detection remains heterogeneous. Interestingly, passively collected physical activity data has shown promising results in predicting GAD symptom deterioration and sleep quality [52, 55]. Jacobson et al. used daytime movement and nighttime sleeping patterns collected from week-long actigraphy data to predict long-term deterioration in GAD symptoms. Findings showed that the passively collected data could significantly predict symptom deterioration in an individual with GAD. Specifically, these results provide evidence for the use of passive sensing as a method for long-term (17–18 years) GAD prognosis and avenue for early GAD-related interventions [52]. Passively collected physical activity data was also collected by Mullin et al. who sought to assess the relationship between sleep parameters and anxiety symptomatology. Using 1 week of sleep actigraphy data, results showed greater overall sleep duration, but longer sleep onset latencies in

participants with GAD compared to controls [55]. Such findings reinforce the advantage of integrating objective measures of data collection as a complement to more subjective data collection methods (e.g., participant sleep diary). Taken together, these two studies highlight the potential benefit of using passively collected physical activity data to study GAD, despite less robust results found in the aforementioned studies.

However, the use of passive sensing to detect GAD has also shown to produce less robust findings, particularly when compared to other anxiety disorders. Saeb et al. used global positioning system (GPS) coordinates, in conjunction with movement, light, and sound collected via participants' mobile phones to detect the relationship between semantic location and GAD-7 scores. Although relationships between time spent in a given location and GAD symptoms were not consistent, features derived from the phone sensor data resulted in model accuracies that were more than 20% greater than those containing strictly GPS data [56]. Despite an absence of statistically significant results, these findings still underscore the potential utility of including passively collected data in estimating an individuals' daily life behaviors, providing additional information to more traditional approaches by capturing signals that would be otherwise unavailable [56].

Di Matteo et al. used a combination of passively measured variables (e.g., environmental audio, GPS location, screen state, and light sensor data) collected from a participant's smartphone to predict GAD and SAD. High-level features from the passively measured variables were used to predict participant's self-reported GAD-7 and Liebowitz Social Anxiety Scale (LSAS) scores. The models failed to detect GAD; however, models of SAD obtained a significantly greater screening accuracy than uninformative models, and key features of the models were found to be predictive of SAD. The authors suggest the inconsistent findings between GAD and SAD may stem from the difference between the manifestation of the anxiety disorders symptoms. While persons with SAD exhibit behavioral avoidance, which may correspond to daily life decisions that are detectable by passively collected data, persons with GAD exhibit cognitive avoidance, a symptom less translatable to detectable alterations in daily life decisions and thus may be more difficult to detect in passively collected data [57–59].

Overall, additional research must be conducted to further investigate the efficacy of passively collected data in detecting GAD and GAD-related symptoms. However, there are certain limitations to passively collected data that should be addressed. First, nonspecific to GAD research is that the potential analytic utility of passively collected data is heavily reliant on participant's compliance with study protocols for the provided device/sensor. Non-compliance with device protocols can result in substantial missing data that may impact data usability or interpretability. Second, a GAD-specific concern that was previously highlighted is that the cognitive symptoms of GAD (e.g., cognitive avoidance) [60] may be more difficult to detect via passive sensing and thus limit the utility of incorporating such information into a GAD model. However, this concern may be related to the fact that a more robust body of research exists for other anxiety disorders and passively collected data, and

that previously conducted research on GAD lacked the diagnostic criteria to properly differentiate GAD from other anxiety disorders [21].

Passive Sensing of GAD with Social Media Data

Social media has become a rich source of data over the last two decades, with 72% of US adults being users of at least one social media site as of February 2021 [61]. Refer Table 2.4 for some examples of data types obtainable by social media. In this section, social media is defined as any internet-based network or technology that facilitates the sharing of user information or media with others in an online community. Popular examples of social media platforms include Instagram, Twitter, Reddit, Facebook, TikTok, and YouTube. Social media users share a wide variety of content, including their personal information, moods, attitudes, beliefs, and opinions with varying degrees of frequency and quantity [62]. Users organize information with accounts, hashtags, folders, pages, and community groups. These filters help to sort relevant mental health information, making social media data an important database to assess widespread mental health and identify risk factors [63].

Over the last decade, research tapped into these expansive datastores to assess the mental health status of users on both the population and individual levels. Language analyses can be used to (1) uncover markers of illness in users who suffer from psychiatric disorders and (2) predict whether a user suffers from a particular psychiatric disorder. Many users allow researchers easy access to posts on social media sites, including Facebook [64], on a variety of mental health illnesses from anxiety disorders to bipolar disorders [65, 66]. It is also common to find community channels, accounts, subreddits, and other groups that are centered around discussing

Table 2.4 Data types obtainable from social media

Data collection type	What is measured?	Structured or unstructured format
User posts	Content	Unstructured
	Self-disclosure	Unstructured
	Length	Structured
	Frequency	Structured
Reactions to users' posts	"Likes"	Structured
	Comments	Unstructured
Profile media (photos and videos)	Content	Unstructured
	Frequency of updates	Structured
User demographics	Age, gender, location, and others	Structured
Friends/followers	Magnitude	Structured
	Interaction	Structured/unstructured

psychiatric symptoms, so that users can connect with others suffering from similar mental health problems for the purpose of support, advice, or encouragement [67]. For example, Reddit contains more than 130 subreddits dedicated to mental health, with "r/anxiety," an anxiety subreddit, totaling almost 500,000 members [68, 69].

Although research to date has used social media data to better understand a broad range of mental disorders [70], this section will focus on its applications to GAD. Across research, two primary processes were used to separate individuals with anxiety from those without anxiety. In one, researchers established a group of users with anxiety who had self-disclosed a ground truth that explicitly stated that the user suffered from [GAD] or prominent anxiety symptoms [71]. This is typically punctuated by posting statements like "I was just diagnosed with [GAD]" or "I've suffered from [SAD] since I was a teen." The other approach relies on researchers assessing generalized anxiety levels by contacting participants and administering the GAD-7 questionnaire directly, which requires more effort and time but improves validity and yields more descriptive information [71].

Sentiment analysis involves extracting meaningful information from unstructured text, including individual subjective attitudes, beliefs, and overall tone, often categorizing it as positive, neutral, or negative [72]. Using sentiment analysis, multiple studies to date have revealed differences in how users with GAD interact with social media compared to users without GAD. Given that people with GAD tend to experience negative emotion more strongly than others [73, 74], users with GAD may display tendencies toward using less positive words and more negative ones to reflect their emotions [73, 74]. As Loveys et al. reported, micropattern fluctuations (i.e., changes in attitude observed in small time increments) within a set of social media posts revealed that users with GAD tended to post less consecutive positively valenced tweets than the control participants [66]. This may be because having GAD is correlated with experiencing a negative attentional bias [73, 74] and a propensity to negatively sustain one's negative emotion to go from feeling unexpectedly positive to negative (i.e., contrast avoidance [75]). The results from this study highlight the importance of understanding study group characteristics prior to generalizing results. In order to detect these minor shifts in mood, the user must post frequently and be comfortable posting about their struggles with anxiety, despite mental health being stigmatized by society [66]. Another study used Twitter to assess the differences in social media behavior between those with GAD and those without it; it concluded that, on average, users with GAD tended to post more often and used more negative words, but had less followers and shared less personal information than the controls [62]. In addition, GAD users were more passive, as they tended to have more followings than followers and posted less original content (i.e., they re-posted more content) [62]. This is consistent with the Loveys et al. micropattern study, as both suggest that those with GAD interact with social media differently than non-GAD participants; specifically, those with GAD display negative attentional bias by using more words with negative connotations on social media.

There is evidence to suggest that GAD users overall have less fluency in text, and those in anxiety social media groups tend to focus on physical and psychiatric symptoms. For example, O'Dea et al. found that, over 36 weeks, the degree of uncertainty and non-fluencies (i.e., breaks in composition) likely due to anxiousness or a pause in thought, in blog posts was correlated with anxiety symptoms [76]. This

may be attributed to GAD causing worry and uncertainty, to the point where this excessive anxiety causes functional impairment and/or significant distress [77]. On Reddit, a self-selected interest-based group, the most frequently used words were related to feelings, including "feeling," "thought," "better," and "anxious," while the most common trigrams, or 3-word phrases, asked others for help, like "does anyone else…" [70] This anxiety community also used bigrams, or 2-word phrases, like "self-esteem," "heart rate," "physical symptoms," and "mental health," which suggests that they tended to focus on self-esteem issues, drug side effects, impact of social media, and their physical experiences with symptoms [70]. Similar studies analyzing user sentiment related to anxiety have also been conducted during and following distressing events, like the COVID-19 pandemic [78] and in the aftermath of natural disasters [79].

Although only one study to date has done this specifically with respect to GAD [70], other studies have been able to predict whether a user has another mental illness, most notably depression, to a high degree of accuracy [80]. Still, by combining text feature techniques, including N-gram frequencies which are used to determine how often specific words appear, Shen and Rudzicz were able to predict whether a Reddit user posted in an anxiety subreddit or in a control subreddit with up to 98% accuracy by analyzing the most often used words and their collocations [70]. A review by Chancellor et al. found that across research in social media-based predictive modeling for mental disorders, the algorithms used varied significantly, with the most popular being support vector machines, which are used for classification and regression [71]. Also, recently, deep learning has been used in creating predictive models, with some studies using deep neural networks [70, 80, 81] and recurrent neural networks, which generally use time series or sequential data [82].

Machine Learning Pearl: Model Validation and Testing

In addition to being used to uncover trends present in GAD user behavior, deep learning algorithms also have the potential to *predict* whether a social media user may suffer from GAD. Predictive models are typically trained on a dataset with known inputs and known outcomes of interest (a.k.a., ground truth, target variable). This comes with the potential problem of machine learning models **overfitting** to training data, and hence, losing their ability to generalize to new unseen data (to make predictions). To combat this, researchers often split the data into 3 sets: a (1) a training set, (2) a validation set, and (3) a test set. Researchers "fit" or calibrate a model iteratively to the training set (1); as they train the model, they intermittently check to make sure the model is not too closely fitting to the training data by testing the model's predictive performance with the validation set. If the model starts to lose capacity to perform using the validation set, it is a good sign the model may be losing its ability to generalize and may suggest the need to stop training. Once training and validation are finished, the model is "tested" on the held-out test set. So far through training the model has not "seen" the test set. The model's predictive performance on the test set provides a good indicator of how well the model will generalize to new data (that is, how well it will predict unknown outcomes).

Social media presents unique, cost-effective possibilities to better understand anxiety in the general population [83], a necessary step for guiding health policy decisions and allocating mental health resources. Consider, first, the significant challenge of gauging population mental health using traditional methods of

assessment, alone. Such a method currently would require the wide distribution and interpretation of self-report measures, requiring significant and costly human effort. This method would also require participant compliance, without obvious personal incentive. Using passively generated data, as individuals engage and interact with one another via social media, in contrast, has inherent scalability and comes with significantly reduced cost and resource demand. This data combined with machine learning has the potential to uncover population level trends relating to anxiety disorders, in effect (1) guiding key public health decisions by identifying prevalence and (2) documenting public health statistics, like morbidity and mortality. Recall from the introduction that a major aim of DSM-5 is to address these public health goals [2]. In the face of national or worldwide stressors (e.g., COVID-19), understanding population level trends in mental illness is necessary in appropriately allocating resources and making public health decisions.

Conclusions

GAD is a debilitating, chronic, and fluctuating illness, which is heterogeneous in its presentation. Current assessment and screening measures like the GAD-7 and GAD-Q IV, though validated and widely used, rely on retrospective self-report, and have limited ability to account for naturalistic and time-dependent contextual factors. Objective, passively collected data have the potential to complement these measures, thereby improving GAD understanding and assessment. Passively collected data are widely available due to the widespread use of EHRs, social media, and mobile and wearable technologies. Combined with deep learning models, harnessing greater computing power, passive data allow for a greater understanding of the complex relationships between many variables that may inform GAD screening and diagnosis. GAD has been widely studied over the last several decades, with the development of theoretical models incorporating cognitive, metacognitive, and (to a lesser extent) behavioral phenomena, supported by empirical research [84]**.** Understanding such GAD models in conjunction with the GAD DSM-5 criteria helps to form the basis for using passively collected data in clinical assessment.

Using passively collected data with machine learning to complement traditional GAD assessment measures, like the GAD-7 and GAD-Q IV, has the potential to improve assessment and diagnosis. In EHRs, for instance, routinely collected biodemographic features [26] have shown promise in detecting GAD. Ongoing work in this area may focus on exploiting the wealth of information stored in unstructured clinical narratives and structured biomedical data (e.g., demographics, labs, medications). Using powerful computing alongside deep learning models will allow for the investigation of many variables and their relationships to inform GAD assessment. One may imagine the potential for predictive mental health models to power clinical decision support systems embedded in EHRs.

Research using mobile and wearable device data to inform GAD assessment has been limited and results have been mixed. Although Jacobson et al. and Mullin et al. were able to detect GAD symptom deterioration and sleeping patterns using

passively collected physical activity data, respectively, a study by Di Matteo et al. did not find any models using passively collected data capable of predicting GAD [52, 55, 59]. The nature of GAD, as a highly contextualized, predominantly cognitively driven illness may explain these challenges. Despite these challenges, there is theoretical basis to expect that GAD can be effectively modeled by mobile and wearable data.

Although limited, research using social media data to understand GAD has shown that machine learning algorithms are very effective in predicting whether a user suffers from GAD because users with GAD tend to demonstrate patterns in their posts that non-GAD users do not [70]. For example, someone with GAD is likely to use more words with negative connotations than a control user [66]. However, GAD is often difficult to diagnose [20], which increases complications. Still, using social media data to screen for GAD is promising, as it opens the door to screenings, follow-ups, and interventions to improve mental health outcomes.

Limitations

The nature of GAD presents particular challenges, especially to the relatively nascent domain of deep learning in mental health. GAD has had quite substantial changes across revisions of the DSM over the last 2 decades [40, 85]. Worry has become a distinguishing feature of GAD [44, 45], and while this has contributed to greater diagnostic reliability, it also may underscore a defining characteristic of the illness that makes it more difficult to detect objectively. Compared to anxiety disorders like social anxiety disorder and panic disorder, GAD has relatively fewer overt behavioral and physiologic manifestations. This may pose challenges for using objective data streams to detect illness. We hypothesize that detection *is* possible with such data (given both theoretical models and empirical studies to date, e.g., Jacobson et al. [52]); however, it will require intensive, dense longitudinal data to identify likely subtle and cognitively mediated behavioral and physiologic features. Adding to this challenge, GAD is known to be highly contextually dependent [86], meaning individuals might appear as non-GAD controls when avoiding subtle, environmental triggers. To overcome this challenge, models (particularly those using mobile and wearable derived data) would need to detect subtle contextual cues suggesting avoidance, agitation, and arousal.

Ethical and Privacy Considerations

The use of personal passively collected data necessarily includes important privacy and ethical considerations [87]. Such data contains highly sensitive and personal information and is often identifiable, either directly (e.g., full name) or indirectly (e.g., usernames, locations, social media post content). Some studies to date have addressed the issue of privacy through: (1) ensuring secure communication with

remote data-storage servers; (2) anonymization of participants (i.e., assigning non-identifiable participant ids to participants); (3) local storage of sensitive participant data, and (4) scrambling of participant audio [88]. Further measures are needed (recommended by Cornet and Holden [88]), including a better understanding of passive data ownership and end user preferences, improved tools for end users to understand how and to what extent their data is used and to adjust privacy settings, a legal framework addressing sensitive data use and ownership, and further research aimed at understanding end user privacy preferences. Importantly, users with GAD (or other mental health disorders) constitute a vulnerable population, so great care should be taken to ensure their data is not leaked to advertisers or third parties, who may try to exploit their mental state [62].

When dealing with sensitive, personal information, records should be completely de-identified, including indirect potential identifiers, like location. Individuals should provide informed consent after being explicitly instructed as to how their data will be used and for what purpose. Statistics derived from potentially identifying information should always be reported in aggregate. Developments in data storage and exchange such as blockchain technology offer promising solutions to pool data and have also been integrated with decentralized learning strategies (e.g., swarm learning) and edge computing for secure, versatile, and meaningful passive sensing [89]. Integrating these innovations offer means to improve internal and external validities associated with passive sensing and presents ways to precisely diagnose and manage GAD.

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Chapter 3
Digital Phenotyping in Mood Disorders

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Introduction

Driven by the growing complexity of human interaction with digital technological resources, the concept of digital phenotyping emerges as a potential instrument for expanding psychiatric knowledge on mood disorders. Defined as "the moment-by-moment quantification of the human phenotype at an individual level in situ using data from personal digital devices and smartphones" [1], digital phenotyping consists of continuously and instantly acquiring clinical information about patients through metadata collected from multiple sources and applying it for health care. For instance, inputs from GPS trajectory, voice sampling on the phone, and message logs could inform metrics on sociability, mobility, and activity [2]. Then, this information is used to constitute a social and behavioral fingerprint [3], providing a whole new set of instantaneous clinical data which is unseen in traditional assistance and

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research scenarios. By surpassing the boundaries of mental status examination and clinical interviews, digital phenotyping holds a promise to reach a next-level clinical characterization of mood disorders, offering complete new insights on their signatures. In a similar way, it may also shape mental health assistance towards the principles of precision medicine: by using this "high-resolution" grasp into human behavior, it could inform earlier and more accurate diagnosis, closely monitoring treatment outcomes and tailoring interventions to best suit each individual.

In this chapter, we debate relations of digital phenotyping to mood disorders. We first discuss sources of data, distinguishing active and passive data collection and how raw data is processed into high-level information that informs patterns of mood and behavior. Next, we explore the clinical and research applicabilities of such a tool. This includes a deeper clinical characterization of mood disorders, as well as opportunities for diagnosis and management. Finally, we debate implicated barriers and limitations, also discussing ethical concerns involved in the process.

Digital Phenotyping Data

Data Sources

Digital phenotyping utilizes multiple sources of information from personal devices, allowing a range of data that is commonly classified into active and passive data. The first are the ones actively provided by the patient, as through an internet search or answering questionnaires, while the latter relates to data capture without active involvement, requiring only user permission to access context data from their devices [2, 4].

Passive data constitutes the primary source of data for digital phenotyping, as it provides groundbreaking information on the daily life and mood of a patient. For instance, GPS data may demonstrate how the number of locations and the time spent in different places change over time and according to mood episodes. Data recorded on the accelerometer could further complement such information, quantifying patterns of physical mobility and metabolic expenditure. Voice logs from embedded microphones may be used to detect vocal mood markers that signal mood episode symptoms, such as sadness and excitement. In its turn, registers from the very use of a smartphone constitute a valuable source of information. Screen on-of events could indicate anxiety, and patterns of sociability could be inferred from social network apps, SMS text messages, call logs, and the use of chat applications. Multimedia and material consumption could also provide clues on a person's internal state, including music styles chosen from a streaming program, time spent binge-watching TV series, or the kind of products ordered from delivery apps. Additionally, physiological data, such as heart-rate index, can be collected by wearable devices and integrate the arsenal of clinical information.

When it comes to active data, users' conscious participation is central to collection. While such methods do not carry the innovative essence of passive data

collection, they are a reliable source of complementary data to digital phenotyping, adding convergent validity to information granted from other means. The most evident examples are mental apps that obtain sequenced measures of symptoms by applying self-rated instruments, as is the case of MoodRhythm [5] and eMoods Bipolar Mood Tracker [6]. Both apps allow patients to self-report their mood status with daily subjective assessments through an electronic diary and include features to record medication use routine, sleep hours, and anxiety levels, to name a few. Such records can be shared with mental health professionals, aiding clinical monitoring.

Data Processing

While passive data stream is massive, a series of steps in data processing is necessary to allow for its analysis and gaining utility for mental health practices (see Fig. 3.1). As a first stage, data is collected from devices in its raw state, which is not

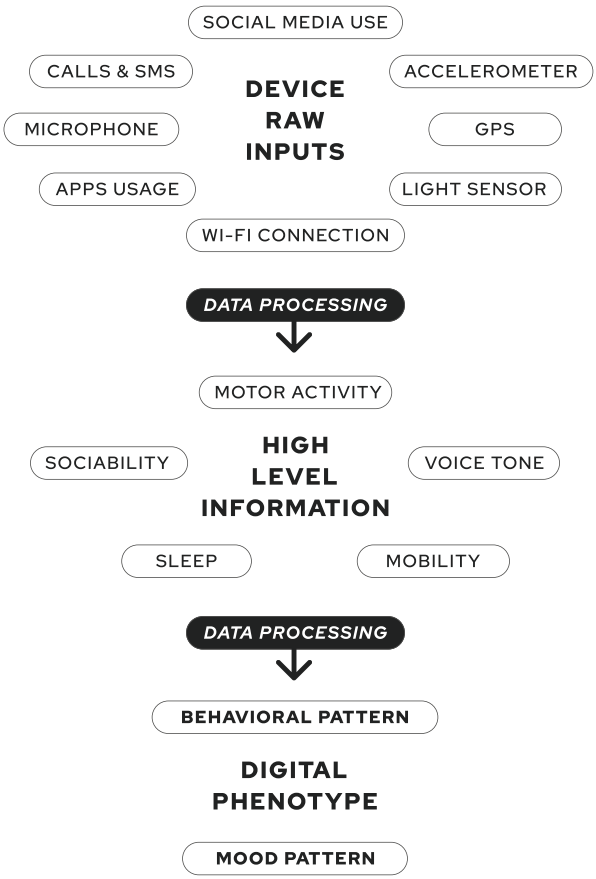

Fig. 3.1 Overview of data processing in digital phenotyping

informative by itself and needs to be processed into higher-level information [7]. Over this, pattern detection can finally occur and establish digital phenotyping, considered the applicable high-tier product of data processing.

First, raw data collection occurs from diverse sources. Mobile and wearable devices input data from sensors, location, keyboard, voice detector, social media, screen on-off events, and a wide range of human–device interactions. While this is the very basis of digital phenotyping, this first-level information is not intelligible unless otherwise transformed and contextualized. Logs from different sources are combined into progressively more comprehensible information [7]. For instance, data from sensors such as accelerometer, gyroscope, and heart-rate monitoring achieve meaning when converted to data on activity as stationary, walking, and running, which can be further processed into the metrics of "physical activity" [8]. Similarly, location logs must be understood through parameters such as places visited, distance traveled, or time spent at locations, which could be telling of "mobility." In the same way, logs from calls, typing and chatting registers, or social media use can be quantified as "virtual sociability," while microphone logs and Bluetooth encounters can inform "physical sociability." When combining different sources, multimodal information can improve accuracy of the aforementioned categories, or even inform more complex ones as would be the case of "daily routine" [9]. While such data is by itself informative and usable in clinical scenarios, there is still a next layer of processing, where computational tools are employed to dig and combine data to detect mood and behavior patterns, establishing the digital phenotype [8].

Digital Phenotyping as a Resource for Mood Disorders

For counting on a complete new set of variables collected in an instantaneous fashion, digital phenotyping could broadly amplify the scope of data available for mental health practice. Currently, clinical interviewing is the main tool to elicit information for psychiatry. While unreplaceable, it is restricted on time and is subject to intrinsic limitations, including selective recall, memory biases, and restricted capacity of tracking daily events. In its turn, digital phenotyping surpasses such constraints, allowing for a 24/7 monitoring of passively collected data with the potential to construct an unbiased and detailed picture of traditional and new parameters related to mental health. This way, it brings novel opportunities to characterize mood disorders, with possible applications in diagnosis, monitoring treatment, and tailoring interventions.

As a Biomarker

Biomarkers are individual characteristics that can be quantified to indicate pathological processes, including anatomic, biochemical, and physiological measures [10]. Recently, they included "digital biomarkers," which refer to markers of

individual processes obtained through sensors and computational tools. Increasingly researched for use in mental health, it has the potential to facilitate diagnostic and prognostic measurements by offering a complementary approach for assessing mood disorders. They are especially promising as indicators of depressive and manic episodes, as the clinical features of such conditions include externalized behaviors that are likely to be captured through passive data collection, including increases or decreases in energy and movement levels and changes in sleep patterns or sociability [11].

Indeed, a few associations between digital markers and mood disorders are emerging in literature. For bipolar disorder, a report described that outgoing phone calls and SMS frequency were positively associated with manic episodes and that these same markers decreased during depressive episodes [12]. Another study corroborates such findings, also describing a longer duration of voice calls during periods of mania and longer screen time during depression [13]. When it comes to major depressive disorder, a wider range of associations is established. In a 10-week cohort, data on GPS, accelerometer, microphone log, Wi-Fi activity, and device use informed metrics of speech duration, geospatial activity, and sleep duration, which were shown to correlate with depressive symptoms [14]. Data on actigraphic registration of people with major depression showed expressive reductions in motor activity when compared to controls [15]. A study reported an association between depression score and several metrics of cell phone use, including the total number of clicks on notifications, number of notifications clicked among the total received, and decision time between seeing a notification and clicking on it [16]. Using wearable and mobile devices, one report accurately predicted stress ratings using behaviors tracked throughout the day, such as the number of naps, hours spent studying, amount and duration of phone calls, phone screen time, and mobility patterns [17]. Another study obtained passive data on vocal characteristics, distance traveled, texting and call logs, and uncovered associations with depressive symptoms [18].

As readily available biomarkers of mood disorders, digital phenotyping holds the potential to enhance performance of risk scoring tools. Current depression risk calculators usually involve two cuts of time and a limited set of predictor variables [19, 20]. For instance, an adolescent depression calculator employs 11 social and demographic variables assessed at age 15 to estimate a future onset of adult depression at age 18, reaching above-chance predictive performance [21]. Other tools include analysis of neuroimage exams to enhance prediction, also achieving satisfactory accuracy [22, 23]. By using digital phenotyping, a wider array of variables could be integrated into calculators, potentially enhancing its predictive value. Additionally, such variables could constitute a more refined kind of data. For instance, sleep duration or activity level configures continuous information with more discrimination than binary variables usually included in such tools, as gender or history of drug use. Moreover, digital phenotyping captures variables on an ongoing, lively basis, and risk scoring would benefit from expanding the current limits of two time-point assessments.

As a Diagnosis Tool

Given digital phenotype can inform a series of biomarkers for mood disorders, it also holds the possibility of constituting diagnosis tools. As a first step, mental health apps could assist physicians by providing a collection of signs that are indicative of a mood episode, therefore auxiliating clinical decision. In this sense, listed symptoms could include social anhedonia, diminished activity, and altered sleep patterns, all of them susceptible to collection by mental health apps and predictors of mood disorders [9, 14, 15]. This symptom assessment would be potentially more accurate than usually reached through clinical interviewing, as it would be devoid of recall and other memory biases that compromise traditional assessments. Beyond that, a further step would involve processing such signs into high-level information as mood and behavior patterns, providing an enhanced perspective of how a person's mood evolved throughout time. In this sense, information of the current period can be compared against previous patterns and estimate the variation from a person's baseline, which is a relevant quantification for ascertaining diagnosis. Similarly, an individual's behavior could be situated in relation to the ones of other individuals, providing statistical information on how they differ from normative population and clinical data. By such means, it is expected that digital phenotyping could enhance detection of initial signs of a mood disorder, informing clinicians about early detection. This would be a significant improvement for management of bipolar disorder, a condition for which diagnosis is frequently delayed [24].

While several possibilities are foreseen in diagnostic applications of digital phenotyping, some studies already report the use of digital data to establish diagnosis of mood disorders. For instance, psychomotor retardation in young people was assessed through smartphone typing patterns, which was used to inform a machine learning model that detected depressive tendency with an accuracy of up to 89% [25]. Another report processed smartphone location data into a measure of "normalized entropy," which takes into account the clusters of visited locations. Employing this higher-level information, a discriminatory performance of 86.5% was reached in identifying individuals with a score equal or greater than 5 in the Patients Health Questionnaire (PHQ-9) scale [26]. In another classification effort, a report using smartphones and smartwatches collected variables from light sensors, location, accelerometer, call logs, and social communication logs to track five indicators of depression, namely physical activity, mood, social activity, sleep, and food intake [27]. Then, a machine-learning model was built for automatic classification of depression in categories that ranged from absence to severe, achieving 96% accuracy. Additionally, a study with the Moodable app acquired data from voice records, browser history, GPS, phone calls, text messages, and social media activity logs to classify depressive symptoms using a machine-learning approach, reporting a score of 76.6% in the task [28].

Monitoring Treatment

Beyond assisting the diagnosis of mood disorders, the use of active and passive smartphone records could provide valuable information in treatment follow-up. Currently, measurement-based care is an evidence-based recommendation associated with better outcomes [29] and consists of employing sequenced measures of symptoms to inform decisions. Digital phenotyping could enhance this standard of care, as a range of lively collected objective parameters may facilitate closer monitoring of symptoms, adequating interventions accordingly [30]. In addition, the continuous monitoring of people with a diagnosis of a mood disorder offers an advantage over intervaled follow-up consultations, as it counts on potential to gauge early patterns of a relapse closer to the instants they occur. For instance, sleep disturbances are known prodromes of mania [31] and are prone to close monitoring using digital applications. Furthermore, monitoring side effects is often challenging for mental health professionals, as there are plenty of possible manifestations that evolve insidiously and pose issues to be quantified. In this direction, mental health tools could keep track of how such symptoms evolve over a period of time and compare to retrospective assessment. For instance, data on activity could inform drowsiness or insomnia, and data from sociability could inform a diminished sexual interest.

A few initiatives are already setting the ground for monitoring mood disorders with digital phenotyping, mainly on predicting phase switch in bipolar disorder. Using inertial sensors and GPS, a smartphone application monitored mobility traces of 12 patients with a diagnosis of bipolar disorder over a period of 1000 days [32]. It was able to detect changes in depressive and manic state with up to 96% accuracy**.** Another initiative combined voice and motor data from smartphone sensors in a 12-week follow-up of participants with bipolar disorder, being able to automatically predict relapse with over 80% of accuracy [33]. Yet another study showed that it is possible to discriminate depressive, euthymic, and manic phases using a collection of passively collected data, including the duration that screen is on, number and duration of phone calls, number of missed phone calls, cell tower ID changes, and number of characters in text messages [13].

Tailored-Treatment Delivery

By having a "high-resolution" view into human behavior, digital phenotyping may also identify opportunities to tailor interventions according to each individual. We saw that digital information such as decrease in physical activity [15], changes in speech duration [14], and patterns of cell phone use [16] can be markers of mood episodes. In digital phenotyping, this information is detected in an instantaneous fashion, and then tools could identify early signs of disorders and deliver context-sensitive care. For instance, early changes in the sleep-wake cycle may predict a

depressive episode [34], and their detection could allow for prompt interventions such as enhancing sleep hygiene. When monitoring depressive symptoms, a worsening of parameters in the app could check treatment adherence ("you may be experiencing early signs of depressive relapse, are you regularly taking your medications?") or launch behavior activation messages ("consider seeing your friends or engaging in leisure activities"). Noteworthy, applications featuring medication reminders already suggest benefits for adherence to treatment with antidepressants [35], and such results could be further developed by digital phenotyping resources. Beyond predicting early signs of disease, pattern detection could provide more detailed information on symptom specificities for each patient and then personalize interventions accordingly. For instance, detecting days and times when anxiety is more intense could permit adjusting medication to cover such periods. Similarly, recognizing patterns of how anxiety evolves throughout the day could launch a relaxation technique reminder just before anxiety builds up, approaching symptoms in their most manageable stage.

Again, a few initiatives already apply principles of digital phenotyping in tailoring interventions. A Mobile Sensing and Support application aimed to monitor behavior of individuals with high depression levels in order to deliver personalized intervention [36]. Data collected included general activity, walking time, time at home, phone usage, number of calls and text messages, and quantity of calendar events, which informed the adjustment of nearly 80 cognitive-behavior personalized interventions such as social, relaxation, thoughtfulness, and physical activity exercises. For participants with a strong app adherence, a significant reduction in PHQ-9 scores was observed. Similarly, the Mobilyze app delivered a 8 week multimodal intervention for depression [37]. Cell phone sensors provided passively acquired data used to inform participants' level of mood. Then, a treatment based on behavioral activation strategy employed context-aware automatic monitoring to identify mood states and suggest coping strategies. When difficulties and obstacles to completing tasks were detected, users received tips on dealing with them. Throughout the experiment, anxiety and depression symptoms significantly reduced.

Addressing Special Populations

While digital phenotyping could enhance mental health delivery for the general public, it also brings an opportunity to address special populations for which mental health assistance is generally suboptimal. To begin with, children and adolescents often present difficulties in reporting clinical information during medical appointments, and treatment is informed using secondhand information by teachers and parents. Similarly, people with speech disability, intellectual deficiency, and dementia can also encounter barriers in identifying, recalling, or communicating clinical information. In a different sense, language barriers are encountered by immigrants, refugees, and travelers when receiving mental health assistance in countries of an

unspoken idiom. For all these publics, digital phenotyping could elicit valuable information and facilitate assistance, presenting an assessment of mood mental health professionals. Moreover, under-resourced countries and remote areas are generally unaddressed by scientific research, as most data collection and observational studies on mental health are conducted in middle to high income countries [38]. By facilitating data collection, digital phenotyping could facilitate research in such locations, bridging academic gaps.

A few initiatives are working in this direction and support the feasibility of such ideas. For instance, an enactment experiment showed that anxiety of people with dementia could be detected using physiological data collected by a wearable monitor [39], and a recent systematic review focused on elderly and dependent people and summarized studies using sensor-based datasets for recognizing human activity, mostly showing satisfactory accuracy [40]. For instance, a study using a wrist device evaluated depression among the elderly [41]. Compared with health controls, an association with decreased patterns of physical activity is described, mainly during the morning and afternoon.

Limitations

As an experimental area in the edge of research, digital phenotyping faces a series of barriers in its development. A first challenge arrives from the necessity to manage massive amounts of continuously captured data. Transferring and storing this data requires hardware capacity, and it is necessary to consider that much of this data will be irrelevant for detecting mood patterns. In this sense, the main issue lies in data mining, i.e., to select through large datasets to find an exception that signals a change in behavior pattern. As a second barrier, the interindividual variability in smartphone use imposes challenges to analysis [42]. There are considerable differences on how individuals use their devices, including time and places. For instance, many people turn off their phones at night or leave them away during recreational times, and then relevant events will be undetected, causing certain signals to be lost. Conversely, some people might have opposite patterns, such as increased use at night or during celebrations, which might input biased information on algorithms. In this sense, differences are also expected on how people experiencing mood episodes relate to their smartphones. To say, a depressed person might both increase or decrease screen time depending on individual factors. Tools need to embrace such interindividual variability without causing significant losses of accuracy when detecting patterns. To deal with these issues, big data and machine-learning techniques stand out as possible solutions [43, 44]. Big data involves strategies to deal with large volumes of data collected at high-stream rate, making it accessible for further analysis [45]. In its turn, machine learning is a form of analytics to deal with big data that utilizes computational strategies with artificial intelligence to uncover patterns and associations [44]. While some initiatives already employ such

techniques to find associations on mood disorders using digital devices [25, 27, 28], broadening its use may involve an enhanced necessity of data processing [44]. This raises concerns on the necessity of high-tech alternatives that might not be widely available for the general public, restricting digital phenotyping to specific groups.

Ethical Issues

A promising field for mental health science, the applications of digital phenotyping to mood disorders are not devoid of ethical issues. Patient and participant privacy is of utmost importance in clinical and research settings and may be particularly troublesome in mental health applications. As digital phenotypes involve the use of personal data flowing across multiple platforms, a significant worry arises over its misuse, which could include branding products through personalized ads to impact consumption on a vulnerable population, or providing private information on mental health of participants to third parties. While most of these issues are debated in anticipation, such worries are founded on solid basis. Studies indicate that most mental health apps on the market do not follow clinical and ethical guidelines, as many applications do not respect the privacy of personal health information and often the patients' data are traded [46]. An analysis of privacy policies from 183 apps in the Apple iTunes Store and the Google Play Store revealed that they were absent for 66.1% of apps and had significant flaws in transparency when present [47]. Furthermore, these mental health technologies have not yet been properly regulated by standardized regulatory means. In the USA, there is no federal regulation on mobile app research or a standard regulation over the collection and use of data [48, 49]. Perhaps for those reasons we notice a lack of confidence in public opinion, as only 8% of users are willing to share their health data with technology companies [46].

To ensure privacy and public trust, mental health apps must comply with a series of requisites which should be warranted by regulation. Mental health apps must be aware of where the data go, what happens to it, and which security vulnerabilities might exist [50]. Therefore, protection of all stages of data collection and analysis must be guaranteed by law. In this direction, state privacy laws are emerging in the field. For instance, the European Union's General Data Protection Regulation (GDPR) is considered a robust privacy and security law [50]. It defines a number of legal terms covering the use of personal data and data processing, determining principles such as a lawful, fair, and transparent processing of data that must be used for legitimate and previously specified purposes. While regulation may protect clients, there is also some concern that digital apps may be exposed to multiple legal jurisdictions, as tools may be available to people from different states or countries [48]. While this could impose difficulties in complying with distinct local law, international agreements could set a common ground on regulatory internet law.

Conclusion

Digital phenotyping is an expected future that could enhance clinical characterization and treatment delivery for mood disorders. A few initiatives already feature digital phenotyping resources in approaching mental health care, demonstrating its feasibility. Using smartphone data, biomarkers of mood disorders were identified, including motor activity, voice call patterns, and screen time. Furthermore, some apps used digital data to perform accurate diagnosis of major depression disorder or to successfully monitor phase switch on participants with bipolar disorder. Similarly, a few tools captured context-sensitive information and tailored behavior intervention to best suit individual specificity, achieving clinical improvement. Currently at its initial steps, several possibilities are foreseen as digital phenotyping develops and disseminates. For potentially capturing a 24/7 accurate picture of mood patterns, novel standards of care are expected on informing early diagnosis and close monitoring symptoms of patients. Notwithstanding, ethical issues also surround the field, with utmost attention to privacy concerns that are yet to be addressed by regulatory law.

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Chapter 4
Mental Health Assessment via Internet: The Psychometrics in the Digital Era

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Introduction

Mental health assessment is a critical step in the clinical practice and research guiding the treatment and follow-up of patients by clinicians. So far, much of the tools utilized for screening and diagnosis have been paper-and-pencil assessments to evaluate psychopathology of several mental disorders such as depression, anxiety disorders, bipolar disorder, and schizophrenia. As the need to easily handle information about the patient's psychiatric symptoms has increased over time, the paper-and-pencil instruments have been transformed into digital questionnaires and used in different digital formats to assess mental health. Recently, there was a high number of mobile phone mental health assessment applications (apps) available on platforms such as Google Play (Android) and iPlay (iOS) accessible to anyone with a smartphone or tablet. Mobile health (mHealth) is a promising field available to clinicians and patients from distinct areas of medicine including psychiatry. In this

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chapter, we review the current literature regarding the psychometric properties of the self-reported digital instruments used for screening, diagnosis, symptoms, and treatment response of mental illness. When available, the paper-and-pencil questionnaires are compared to its transformed digital version. In addition, we discuss the potential and limitations of mHealth in the assessment of mental disorders.

Psychometrics: A Brief Overview

There are several psychological scales available that are able to assess aspects of human behavior such as personality traits, thoughts, memory, cognition, mood, and motivation. However, all scales used to measure these psychological characteristics must be meaningful and reliable. The science that analyzes the basic principles of psychological scales is known as psychometrics [1] and deals with the validity and reliability of instruments that measure some hypothetical construct (for example, depression, anxiety, self-esteem, intelligence, etc.).

When we say that a scale is valid, we are referring to the degree of an instrument that explains the behavior that is intended to be measured. According to the Standards for Educational and Psychological Testing, "validity refers to the degree to which evidence and theory support the interpretations of scale scores for proposed uses of scales. Validity is, therefore, the most fundamental consideration in developing and evaluating instruments" [2]. Furthermore, in case an already developed scale is transformed from paper-and-pencil format to digital format (web page, computer software, and mobile application), there are some steps necessary to assess whether the two formats are equivalent, such as some problems they may arise from differences in the visual presentation of the items and the environment in which the assessment was carried out [3]. Thus, studies that assess psychometric equivalence in different formats of a scale (e.g., paper vs. digital) are needed to ensure that both instruments measure the same construct.

In terms of psychometric properties, there are objective ways to analyze the validity and reliability of an instrument based on the contemporary view that *construct validity* is the essential concept of validity. In this sense, construct validity is the degree to which an instrument score represents or can be interpreted as reflecting a psychological construct (e.g., anxiety, depression, self-esteem, motivation, etc.). According to some authors, the validity of an instrument can be assessed by types of evidence, such as *content validity* (*face validity*), *the internal structure of the scale or reliability* (*internal consistency and test-rest*), *construct validity* (*convergent validity and discriminant validity*), and *criterion validity* (*concurrent and predictive validity*) [4]. Thus, validity is a unitary concept and those types of evidence taken together add information about the scale validity.

Content Validity

The content validity refers to the items or questions of a scale and the content that would be expected in this instrument to measure a specific construct. The items of an instrument must include all relevant facets of the construct; otherwise, this instrument may have irrelevant content of the construct (question or items) and reduce validity. For example, an instrument to measure occupational functioning includes some questions relating to the ability to work, or looking for a job, or the ability to take care of one's home on their own [5]. However, if the instrument had included questions about work preferences or house cleaning skills, they would likely be irrelevant items for measuring occupational functioning and would not reproduce the functioning construct. In addition, the construct facets should be composed of as many questions or items as possible that represent the construct to avoid reduced validity by under-representation of the construct.

Another important aspect in assessing the content validity of a scale, especially in the process of developing a new one or translating it into different languages, is face validity [4]. Face validity deals with how the respondent perceives the items of an instrument as relevant to measure the construct under study. For example, Mustafa et al. [6] translated and adapted the mHealth App Usability Questionnaire (M-MAUQ) into Malay, an app that aims to assess the usability of mobile apps and measure face validity by comparing expert scores and target user opinions on the understandability of the translated M-MAUQ items. In this example, all items had an excellent level of agreement (modified kappa >0.75) with a mean face validity index for 18 items (understandability = 0.961), indicating equivalence of face validity with the original version.

The Internal Structure of the Scale

The internal structure of the test is another important aspect while analyzing the validity of a new instrument. The internal structure refers to the items (or questions) in a scale and how they are related to each other to form one or more clusters that reflect the construct intended to be measured. Usually, items that strongly correlate with some items but weakly correlated with other items form clusters, indicating more than one domain is being measured. This is particularly useful to understand if the scale allows the assessment of a global measure or specific domains of the construct. Therefore, if a test was developed to have one dimension and the factor analysis shows a good correlation between items, there is good evidence that the internal structure predicted was achieved [7]. The internal structure of scales is commonly measured by means of factorial analysis (exploratory or confirmatory factor analysis) or principal component analysis.

Internal Consistency Reliability

Internal consistency reliability assesses the degree to which questions on an instrument measure the same underlying concept. It can be used to determine the consistency of instrument score when it is applied at once or across replications of the same test. When the test–retest approach has been applied the analysis of scores in distinct periods of time may be assessed by correlation analysis, while coefficient alpha or Cronbach's alpha may be used when the instrument was applied once [1, 2, 8]. Furthermore, the reliability of a score can be estimated empirically by its reliability coefficient, generalizability coefficient, item response theory (IRT) information functions, standard errors, error/tolerance ratios, or various indices of classification consistency [2]. Based on the classical test theory (CCT), the reliability coefficients are estimated by statistical analysis of internal consistency.

In general, reliability can be considered as strong or weak as there is no score that represents a 100% reliablility. Keeping that in mind, and according to CTT, the reliability coefficient of a score ranges from 0 to 1, with 0 indicating no evidence of reliability and 1 a perfect measure of reliability. As the CTT takes into account observed scores, true scores, and measurement error, a score with a reliability coefficient of 0.70 would indicate that 70% of the score is actually measuring a true score of a construct and 30% of the score is a measuring error of any source [2]. According to some authors, a reliability coefficient >0.70 means a satisfactory level of reliability [8].

Construct Validity (Convergent Validity and Discriminant Validity)

Convergent Validity

Convergent validity refers to a construct measured in different ways that produce similar results. Specifically, it is the degree to which scores on a studied instrument are related to measures of other constructs that can be expected on theoretical grounds to be close to the one tapped into by this instrument. Evidence of convergent validity of a construct can be provided by the extent to which the newly developed scale correlates highly with other variables designed to measure the same construct. Therefore, if the score of the newly developed scale is highly correlated with another scale that measures the same construct, we conclude there is some level of convergent validity [4].

Discriminant Validity

Discriminant validity refers to a measure that is novel and not simply a reflection of some other construct [4]. In other words, it is the degree to which the scores of a studied instrument are differentiated from the behavioral manifestations of other constructs, which, from a theoretical point of view, cannot be related to the underlying construct of the investigated instrument [4]. For instance, González-Robles et al. [9] studied the psychometric properties of the online version of the Overall Anxiety Severity and Impairment Scale (OASIS) among Spanish patients with anxiety and depressive disorders, including discriminant validity. In this study, correlation of OASIS with the Positive and Negative Affect Schedule-Positive Affect was not as high ($r = -0.40$, $p < 0.01$) as for Beck Anxiety Inventory (BAI, $r = 0.61$, $p < 0.01$), suggesting OASIS maintained the property to evaluate symptom of anxiety and not positive affect.

Criterion Validity (Concurrent and Predictive Validity)

In addition to what has been mentioned so far, the other relevant aspects of validity are concurrent validity and predictive validity [4].

C*oncurrent validity* refers to the relationship between the scores of two instruments measuring the same construct taken at the same time, usually the new instrument compared to another "gold standard" for the construct of interest. For example, the BDI score of depression delivered through the ReMAP app showed good correlation with "gold standard" clinician-rated depression severity using the HDRS in a subset of the sample ($r = 0.78$), suggesting evidence of concurrent validity [10].

Contrary to concurrent validity, *predictive validity* is the extent to which a measure predicts the answers to some other question or a result to which it ought to be related with, i.e., the scale should be able to predict a behavior in the future [4]. For instance, the online version of the Dutch Penn State Worry Questionnaire (PSWQ), a self-reported assessment of pathological worry, had their predictive validity estimated by relationship with worry frequency and worry duration variables [11]. In this study, score of PSWQ was significantly associated with the total time spent worrying during the day ($r(187) = 0.446$, $p < 0.001$) and during the night time ($r(187) = 0.324$, $p < 0.001$), as well as with the frequency of worry episodes during the day ($r(187) = 0.418$, $p < 0.001$), and during the night time ($r(187) = 0.310$, $p < 0.001$), suggesting that worry frequency and worry duration were predicted by PSWQ scores.

The Psychological Process Used in the Scale Responses

The psychological process used in the test responses deals with the cognitive process that a respondent uses while answering a test and the cognitive process they should use to answer the test [1, 2]. This is an important step in assessing the validation degree of a measure as any deviation of expected process to answer a test can affect the test score beyond the intended purpose of the test. Some authors exemplified the issue of process used in a test when test takers used more than cognitive attentional resources to answer a word task [1]. In this example, the scores were inflated because one group did not follow the rules and the scores did not show strong evidence of validity.

Consequences of Using Test

The consequences of using the test deal with sources of bias and useful application of scores when making decisions, affecting the degree of validity of the construct measure and their intended use. For example, men who take the test score higher than women on a screening for depression and, for that result, are referred to see a psychiatrist. However, there are some concerns that the test items were not truly gender balanced and therefore male was given priority in the consultation. In this hypothetical scenario, construct validity is impaired, as scores can be biased and result in adverse consequences for test participants. Typically, most instrument comparisons in clinical practice do not assess this aspect of construct validity.

In sum, we must give an overview of the main components of the psychometric properties commonly used by researchers to assess the validity and reliability of scales when they are developed or for existing instruments that are transformed into digital format, mainly for the purpose of helping the reader in the following sections. However, it is beyond the scope of this section to discuss Item Response Theory (IRT) as another method for evaluating measurement at scale. For this, we suggest readers to read [12] as a starting point. Finally, we have chosen examples to clarify most definitions of validity, although we cannot guarantee that the results given in the examples are in fact a confirmation of validity, as validity is a matter of degree rather than a matter of yes/no.

Psychometric of Mental Health Instruments: Paper-and-Pencil Versus Digital Formats

With the widespread use of the internet in the 1990s, the assessment of mental disorders started a new era of digital assessments through computer-based assessment, internet web page assessments, and more recently by mobile apps through

smartphone or tablets [7, 13, 14]. While in the previous section we discussed the main steps to consider when assessing the validation of new instruments in psychiatry, here we describe the process that must be followed for those instruments to be transformed from paper-and-pencil format to digital versions.

While the instruments available in digital format cover a broad range of mental illnesses [15], there are some concerns that psychometrics of the digital format may not be the same as the original paper-and-pencil format and can affect, to some extent, the validity and reliability of the scores measured [16]. For instance, the assessment of mild cognitive impairment by the Cambridge University Pen to Digital Equivalence assessment (CUPDE) showed significant differences in reliability and validity of scores to its paper-and-pencil version Saint Louis University Mental Status examination (SLUMS) [17], even after change from web-based to app-based interface/layout [18]. In addition, the assessment of anxiety in patients with panic disorder by the internet-based BDI questionnaire showed significant difference in means scores, with lower scores observed in the internet version compared to pen and paper assessment [19]. Furthermore, not all studies assessing psychological symptoms by mobile apps have been validated suggesting that more studies are needed to analyze the equivalence between instruments [16].

In this sense, the equivalence of different formats of instruments used in psychiatry has been reviewed by some studies [7, 13, 14] considering some aspects of validity and reliability. According to van Ballegooijen et al. [13] the equivalence between distinct formats should be assessed by the same steps used in the validity and reliability studies of newly developed scale. Therefore, the following tests should be considered in order to examine equivalence between formats: internal consistency, test-retest reliability, measurement error, internal structure and model fit or explained variance, correlation between the two instruments, difference in mean scores between online and paper versions and criterion validity in terms of sensitivity and specificity (for the optimal cut-off point). Likewise, another systematic review [7] highlighted the importance of performing test-retest reliability, internal consistency, and mean differences between instruments, including the effect size test.

Furthermore, there is some evidence that respondent's perception of the questions delivered should be taken into account and may produce evidence of face validity. For instance, participants reported preference for single items instead of multiple items per web page when they answered instruments such as Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Quality of Life Index (QOLI), and Montgomery-Åsberg Depression Rating Scale (MADRS) [20]. It is also important to consider the respondent perception of the digital layout along with functionality, navigation, personalization, and appearance of a mobile app [21].

In sum, all those aspects might influence the way that respondents answer questions, thus affecting the validity and reliability of the instrument. Thus, instruments that assess psychological symptoms need further validation study when the original format is adapted to digital devices, including original paper-and-pencil versions transformed to computer-based instruments, web page instruments, and mobile applications. In the tables below, we summarize psychometric properties (i.e., face validity, discriminant validity, concurrent validity, internal consistency, intraclass

correlation coefficients (ICC), correlation, and mean scores comparisons) of some digital instruments based on pen and paper scales commonly used to measure symptoms in the field of psychiatry.

Online Web Page Self-Reported Questionnaires

The online web page includes any platform accessed over the Internet using a browser. This digital format requires an Internet connection and a mouse, keyboard, or fingertip as devices to navigate and select web page content. In the field of mental health, few studies have compared the equivalence of an online web page with pen and paper [7, 13]. Overall, online and pen and paper versions have been compared in terms of correlation between scores, comparing score's mean, effect size of differences, internal consistency, convergent validity and criterion validity [13] (see Table 4.1). For example, instruments that assess symptoms of anxiety have shown

Table 4.1 Psychometric properties of instruments to assess self-reported symptoms of depression and anxiety in online web pages

Study	Instrument	Format correlation[a]	Means (SD)		Format difference	Test–retest reliability[b]	Internal consistency[b] (Cronbach's alpha)
			PnP	Digital			
Depression							
Brock et al. [3]	CES-D	N/a	12.00 (7.09)	12.17 (7.75)	N.s.	ICC = 0.84	N/a
Bush et al. [22]	PHQ-9	ICC = 0.92	5.9 (5.6)	5.1 (4.9)	N.s.[c]	N/a	0.85
Carlbring et al. [19]	BDI-II	$r = 0.94$	17.52	18.01	$F = 6.3$, $p < 0.05$, $d = 0.27$[d]	N/a	0.88/0.89
	MADRS-S	$r = 0.91$	16.69 (7.4)	16.42 (7.1)	N.s.	N/a	0.82/0.83
			17.11 (9.4)	16.79 (8.3)			
Fortson et al. [23]	CES-D	N/a	13.81 (8.89)[e]	12.34 (8.59)[e]	N.s.	N/a	0.88/0.89
Fortson et al. [23]	CES-D	N/a	13.81 (8.89)[e]	12.34 (8.59)[e]	N.s.	N/a	0.88/0.89
Holländare et al. [29]	BDI-II	$r = 0.89$	30.55 (10.72)	29.68 (10.07)	N.s.	N/a	0.87/0.89
	MADRS-S	$r = 0.84$	24.43 (6.97)	23.79 (7.98)	N.s.	N/a	0.73/0.81
Herrero and Meneses [30]	CESD-7	N/a	11.85 (3.78)	11.57 (3.79)	N.s.	N/a	0.82

Table 4.1 (continued)

Study	Instrument	Format correlation[a]	Means (SD)		Format difference	Test–retest reliability[b]	Internal consistency[b] (Cronbach's alpha)
			PnP	Digital			
Thorén et al. [31]	HADS	$r = 0.67$	7.3 (5.9)	6.6 (5.4)	N.s. subscales.	N/a	0.85
Whitehead [27]	HADS-depression	N/a	3.24 (3.05)	3.52 (3.04)	N.s.	N/a	0.76
Yu and Yu [32]	CES-D	N/a	12.14 (8.02)	11.03 (7.87)	$t = 2.39$, $p = 0.02$[c]	N/a	N/a
Zimmerman and Martinez [33]	CUDOS	ICC = 0.96	20.0 (14.6)	20.6 (13.9)	N.s.	N/a	0.93
Anxiety							
Brock et al. [3]	BAI	N/a	8.55 (6.87)	6.21 (6.42)	N.s.	ICC = 0.84	>0.70
			9.08 (8.72)	9.43 (6.96)			
Carlbring et al. [19]	BAI	$r = 0.84$	22.62	19.63	$F = 82.2$, $p < 0.01$, $d = 0.98$[d]	N/a	0.88/0.91
Hirai et al. [34]	SIAS	N/a	20.5 (12.39)	20.0 (13.23)	N.s.	N/a	0.93
	SPS	N/a	15.6 (10.68)	16.4 (12.66)	N.s.	N/a	0.93
Whitehead [27]	HADS-anxiety	N/a	6.31 (3.72)	6.39 (3.68)	N.s.	N/a	0.80

 Note: Results are shown for total sample in studies with many groups. *PnP* pen and paper, *N.s.* non-significant, *N/a* not available, *CES-D* Center for Epidemiological Studies Depression, *PHQ-9* Patient Health Questionnaire-9, *BDI-II* Beck Depression Inventory-II, *MADRS-S* Montgomery–Asberg Depression Rating Scale-Self-report, *CESD-7* Center for Epidemiologic Studies Depression scale-7, *HADS* Hospital Anxiety and Depression Scale, *HADS-Depression* Hospital Anxiety and Depression Scale-Depression, *CUDOS* Clinically Useful Depression Outcome Scale, *BAI* Beck Anxiety Inventory, *SIAS* Social Interaction Anxiety Scale, *SPS* Social Phobia Scale, *HADS-Anxiety* Hospital Anxiety and Depression Scale-Anxiety

[a] ICC = Intraclass Correlation and r = Pearson's r

[b] Digital version

[c] t-tests conducted and interpreted by ref. [7] based on values from original article

[d] Effect sizes calculated by ref. [7] based on values from the original article

[e] Mean score calculated and standard deviation estimated by ref. [7] based on values from the original article

good degrees of reliability (Table 4.1). However, the Beck Anxiety Inventory (BAI) assessed online showed a remarkable difference in terms of average compared to the paper-and-pencil version.

In general, instruments that assess post-traumatic stress disorder had a good level of reliability when delivered in web page format compared to their pen and paper instrument counterpart. For example, means scores of the PTSD Check List–Civilian Version (PCL-C), Trauma Symptom Screen Frequency (TSS Frequency), Trauma Symptom Screen Distress (TSS Distress), and Traumatic Life Events Questionnaire (TLEQ) were similar to pen and paper version [7]. In addition, all showed format correlation (ICC and/or $r > 0.65$) with pen and paper and internal consistency >0.80 in the web page format [22–24].

As for other measures summarized so far, questionnaires that assessed self-reported symptoms of panic disorders (Body Sensations Questionnaire, BSQ; Agoraphobic Cognitions Questionnaire, ACQ; Mobile Inventory Accompanied, MI Accompanied; Mobile Inventory Alone, MI Alone) showed a good reliability, with format correlation (ICC or $r > 0.90$) with pen and paper and high internal consistency (Cronbach's alpha >0.9) [19, 25]. However, assessment of web page means scores showed that BSQ, ACQ, and MI alone might slightly differ from pen and paper score [7]. Even though the results are informative, researchers have to consider such differences when transforming the pen and paper format to web page format of those instruments.

The instruments used to measure perceived physical and mental health had not performed well in web page format. For instance, there were some differences in scores on subscales of General Health Questionnaire-28 (GHQ-28) and Symptom Checklist 90 Revised (SCL-90-R) [7], indicating the scores of subscales might not be consistent with the pen and paper versions. However, format correlation (GHQ-28 $r = 0.49–0.92$; SCL-90-R $r = 0.74–0.96$) and internal consistency (Cronbach's alpha >0.90) showed some evidence of validity [26]. Other scales such as the Short Form [12] Health Survey Version Two (SF12V2) had similar scores compared to paper-and-pencil version [7] with moderate to good internal consistency (Cronbach's alpha of 0.68) [27]. Thus, researchers should use GHQ-28 and SCL-90-R with caution regarding scores of subscales, while SF12V2 might be a good alternative to assess the physical and mental health construct.

The instruments to assess self-reported drug abuse had shown a good level of evidence of reliability. For example, the Alcohol Dependence Scale (ADS), the Alcohol Use Disorder Identification Test (AUDIT), the Rutgers Alcohol Problem Index 1 month (RAPI 1 month), the Rutgers Alcohol Problem Index 6 months (RAPI 6 months), and the Rutgers Alcohol Problem Index 1 year (RAPI 1 year), all showed equivalence of means scores to pen and paper versions [7]. In addition, all performed very well regarding test-retest reliability ($r = >0.78$) [28].

The only instrument analyzed by Alfonsson et al. [7] to assess symptoms of insomnia, the ISI, showed a good reliability compared to the pen and paper version. For instance, analysis showed format correlation of 0.99/98 and internal consistency of 0.61/0.88 [20], with identical mean scores in paper and pen (15.86 ± 3.80) compared to online version (16.00 ± 3.87) when compared by statistical analysis [7].

Altogether, there is a good level of evidence that instruments that assess a wide range of psychological symptoms by online web pages maintain equivalence with pen and paper measurements, except for a few subscales that assess panic symptoms (BSQ and ACQ, with lower and upper marginal scores, respectively, compared to pen and paper format) and physical and mental health (SCL-90-R and GHQ-28) which showed some differences in mean scores.

Computer-Based Instruments

Computerized self-report instruments are digital versions of pen and paper questionnaires delivered through desktop software [35] instead of a web page accessed through the internet. For instance, the PHQ-9 and BDI-II were part of a computer-based therapy design to improve symptoms of depression delivered by a flash drive on a designated computer onsite in an outpatient clinic [36]. The assessment of mental health by computer-based instruments also covers a broad range of self-reported symptoms, including depression and anxiety (Table 4.2).

In the assessment of depression, the BDI was studied by four independent authors [35, 37–39], with a good reliability (Table 4.2). For the assessment of reliability

Table 4.2 Psychometric properties of instruments to assess self-reported symptoms of depression and anxiety in computer-based studies

Study	Instrument	Format correlation[a]	Means (SD)		Format difference	Test–retest reliability[b]	Internal consistency[b] (Cronbach's alpha)
			PnP	Digital			
Depression							
George et al. [37]	BDI	N/a	6.02 (5.17)	8.21 (4.69)	$t = 2.18$, $p < 0.05$, $d = 0.44$[c]	N/a	N/a
Glaze and Cox [43]	EPDS	$r = 0.98$	13.34 (7.60)[d]	13.59 (7.75)[d]	N.s.[e]	N/a	N/a
Kurt et al. [44]	GDS-15	$r = 0.72/0.83$	17.68 (2.48)[d]	17.59 (2.38)[d]	N.s.[e]	$r = 0.70$	N/a
	CESD-R 20	$r = 0.61/0.74$	10.19 (14.11)[d]	10.59 (10.85)[d]	N.s.[e]	$r = 0.85$	N/a
Lankford et al. [38]	BDI	N/a	5.72 (3.83)	6.32 (4.34)	N.s. effect of format	N/a	N/a
Lukin et al. [39]	BDI	N/a	7.68 (5.88)	7.67 (5.84)	N.s.	N.s. effect of time.	N/a
Murrelle et al. [42]	CES-D	$r = 0.54$	N/a	N/a	N/a	N/a	N/a
Ogles et al. [45]	CES-D	$r = 0.96$	N/a	N/a	N/a	N/a	0.91

(continued)

Table 4.2 (continued)

Study	Instrument	Format correlation[a]	Means (SD)		Format difference	Test–retest reliability[b]	Internal consistency[b] (Cronbach's alpha)
			PnP	Digital			
Schulenberg and Yutrzenka [46]	BDI-II	$r = 0.98$	8.83 (6.80)	10.09 (9.08)	N.s.	N/a	0.91
Anxiety							
George et al. [37]	STAI-S	N/a	34.88 (7.03)	38.69 (9.61)	$t = 2.23$, $p < 0.05$, $d = 0.45$[c]	N/a	N/a
Lukin et al. [39]	STAI-T	N/a	46.35 (6.77)	46.06 (8.23)	N.s.	N.s. effect of time	N/a
Murrelle et al. [42]	STAI	$r = 0.35$	N/a	N/a	N/a	N/a	N/a

This table has been adapted from ©Sven Alfonsson, Pernilla Maathz, Timo Hursti. Originally published in the Journal of Medical Internet Research (http://www.jmir.org), 03.12.2014. This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in the Journal of Medical Internet Research, is properly cited. Note: Results are shown for total sample in studies with many groups. *PnP* pen and paper, *N.s.* non-significant, *N/a* not available, *BDI* beck depression inventory, *EPDS* Edinburgh Postnatal Depression Scale, *GDS-15* Geriatric Depression Scale-15, *CESD-R 20* Center for Epidemiologic Studies Depression scale -R-20, *CES-D* Center for Epidemiologic Studies Depression scale, *BDI-II* Beck depression Inventory-II, *STAI-S* State-Trait Anxiety Inventory-State, *STAI-T* State-Trait Anxiety Inventory-Trait, *STAI* State-Trait Anxiety Inventory

[a] ICC = Intraclass Correlation and r = Pearson's r

[b] Digital version

[c] Effect sizes calculated by ref. [7] based on values from the original article

[d] Mean score calculated and standard deviation estimated by ref. [7] based on values from the original article

[e] t-tests conducted and interpreted by ref. [7] based on values from original article

between pen and paper to computer-based format, studies performed with anxiety instruments showed few data to allow a full analysis, including few with scores and intraclass correlation (Table 4.2).

The study of Schmitz et al. [40] reported comparison of pen and paper and computerized versions of the SCL-90-R to assess perceived mental health. In this study, there was high internal consistency (Cronbach's alpha =0.98), but there was no information regarding interformat correlation. In addition, there was no statistical difference in mean scores between formats (pen and paper: 1.20 ± 0.66 vs. computerized version: 1.29 ± 0.66) [7].

The studies performed by Chan-Pensley [41] and Murrelle et al. [42] assessed the psychometrics of instruments delivered by computer to measure alcohol and tobacco dependence or misuse. The instruments AUDIT (mentioned in item 3.1), Michigan Alcohol Screening Test (MAST), CAGE Substance Abuse Screening Tool

(CAGE), Drug Abuse Screen Test (DAST), and Fagerstrom Tolerance Questionnaire (FTQ) showed format correlation $r = >0.65$. More recent analysis showed that the computerized version of AUDIT had very close scores compared to the paper-and-pencil version, while the other instruments did not report mean scores for comparison studies [7]. However, not all studies have assessed format correlation and internal consistency between instruments, which may limit the interpretation of results.

The paper-and-pencil scales transformed to computer-based instruments were the earliest digital format used to assess psychological symptoms. In general, most scales delivered through computer software showed some evidence of equivalence to pen and paper format, except for BDI (depression) and STAI-S (anxiety) that had higher means scores in the pen and paper version [7].

Mobile Application (App) Format

The number of health apps available for download can be as high as 325,000 according to estimates published in 2017 [47], with >10,000 related to mental health [48]. The use of mHealth technologies in severe mental disorders such as bipolar disorder, schizophrenia, and major depressive disorder has been systematically reviewed yielding valuable results regarding the psychometric properties of some apps [15]. Most studies in the area of mental health assessment through mobile apps were published after 2013 [13], probably as a result of the widespread use of smartphones. Thus, in this section, we summarize some findings in the field published in recent years.

The Mobile Screener was an app developed in an iOS platform (iPhone) to assess symptoms of PTSD (PTSD Checklist, PCL-C), depression (Patient Health Questionnaire-9, PHQ-9), suicidal ideation (Revised Suicidal Ideation Scale, R-SIS), anger (Dimensions of Anger 5, DAR5), common sleep difficulties and daytime tiredness (Sleep Evaluation Scale), and clinical symptoms (BI Self-Report of Symptoms) in health volunteer soldiers [22]. All measures were analyzed by internal consistency and intraclass correlation between app and pen and paper formats. In general, digital scores in all instruments were close to the original format and with intraclass correlation ranging from 0.62 (DAR5) to 0.95 (Sleep Evaluation Scale). In addition, these apps were satisfactorily qualified by the respondents as easy to submit answers, navigation through pages, sections, and questions. Indeed, more than 70% of them prefer digital app format rather than other formats of questionnaires [22]. However, the limitations of the study included the assessment of symptoms in healthy volunteers and sample ($N = 46$) meaning the results may not be generalized to patients.

Another study developed a mobile tablet app to measure psychosocial functioning in patients with schizophrenia based on the pen and paper full version of University of California San Diego Performance-Based Skills Assessment (UPSA) [49]. The mobile app (UPSA-M) retained 4 out of 5 subsets (planning recreational

activities, finance, communication, and transportation) of the original version. The UPSA-M app showed feasibility and 80% sensitivity to differentiate health subjects from patients with schizophrenia, and the app scores significantly correlated with UPSA pen and paper version ($r = 0.61$). However, in the health controls the correlation did not reach significance ($r = 0.24$). The authors stated that the USPA-M may possess the same psychometric properties of full UPSA and further studies are needed to validate for use in clinical practice [49].

The app ClinTouch was developed to assess daily self-reported psychosis compared to face-to-face Positive and Negative Syndrome Scale (PANSS) and Calgary Depression Scale (CDS) interview [50]. The app was developed in the Android platform and contained two sets of questions based on PANSS and CDS. Set 1 consisted of questions to assess guilt, hopelessness, depression, social withdrawal, conceptual disorganization, excitement, and hallucinations, while set 2 assesses anxiety, grandiosity, hostility, somatic concern, guilty ideas of reference, paranoia, and delusions. The validity of ClinTouch was evaluated in remitted patients, acutely psychotic patients, and those with ultra-high risk of developed psychosis. The patients showed good compliance with the study procedure and only those who had negative symptoms were likely to show greater reactivity to the app (i.e., changing thoughts or mood by answering the questions). In addition, alpha scores showed satisfactory internal consistency (Cronbach's alpha >0.76). In general, there were significant correlations with PANSS positive and affective symptoms while no correlation between the passive and apathetic social withdrawal, hostility, excitement, and cognitive disorganization subscales with the PANSS subscales, suggesting there are some limitations in self-reported assessment in this group of patients.

Apps that allow patients to assess daily measures of mania and depression are extremely useful to provide data on mood changes over time and be used as a guide to prevent relapse in individuals with bipolar disorder. The "Monitoring, treatment and prediction of bipolar disorder episodes" (MONARCA) is a specific app developed to assess mood symptoms in bipolar disorder. This app asked participants to assess every evening (during 3 months) items regarding subjective mood, sleep duration, medicine intake, irritability, activity level, mixed mood, cognitive problems, alcohol consumption, stress, and individual warning signs. In addition, objective measurements were automatically taken regarding social activity, physical activity, speech duration, and cell tower ID. The MONARCA validity study showed 88% adherence to self-report measures using the app and significant correlation between depressive symptoms measured by the app and the Hamilton 17-item Depression Rating Scale interview. However, no correlation was found between Young Mania Rating Scale and self-reported manic symptoms, which was explained by the low prevalence of mania in the sample subpopulation (YMRS score = 2.7) [51].

The Mindful Moods app was developed to assess real-time symptoms of depression in real life in a sample of adult patients with major depressive disorder ($N = 13$) using a smartphone version of the PHQ-9 three times a day for 29–30 days [52]. Respondents received survey notifications via the app with three random PHQ-9

pen and paper questions to answer throughout the day on a Likert scale. In addition, patients attended personal visits to respond to a PHQ-9 pen and paper at the beginning and end of the study. The analysis showed good scoring correlation between the two formats ($r = 0.84$), although the app's scores were on average 3.02 points higher than the pen and paper version. Furthermore, suicide at levels 2 and 3 was reported only in the PHQ-9 app version, suggesting the scenario and may have influenced responses and scores. In addition, adherence to the study protocol was 77% for 30 days, suggesting the feasibility of a long-term protocol to assess symptoms of depression in real time.

Another study developed the Remote Monitoring Application in Psychiatry (ReMAP) app to collect ecological momentary assessment (EMA) symptoms of depression in a sample of healthy controls, patients with Major Depressive Disorder (MDD), bipolar disorder, social anxiety disorder (SAD), MDD with comorbid SAD, or specific phobia (SP) with spider subtype [10]. The study app was the digital format of the BDI and the concordance of scores with the paper-and-pen versions of the BDI, BDI-II, and HDRS assessed by the physician was compared by correlation of the intraclass coefficient and internal consistency (Cronbach's alpha). The overall agreement of the BDI between formats was high (ICC = 0.92), but lower for healthy controls (ICC = 0.63) and patients with anxiety disorders (ICC = 0.72). The internal consistency of ReMAP BDI (Cronbach's $\alpha = 0.944$) was similar to pen and paper BDI (BDI-I: $\alpha = 0.945$; BDI-II: $\alpha = 0.944$). In addition, concurrent validation was established for the ReMAP BDI, which was correlated with clinician-rated depression severity using the HDRS in a subset of the sample ($r = 0.78$) that was comparable to the association between the HDRS score and the score of the pen and paper BDI ($r = 0.68$), suggesting ReMAP showed evidence of equivalence with pen and paper BDI in bipolar patients.

Lastly, a recent systematic review determined the feasibility and evidence of validity of mobile apps developed to monitor episodic symptoms and course of symptoms over time in bipolar disorder patients [14]. The review included 13 studies, but only eight studies assessed the equivalence of the scores obtained in the digital version with clinician-rated assessment or pen and paper self-reported scales. In general, the authors concluded that there is some evidence of concurrent validity for the app Monsenso system (compared to clinician-rated HDRS and YMRS) and MONARCA (compared to clinician-rated HDRS-17 and YMRS), while a mood chart scale app did not show concurrent validity compared to pen and paper mood chart, MADRS and YMRS. In addition, there was convergent validity between the app MONARCA self-reported mixed symptoms and Cohen Perceived Stress Scale (PSS), but not with the abbreviated World Health Organization Quality of Life scale (WHOQoL-BREF) scores. Furthermore, the app MONARCA showed convergent validity for both irritability and mood instability with the Functional Assessment Short Test (FAST), PSS, and WHOQoL-BREF. These findings suggest that mobile app-based self-report tools are valid in the assessment of symptoms of mania and depression in euthymic patients with bipolar disorder.

Conclusion

The evaluation of psychometric properties of instruments transformed into digital format has great potential in psychiatry. When developing a scale, the researcher must carefully examine all types of validity evidence when developing new scale formats based on previous excellent mental health instruments. First, the selection of gold standard instruments is suggested, ideally those that were studied in the target population (general population or clinical sample). In the case of developing new instruments in digital format from scratch, it would be extremely important to choose the appropriate construction and content of the instrument, usually based on previous instruments and the opinions of experts in the field. Second, another key aspect of developing a digital assessment is testing whether the target population is able to use the format, especially considering their ability to use mobile devices. Ideally, pilot studies with the target population would improve face validity before establishing a new scale in digital format. Third, after collecting data in a pilot study, check the agreement of the internal structure of the digital instrument with the original paper-and-pen version, usually by internal consistency and factor analysis. If not fully adhered to, consider the extent to which the differences might impair the accuracy of the construct being measured. Fourth, it is very important to compare the scores of newly developed digital format instruments with other instruments that measure the same construct to confirm concurrent validity, preferably with a gold standard instrument. Finally, and most importantly, researchers must plan carefully before starting research on scale validation in a new format, as digital health is continually evolving in the way data is collected.

In conclusion, the field of digital mental health assessment has evolved over the past 25 years from computer-based instruments to today's use of mobile apps to measure symptoms across a wide range of mental conditions. Although mobile assessment psychometrics has been studied for some recognized instruments, it is imperative that more psychometric studies be carried out in patients with symptoms of anxiety, post-traumatic stress disorder, and dependence or misuse of alcohol and tobacco. In addition, the respondent's perception of digital layout in mobile apps, along with their judgment on navigation, safety, and ease of use, should be addressed in future studies that compare the psychometric properties of mobile app questionnaires with their paper-and-pencil versions.

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Chapter 5
Smartphone-Based Treatment in Psychiatry: A Systematic Review

Maria Faurholt-Jepsen, Morten Lindbjerg Tønning, and Lars Vedel Kessing

Introduction

Psychiatric disorders represent a major burden of disease worldwide with a major impact on quality of life, socioeconomic factors, and life expectancy [1]. At an international level, there is a gap between the need for treatment and the number of patients receiving treatment. Too few patients have access to appropriate care [2]. In high-income countries 35–50% of patients and in low- and middle-income countries 76–85% of patients do not receive treatment for their disorder [2]. This gap in access to care has been even further emphasized during the COVID-19 pandemic [3].

In 2011, the World Health Organization (WHO) stated that "the use of mobile and wireless technologies to support the achievement of health objectives (mHealth) has the potential to transform the face of health service delivery across the globe" [4]. During the last 10 years there has been a rapid increase in the interest for mobile health (mhealth, a general term for the use of mobile phones and other wireless technologies in medical care) technologies within mental health [5–9]. mHealth technologies may potentially assist in the gap in need for treatment and available clinicians. Due to the limited access to treatment facilities, during recent years, and especially emphasized during the COVID-19 pandemic and log-down, there has been a rapid increase in the international interest on the potential and importance in advancing the use of various mHealth technologies for both monitoring and treatment within mental health. Unlike face-to-face therapy and treatment, mHealth interventions have the potential to reach a large number of people without

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geographic boundaries. The number of smartphone users has exceeded 2.5 billion people in 2018 and in high-income countries 80% of the population own and use a smartphone [10].

In recent years, the use of mHealth solutions for the management of various medical conditions, such as diabetes, cardiovascular disease, hypertension, asthma, chronic obstructive lung disease, HIV, and headache, has been addressed in a large number of studies with varying findings [11–22]. The potential for mHealth solutions to transform access to health care and to provide opportunities for early intervention has been emphasized in most of these studies. However, a number of limitations and ethical complications arising from rapid technological developments, including a lack of scientific studies and publications within the area of mHealth, have recently been emphasized [23–28]. In parallel with the use of mHealth for medical conditions, electronic mental health (e-mental health) services, mHealth [29, 30], and telepsychiatry, referring to mental health services delivered over distances via videoconferencing (virtual face-to-face services) [31] have been used within the mental health field.

Ecological momentary interventions (EMIs) combined with ecological momentary assessment (EMA) [32] make use of smartphone technology to provide support in daily life by providing treatment in the moment when needed [33]. Long-term symptoms monitoring via EMA is an approach designed to support patients to manage their disorder and to develop patients' ability to recognize and monitor symptoms over time and thereby provide opportunities to increase insight and identify signs of relapse and stressors. EMA may minimize recall bias, may be sensitive to daily fluctuations in symptoms, can be performed using smartphones, and provides the potential to collect in an unobtrusive way outside laboratory settings using frequently repeated, fine-grained data collection methods [34–36]. Using mHealth solutions, especially smartphones, to develop a detailed and fine-grained characterization of the symptoms that the patients experience during their everyday life could provide opportunities for early intervention between outpatient visits, and electronic self-monitoring may increase patients' self-awareness and empowerment and support their interaction with clinicians [37–39]. Smartphones may provide novel and innovative ways to improve the effectiveness and reach of psychological treatments. Thus, health interventions may be more accessible and interactive for patients with psychiatric disorders. mHealth and especially smartphone-based technology and solutions are developing at an enormous speed, mainly driven by software and computer scientists and private companies. Despite the hype, very few trials investigating the effect of smartphone-based monitoring and treatment have been conducted [40]. Thus, most available apps have not been scientifically investigated and validity, treatment effect, and safety have been sparingly tested [40]. Nevertheless, hundreds of apps claiming to help/monitor psychiatric disorders are already available in app stores.

The aim of this chapter is to provide an overview and quality assessment of published randomized trials (RCTs) investigating the use of smartphones for treatment in psychiatry.

Methods

To provide an overview of RCTs investigating the use of smartphone for treatment within psychiatry MEDLINE, PsycINFO and Embase were searched for published trials. Eligibility criteria were established by the authors in advance.

Study Selection and Search Strategy

To provide an overview of clinically relevant studies the authors decided to make the following inclusion and exclusion criteria: original RCTs reporting on the use of smartphones for treatments in adult patients with a *clinically validated diagnosis* were eligible for evaluation. Where multiple articles reported on overlapping populations occurred, the article presenting the largest population was included. No restrictions regarding sample size were applied. The following RCTs were excluded from this chapter: trials reporting on children under 18 years of age; psychiatric symptoms as part of somatic disorders (i.e. depressive symptoms in terminal cancer patients); RCTs concerning stress, isolated sleep problems without psychiatric disorders; trials with individuals who self-identified as having a psychiatric diagnosis, but without diagnostic reassurance; trials reporting on symptoms without diagnoses (for instance, depressive symptoms, alcohol use in college students; trials using internet therapy without an active smartphone-based component (i.e. if the webpage was accessible from a smartphone browser); trials using only cell phones in traditional ways with text messages and phone calls (not using smartphone-based features); and trials not available in English).

Searching for studies covering smartphone-based treatment in psychiatry was conducted using the electronic database MEDLINE (and adapted to PsycINFO and Embase) up until February 24, 2021. The following search string was employed:

Search strategy: "*(((Smartphone[MeSH Terms] OR Mobile Application[MeSH Terms] OR Smartphone OR Mobile Application OR Smart phone OR Mobile phone OR App OR Apps OR Cell Phone OR Iphone* OR IOS OR Android Phone OR Smartphones OR Mobile Applications OR Smart phones OR Mobile phones OR Cell Phones)) AND ((((((((mental disorder[MeSH Terms]) OR (Mental disorder OR Mental disorders OR Mental disease OR mental diseases OR Mental diagnose OR Psychiatric disease OR Psychiatric diseases OR Psychiatric disorders OR Psychiatric disorder OR psychiatric diagnose)) OR ((drug OR Substance OR prescription drug OR alcohol OR narcotic OR heroin OR cocaine OR amphetamine OR cocaine OR marijuana OR opioid OR morphine OR phencyclidine) AND (abuse OR dependence OR addiction))) OR (Feeding disorder OR feeding disorders OR Eating disorders OR Eating disorder OR Anorexia OR Bulimia OR binge eating)) OR (autism OR Autistic OR Asperger disease OR aspergers disease) OR Asperger disorder OR aspergers disorder OR ADHD OR Attention Deficit Disorder OR ADD OR Attention Deficit Hyperactivity Disorder)) OR (Personality Disorder OR*

personality disorders OR Obsessive-Compulsive Personality OR Compulsive Personality OR Obsessive personality OR Psychopath OR Sociopathic OR Antisocial OR Passive-Dependent Personality OR dyssocial OR Schizoid OR Schizotypal)) OR (Schizophrenia OR Psychoses OR Psychosis OR Psychotic OR Paranoid OR Schizoaffective OR Schizophreniform OR Delusional)) OR (Major depressive disorder OR unipolar depression OR Unipolar disorder OR Depressive syndrome OR endogenous depression OR Neurotic depression OR melancholia OR Cyclothymic OR dysthymic OR Mood disorder OR Mood disorders OR affective disorder OR affective disorders OR Bipolar OR manic-depressive OR mania OR manic) OR (Anxiety OR anxieties OR Panic disorder OR Agoraphobia OR Obsessive disorder OR Compulsive disorder OR Obsessive-compulsive disorder OR Phobic disorder OR phobic disorders OR PTSD OR Posttraumatic Stress Disorder OR Post-traumatic Stress Disorder OR Post traumatic Stress Disorder))) AND ((Randomized Controlled Trial[MeSH Terms]) OR (Randomized controlled trial OR Randomised controlled trial OR Randomized OR Randomized OR RCT OR Randomized clinical trial OR Randomized clinical trial OR Randomized clinical trial OR Randomized controlled clinical trial OR Randomised controlled clinical trial))".

Study Selection and Data Extraction

All retrieved titles and abstracts were screened for eligibility. All potentially relevant articles were retrieved, and full-text articles were then assessed for fulfilling eligibility. The following data were extracted when available: diagnosis; sample size; design; protocol registration or publication; description of intervention; description of control condition; length of trial; the number of patients included in the statistical analyses; the number of patients the statistical power analyses were based on; specification of the primary outcome measure; findings from the trial; and the number of patients that dropped out of the trial.

Risk of Bias in Individual Studies

The risk and types of bias in the individual studies were assessed independently by two researchers (MFJ and LVK). In case of disagreement studies were discussed with the third researcher (MLT). The risk of bias arising during the randomization process, due to deviation from the intended interventions, due to missing outcome data, due to measurement of the outcome measures, and due to selection of the reported results was assessed as suggested by The Cochrane risk of bias tool for randomized trials (the RoB2 tool) [41].

Results

Search Strategy and Selection of Trials

A total of 1660 potential articles were identified in the electronic databases MEDLINE, PsycINFO, and Embase. After removing a total of 1630 articles consisting of duplicates and studies not involving RCTs investigating the use of smartphones for psychiatric disorders on patients with a clinically validated diagnosis, a total of 30 RCTs were included for evaluation (flow diagram presented in Fig. 5.1). Overall, the RCTs were conducted in the USA [42–47], Iran [48], Sweden [49–54], Australia [55, 56], Switzerland [57], Taiwan [58], Republic of Korea [59, 60], Japan [61], Denmark [7, 62–64], Poland [65], and the UK [66–69]. The RCTs were published between 2013 and 2021, with the most RCTs published in 2018 [45, 46, 54, 57, 59, 67, 70] and 2020 [48, 56, 60, 63, 64, 68, 69], respectively. Overall, a total of 29,571 patients with psychiatric disorders were included in the trials (range in

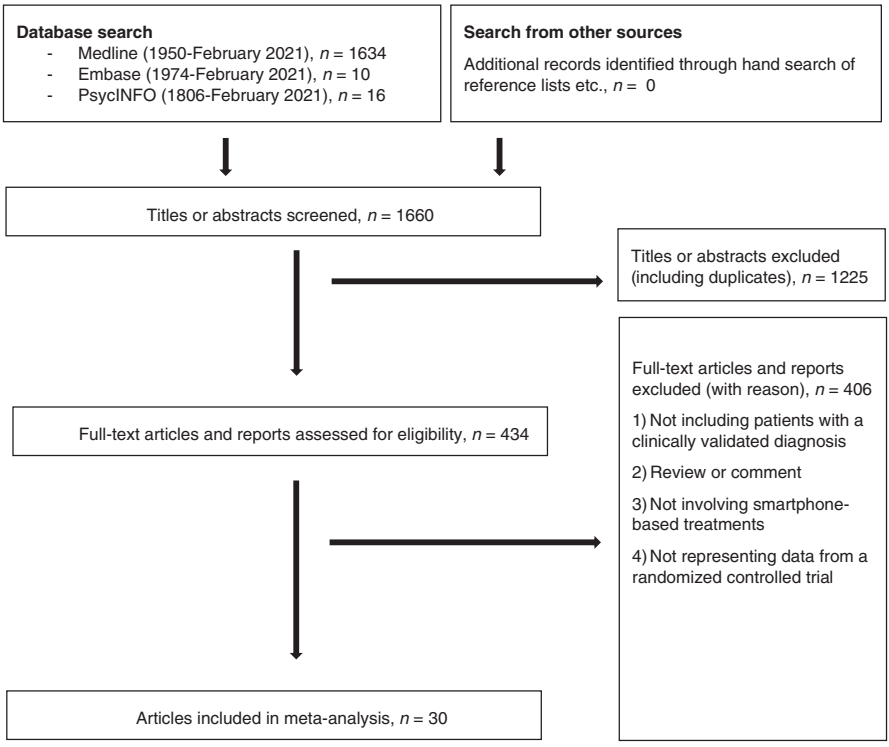

Fig. 5.1 Flow diagram of literature search and study selection process

individual studies between 21 patients [66] to 349 patients [44]). A total of 7 RCTs were including patients with psychotic disorders [45, 46, 56, 65, 67–69], 12 RCTs included patients with affective disorders [7, 42, 43, 48–50, 55, 59, 61–64], and 11 included patients with other psychiatric disorders [44, 47, 51–54, 57, 58, 60, 66, 70]. The length of the trials ranged between 3 weeks [59] and 12 months [44, 54].

Trials According to Psychiatric Disorder

Trials investigating the effect of smartphone-based tools according to type of psychiatric disorder including the risk of bias assessment according to the RoB2 tool are presented in Table 5.1 (psychotic disorders), Table 5.2 (affective disorders), and Table 5.3 (other disorders).

Psychotic Disorders

The seven RCTs including patients with psychotic disorders [45, 46, 56, 65, 67–69] were conducted in the USA [45, 46], the UK [67–69], Poland [65], and Australia [56]. In 2018 three RCTs were published [45, 46, 67], in 2019 one RCT was published [65], and in 2020 three RCTs were published [56, 68, 69]. A total of 687 patients with psychotic disorders were included in the trials (range in individual studies between 34 [56] and 290 [65]). The length of the trials ranged between 8 weeks [56] and 12 months [65, 69]. The included patients were diagnosed with schizophrenia/schizoaffective disorder [45, 46, 65, 68] and other types of psychotic disorders [56, 67, 69]. All of the trials investigated the use of a smartphone-based symptom monitoring system, and two of the trials included feedback to clinicians [45, 68]. Some of the smartphone-based systems included mindfulness exercises [67] and cognitive training, coping strategies, prevention plans, and psychoeducation [56, 65, 69]. Four of the RCTs compared the interventions as add-on to standard treatment with standard treatment alone [46, 56, 68, 69]. One of these trials also included an arm with waitlist condition for comparison [46]. Another trial used clinic-based group intervention as the comparator [45], one trial compared the smartphone-based intervention with an inactive version of the app [65], and one trial compared smartphone-based intervention including monitoring and mindfulness with smartphone-based monitoring only [67]. Of the seven included trials, three of the trials investigated the effect of a smartphone-based system on the severity of symptoms as their primary outcome measure [45, 65, 68], and one used changes in motivated behavior as the primary outcome measure [46]. A statistical power analysis was clearly stated in one of the trials, only [45]. In all four trials there were no statistically significant differences in outcome measures between the intervention group and the control group [45, 46, 65, 68]. The remaining three trials investigated the feasibility and acceptability of the smartphone-based system and were therefore not an investigation of effect [56, 67, 69]. Overall, reported the

Table 5.1 Randomized controlled trials (RCT) investigating smartphone-based treatment in patients with psychotic disorders, $N = 7$

Author, year of publication, country	Diagnosis, sample size	Design	Protocol	Intervention ("name")	Comparator	Trial length	Analyzed (power calculation)	Primary outcome	Findings	Dropout	Risk of bias[a]
Psychotic disorders											
Ben-Zeev et al. (2018), USA [45]	Schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, 163	RCT	N/A	Smartphone-based intervention including symptoms monitoring, clinician dashboard and support (*FOCUS*)	Clinic-based group intervention (*WRAP*)	12 weeks	163 (160)	General psychopathology	No difference between groups	12 weeks	1: Low 2: Some concerns 3: Some concerns 4: Some concerns 5: Low Overall: Some concerns
Bucci et al. (2018), UK [67]	Psychosis, 36	Pilot RCT	Registered online	Smartphone-based monitoring and information on activities and mindfulness exercises (*Actissist*)	Smartphone-based monitoring (*ClinTouch*)	12 weeks	36 (N/A)	Feasibility	Intervention group reported higher feasibility	10	1: Low 2: Some concerns 3: Some concerns 4: Some concerns 5: Some concerns Overall: Some concerns
Schlosser et al. (2018), USA [46]	Schizophrenia, 43	RCT	N/A	Smartphone-based goal monitoring and challenges including communities with others (*PRIME*)	Standard treatment/ waitlist	12 weeks	43 (N/A)	Changes in motivated behavior	Increased motivated behavior in intervention group	5	1: High 2: Some concerns 3: Some concerns 4: Some concerns 5: Some concerns Overall: High risk of bias

(continued)

Table 5.1 (continued)

Author, year of publication, country	Diagnosis, sample size	Design	Protocol	Intervention ("name")	Comparator	Trial length	Analyzed (power calculation)	Primary outcome	Findings	Dropout	Risk of bias[a]
Krzystanek et al. (2019), Poland [65]	Paranoid schizophrenia, 290	RCT	N/A	Smartphone-based medication reminders and cognitive training (*MONEO*)	Inactive version of the app	12 months	290	Clinically evaluated symptoms according to the PANSS	No differences between groups	N/A	1: High 2: Some concerns 3: Some concerns 4: Some concerns 5: Low Overall: Some concerns
Bell et al. (2020), Australia [56]	Psychosis, 34	Pilot RCT	N/A	Smartphone-based monitoring and coping strategies and interventions strategies and in-person sessions (SAVVy)	Standard treatment	8 weeks	(N/A)	Feasibility and acceptability of the app. Also voices, depressive, and anxiety symptoms	No difference between groups. Subitem difference favoring intervention group on coping with voices	2	1: Some concerns 2: Some concerns 3: Some concerns 4: Some concerns 5: Some concerns Overall: High risk of bias
Lewis et al. (2020), UK [68]	Schizophrenia and related disorders, 81	Open RCT	N/A	Smartphone-based symptom management several times per day including feedback to clinicians (*ClinTouch*)	Standard treatment	12 weeks	81	Positive symptoms according to the PANSS and empowerment	No differences between group on any outcome	2	1: High 2: High 3: Some concerns 4: Some concerns 5: Some concerns Overall: High risk of bias

Steare et al. (2020), UK [69]	Psychosis, 40	Feasibility RCT, unblinded	N/A	Smartphone-based relapse prevention plans, recovery goals, symptoms monitoring, medication tracking and psychoeducation (*My Journey 3*)	Standard treatment	12 months	N/A	Acceptability	Most patients reported the app to be acceptable. Between group differences in symptoms not reported	2	1: Low 2: Some concerns 3: Low 4: High 5: Some concerns Overall: High risk of bias

[a]Assessed in five domains as Low/High/Some concerns; Domain 1: Risk of bias arising from the randomization process; Domain 2: Risk of bias due to deviations from the intended interventions; Domain 3: Missing outcome bias; Domain 4: Risk of bias in measurement of the outcome; Domain 5: Risk of bias in selection of the reported result

Table 5.2 Randomized controlled trials (RCT) investigating smartphone-based treatment in patients with affective disorders, $N = 12$

Author (year of publication), country	Diagnosis, sample size	Design	Protocol	Intervention ("name")	Comparator	Trial length	Analyzed (power calculation)	Primary outcome	Findings	Dropout	Risk of bias[a]
Affective disorders											
Watts et al. (2013), Australia [55]	Major depression, 35	Pilot RCT	N/A	CBT delivered from mobile phones (*Get happy*)	CBT delivered from computers (*The Sadness Program*)	3 months	35 (N/A)	Patient health questionnaire and questionnaire-based depressive symptoms	Statistically significant improvement in patient health questionnaire in intervention group	N/A	1: Some concerns 2: Some concerns 3: Some concerns 4: Some concerns 5: Some concerns Overall: High risk of bias
Ly et al. (2014), Sweden [49]	Major depressive disorder, 81	RCT	N/A	Smartphone-based behavioral activation	Smartphone-based mindfulness	6 months—intervention for 8 weeks	81 (yes)	Questionnaire-based depressive symptoms, anxiety, and quality of life	No difference between group	N/A	1: High 2: Some concerns 3: Some concerns 4: Low 5: Some concerns Overall: High risk of bias
Depp et al. (2015), USA [42]	Bipolar disorder, 82 (104)	RCT	N/A	Mobile intervention linking mood with personalized self-management strategies (*PRISM*)	Paper-and-pencil mood monitoring	24 weeks, 10 weeks intervention	82 (N/A)	Clinicians assessed depressive and manic symptoms	Reduced levels of depressive symptoms at 6 and 12 weeks, but not at end of study	N/A	1: Low 2: Some concerns 3: Low 4: Some concerns 5: Some concerns Overall: Some concerns

Faurholt-Jepsen et al. (2015), Denmark [62]	Bipolar disorder, 67	RCT	Published	Daily smartphone-based monitoring of symptoms and clinical feedback to a study nurse (MONARCA)	Standard treatment	6 months	67 (56)	Clinician assessed depressive and manic symptoms	No difference between groups	3	1: Low 2: Some concerns 3: Low 4: Low 5: Low Overall: Some concerns
Ly et al. (2015), Sweden [50]	Major depressive disorder, 93	RCT	N/A	Blended treatment: face-to-face sessions and smartphone-based behavioral activation	Behavioral activation	6 months	93 (93)	Questionnaire-based depressive symptoms, anxiety, and quality of life	No difference between group	5	1: Low 2: Some concerns 3: Low 4: Some concerns 5: Some concerns Overall: High risk of bias
Mantani et al. (2017), Japan [61]	Major depressive disorder, 164	RCT	Yes	Smartphone-based CBT (the *Kokoro app*) + medication	Medication only	17 weeks	164 (164)	Patient health questionnaire	Reduced scores on the patient health questionnaire in the intervention group	–	1: Low 2: Some concerns 3: Low 4: Low 5: Low Overall: Some concerns
Hur et al. (2018), Republic of Korea [59]	Depressive disorder, 34	Pilot RCT	N/A	Smartphone-based CBT (*the Todac Todac*)	Smartphone-based daily mood charting	3 weeks	34 (N/A)	Dysfunctional Attitude Scale	No difference between group	N/A	1: Some concerns 2: Some concerns 3: Some concerns 4: Some concerns 5: Some concerns Overall: High risk of bias

(continued)

Table 5.2 (continued)

Author (year of publication), country	Diagnosis, sample size	Design	Protocol	Intervention ("name")	Comparator	Trial length	Analyzed (power calculation)	Primary outcome	Findings	Dropout	Risk of bias[a]
Faurholt-Jepsen et al. (2019), Denmark [7]	Bipolar disorder, 129	RCT	Published	Daily smartphone-based monitoring of symptoms and clinical feedback to a study nurse (MONARCA)	Standard treatment	9 months	129 (258)	Clinician assessed depressive and manic symptoms	No difference between groups	9	1: Low 2: Some concerns 3: Low 4: Low 5: Low Overall: Some concerns
Stiles-Shields et al. (2019), USA [43]	Depression, 30	Pilot RCT	N/A	Smartphone-based activity scheduling (*Boost Me*)	Smartphone-based thought restructuring (*Thought Challenger*) or Waitlist control group	10 weeks	27 (N/A)	Patient health questionnaire	Post hoc analyses suggested lower scores on the patient health questionnaire in the Though Challenger group compared with waitlist condition	0	1: Some concerns 2: Some concerns 3: Some concerns 4: Some concerns 5: Some concerns Overall: High risk of bias
Faurholt-Jepsen et al. (2020), Denmark [63]	Bipolar disorder, 99	RCT	Published	Daily smartphone-based monitoring of symptoms and clinical feedback to a study nurse (*Monsenso*)	Standard treatment	6 months	99 (200)	Time to psychiatric readmission and duration of readmission	No differences between groups	11	1: Low 2: Some concerns 3: Low 4: Low 5: Low Overall: Some concerns

Jannati et al. (2020), Iran [48]	Postpartum depression, 78	RCT, unblinded	N/A	Smartphone-based CBT with eight lessons on different topics (*Happy Mom*)	Standard treatment	2 months	75 (N/A)	Depressive symptoms from questionnaires	Statistically significant lower levels of depressive symptoms in intervention group	N/A	1: Some concerns 2: Some concerns 3: Low 4: Some concerns 5: Low Overall: Some concerns
Tønning et al. (2020), Denmark [64]	Unipolar depressive disorder, 120	RCT	Published	Daily smartphone-based monitoring of symptoms and clinical feedback to a study nurse (*Monsenso*)	Standard treatment	6 months	120 (200)	Time to psychiatric readmission and duration of readmission	No differences between groups	7	1: Low 2: Some concerns 3: Low 4: Low 5: Low Overall: Some concerns

[a]Assessed in five domains as Low/High/Some concerns; Domain 1: Risk of bias arising from the randomization process; Domain 2: Risk of bias due to deviations from the intended interventions; Domain 3: Missing outcome bias; Domain 4: Risk of bias in measurement of the outcome; Domain 5: Risk of bias in selection of the reported result

Table 5.3 Randomized controlled trials (RCT) investigating smartphone-based treatment in patients with other psychiatric disorders, $N = 11$

Author (year of publication), country	Diagnosis, sample size	Design	Protocol	Intervention ("name")	Comparator	Trial length	Analyzed (power calculation)	Primary outcome	Findings	Dropout	Risk of bias[a]
Other disorders											
Dagöö et al. (2014), Sweden [51]	Social anxiety disorder, 52	RCT	N/A	Smartphone-based CBT modules and monitoring of anxiety levels (*mCBT*)	Interpersonal therapy via mobile computer solutions (*mIPT*)	3 months	52 (N/A)	Questionnaire-based levels of anxiety and depressive symptoms	Intervention group lower levels of anxiety	N/A	1: Low 2: Some concerns 3: Low 4: Some concerns 5: Some concerns Overall: Some concerns
Gustafson et al. (2014), USA [44]	Alcoholism, 349	RCT	N/A	Smartphone-based app to support recovery using monitoring, information, communication, and support (*A-CHESS*)	Standard treatment	12 months	N/A (350)	Risky drinking days	Intervention group lower levels of risky drinking days	N/A	1: Some concerns 2: Some concerns 3: Some concerns 4: Some concerns 5: Some concerns Overall: High risk of bias
Moëll et al. (2015), Sweden [52]	ADHD, 57	RCT	Registered at clinicaltrials.gov	Internet-based course of CBT with support and smartphone-based reminders and to-do lists (Living Smart)	Waitlist	6 weeks	57 (N/A)	Questionnaire-based inattention	Statistically significant lower levels of inattention in intervention group	3	1: Some concerns 2: Some concerns 3: Low 4: Low 5: Some concerns Overall: Some concerns

Ivanova et al. (2016), Sweden [53]	Social anxiety disorder and panic disorder, 152	RCT	Registered at clinicaltrials.gov	Guided acceptance and commitment therapy provided via the internet or smartphone	Unguided acceptance and commitment therapy provided via the internet or smartphone (or waitlist)	10 weeks	152 (150)	Questionnaire-based anxiety symptoms	Reduced levels of anxiety symptoms compared to waitlist	N/A	1: Some concerns 2: Some concerns 3: Some concerns 4: Some concerns 5: Some concerns Overall: High
Hildebrandt et al. (2020), USA [47]	Binge eating disorder, 66	RCT	N/A	CBT guided self-help + smartphone-based monitoring of symptoms	CBT guided self-help	9 months	66 (60)	Objective bulimic episodes	No differences between groups at follow-up	6	1: Some concerns 2: Some concerns 3: Some concerns 4: Some concerns 5: Some concerns Overall: High
Boettcher et al. (2018), Sweden/ Germany [54]	Social anxiety disorder, 209	RCT	N/A	Smartphone-based self-help program	(1) Self-help program and then smartphone-based treatment (2) Waitlist	12 months	209 (N/A)	Social anxiety symptoms	No differences between groups	N/A	1: Low 2: Some concerns 3: Some concerns 4: Some concerns 5: Some concerns Overall: Some concerns
Liang et al. (2018), China [70]	Drug addition, 75	Pilot RCT	N/A	Smartphone-based survey on cravings, affects, triggers, etc.	Received text messages	1 month	75 (N/A)	Urine tests of five drugs	No differences between groups	8	1: Some concerns 2: Some concerns 3: Some concerns 4: Some concerns 5: Some concerns Overall: High risk of bias

(continued)

Table 5.3 (continued)

Author (year of publication), country	Diagnosis, sample size	Design	Protocol	Intervention ("name")	Comparator	Trial length	Analyzed (power calculation)	Primary outcome	Findings	Dropout	Risk of bias[a]
Stolz et al. (2018), Switzerland [57]	Social anxiety disorder, 150	RCT	N/A	Smartphone-based CBT	Computer-based CBT or waitlist	12 weeks	150 (141)	Questionnaire-based symptoms of social anxiety	Reduced symptoms in intervention group and computer-based group compared with waitlist. No differences between smartphone-based and computer-based CBT	N/A	1: Some concerns 2: Some concerns 3: Some concerns 4: Some concerns 5: Some concerns Overall: High risk of bias
Teng et al. (2019), Taiwan [58]	Generalized anxiety disorder, 82	RCT	N/A	Smartphone-based home-delivered attention bias modification (*HD-ABM*)	Placebo-training on smartphones or waitlist	4 weeks	82 (N/A)	N/A	Findings reported within each group	N/A	1: Some concerns 2: Some concerns 3: Some concerns 4: Some concerns 5: High Overall: High risk of bias
Oh et al. (2020), South Korea [60]	Panic disorder, 45	RCT	N/A	Smartphone-based chatbot, information on coping skills and offering treatment, symptom monitoring, and CBT modules (*Todaki*)	Book entitled "*Goodbye Panic Disorder*"	4 weeks	Not clearly reported	Clinicians evaluated severity of panic symptoms	No differences between groups	4	1: Some concerns 2: Some concerns 3: Low 4: Some concerns 5: Some concerns Overall: High risk of bias

Miller et al. (2021), UK [66]	Generalized anxiety disorder, 21	Randomized multiple-baseline single-case experimental design	N/A	Smartphone-based CBT with tailored feedback based on input from patients and symptom monitoring (*Daylight*)	Baseline periods of 2-, 4-, or 6-weeks before smartphone-based CBT and monitoring	12–16 weeks		Daily levels of anxiety (VAS scale). Weekly questionnaire-based measures of anxiety, depressive symptoms and sleep	Intra-individual reduced symptoms over time. Between group differences not reported	0	1: Some concerns 2: Some concerns 3: Low 4: Some concerns 5: High Overall: High risk of bias

[a]Assessed in five domains as Low/High/Some concerns; Domain 1: Risk of bias arising from the randomization process; Domain 2: Risk of bias due to deviations from the intended interventions; Domain 3: Missing outcome bias; Domain 4: Risk of bias in measurement of the outcome; Domain 5: Risk of bias in selection of the reported result

intervention group higher feasibility as compared with the control group. One trial reported higher feasibility of the smartphone-based system including information on activities and mindfulness exercises as compared with smartphone-based monitoring only [67]. Another trial reported higher levels of motivated behavior of smartphone-based goal monitoring and challenges including communities with others as compared with standard treatment or waitlist [46]. None of the included trials clearly stated whether the statistical analyses were adjusted for potential confounders.

Risk of Bias

All the RCTs investigating the effect of smartphone-based treatment in patients with psychotic disorders were assessed to be at high risk of bias or with reason to be concerned (Table 5.1).

Affective Disorders

The 12 RCTs including patients with affective disorders [7, 42, 43, 48–50, 55, 59, 61–64] were conducted in Australia [55], Sweden [49, 50], the USA [42, 43], Denmark [7, 62–64], Japan [61], Republic of Korea [59], and Iran [48]. In 2015 three RCTs were published [42, 50, 62], in 2019 two RCTs were published [7, 43], and in 2020 three RCTs were published [48, 63, 64]. A total of 1012 patients with affective disorders were included in the trials (range in individual studies between 30 [43] and 164 [61]). The length of the trials ranged between 3 weeks [59] and 9 months [7]. The included patients were diagnosed with bipolar disorder [7, 42, 62, 63] or major depressive disorder/unipolar disorder [43, 48–50, 55, 59, 61, 64]. The trials investigated the use of smartphone-based CBT interventions [48, 55, 59, 61], smartphone-based behavioral activation systems [49, 50], smartphone-based symptom monitoring including clinician-based feedback [7, 62–64], self-management strategies based on mood monitoring [42], or smartphone-based activity scheduling [43]. Five of the RCTs compared the interventions as add-on to standard treatment with standard treatment alone [7, 48, 62–64], and one trial also included a group for comparison using waitlist condition [43]. Another trial used computer delivered CBT as the comparator [55], and one trial used paper-and-pencil mood monitoring for comparison [42]. Of the 12 included trials, all the trials investigated the effect of a smartphone-based system on clinically relevant outcome measures. All 12 trials clearly defined the primary outcome measure. A total of three trials used clinician assessed symptoms as the primary outcome measure [7, 42, 62], seven trials used questionnaire-based data on symptoms as their primary outcome measure [43, 48–50, 55, 59, 61], and two trials used data on time to and duration of psychiatric re-hospitalizations collected from the electronic health records as the primary outcome measure [63, 64]. A statistical power analysis was clearly stated in seven of the trials [7, 49, 50, 61–64]. In eight of the trials there were no statistically significant

differences in the primary outcome measure between the intervention group and the control group at the end of the trials [7, 42, 49, 50, 59, 62–64]. Three trials reported statistically significant improvement in scores on the patient health questionnaire in the intervention group [43, 55, 61] (in one of these studies findings were based on post hoc analyses [43]), and another trial reported lower levels of questionnaire-based depressive symptoms in the intervention group [48]. Four of the included trials clearly stated whether the statistical analyses were adjusted for potential confounders [7, 62–64].

Risk of Bias

All of the RCTs investigating the effect of smartphone-based treatment in patients with affective disorders were assessed to be at high risk of bias or with reason to be concerned (Table 5.2).

Other Disorders

The 11 RCTs including patients with other types of psychiatric disorders [44, 47, 51–54, 57, 58, 60, 66, 70] were conducted in Sweden [51–54], the USA [44, 47], China [70], Switzerland [57], Taiwan [58], South Korea [60], and UK [66]. In 2018 three RCTs were published [54, 57, 70], in 2019 one RCT was published [58], and in 2020/2021 two RCTs were published [60, 66]. A total of 1258 patients with other types of psychiatric disorders were included in the trials (range in individual studies between 21 [66] and 349 [44]). The length of the trials ranged between 1 month [70] to 12 months [44]. The included patients were diagnosed with anxiety disorders [51, 53, 54, 57, 58, 60, 66], alcoholism [44], ADHD [52], binge eating disorder [47], and drug addiction [70]. The trials investigated the use of smartphone-based CBT interventions [51, 52, 57, 60, 66], symptoms monitoring including information [44, 47, 54], commitment therapy [53], and attention bias modification [58]. Two of the RCTs compared the intervention with waitlist [52–54, 58], and one RCT compared the intervention with standard treatment [44]. Some of the RCTs compared the intervention with therapy conducted in-person or using a computer [47, 51, 57]. One trial compared the intervention with a book on panic disorder [60]. Of the 11 included trials, apart from one RCT [58], all of the trials investigated the effect of a smartphone-based system on clinically relevant outcome measures. The primary outcome measure was clearly defined in 10 of the 11 trials. A total of six trials used questionnaire-based data on anxiety symptoms as their primary outcome measure [51–54, 57, 66], one trial used clinician assessed anxiety symptoms as the primary outcome measure [60], one trial used questionnaire-based data on binge eating episodes [47], and two trials used patient-reported number of risky drinking days or number of urine tests positive for drugs [44, 70]. A statistical power analysis was clearly stated in four of the trials, only [44, 47, 53, 57]. In four of the trials there were no statistically significant differences in outcome measures between the

intervention group and the control group at the end of the trials [47, 54, 60, 70]. Five trials reported lower levels of symptoms in the intervention group compared with the control group [44, 51–53, 57]. Two trials primarily reported findings concerning change in symptoms over time within the intervention group and focusing on differences between the two groups [58, 66]. None of the included trials clearly stated whether the statistical analyses were adjusted for potential confounders other than baseline variables.

Risk of Bias

All of the RCTs investigating the effect of smartphone-based treatment in patients with other types of psychiatric disorders were assessed to be at high risk of bias (Table 5.3).

Discussion

Smartphones are ubiquitous, and many people own and use a smartphone and carry it with them during large part of the day. Reports suggest that almost three quarters of patients with a psychiatric disorder would like to use an application as part of their mental health care [71]. It has been suggested that mHealth interventions have the potential to minimize the traditional barriers of distance, time, and costs of treatments [21, 27].

This chapter aimed at identifying RCTs investigating the effect of smartphone-based intervention for patients with a clinically validated psychiatric disorder. A total of 29 RCTs were identified and included for evaluation. The RCTs included patients with psychotic disorders (n = 7), affective disorders (n = 12), and other types of psychiatric disorders (n = 10) such as anxiety disorder, alcoholism, and drug addiction were published. Overall, the RCTs were conducted in diverse settings, used different smartphone-based treatment interventions, included rather small samples of patients, and had quite different lengths of follow-up periods. Apart from one trial, all of the 29 trials included a clearly defined primary outcome measure but only 9 trials included a statistical power estimation. Only 11 of the trials found a difference in the primary outcome measure between the allocation groups and only two findings were replicated. Furthermore, the RCTs reported on various outcome measures, which in most of the trials were either unblinded patient-reported information increasing the risk of self-report bias or data on feasibility/acceptability. None of the RCTs specifically stated whether they monitored closely for potential harms (apart from one trial which monitored the frequency, intensity, and burden of side effects ratings [61]), and only four of the trials employed statistical analyses adjusted for potential confounders [7, 62–64]. All of the trials were evaluated to the at high risk of bias or reasons to be concerned. In any non-pharmacological trial, it is always difficult to define a proper control group. The included trials used different control conditions—some used standard

treatment [7, 44, 46, 48, 56, 62–64, 68, 69], others used other types of interventions for comparison [42, 43, 45, 49–51, 53–55, 57–61, 65–67, 70], and some of the trials used waitlist as the comparator [43, 46, 52–54, 57, 58]. However, the potential harm of using waitlist conditions as the control condition has been addressed in numerous studies [72].

It is concluded from the present systematic review that there is a lack of RCTs with large sample sizes using rigorous study methodology and long follow-up periods. Furthermore, most of the trial findings have not been replicated, and there was generally sparingly reporting on important aspects concerning technological features and how these may affect outcomes.

Technological development moves faster than science, and due to rapid development and competitive commercialization, many mHealth solutions are not evidence-based, which undermines the quality and safety of these solutions in treatment settings [24, 26, 27, 73–75]. Most applications are frequently not updated, may be suddenly removed from app stores or malfunction [76]. Such grave limitations are important to consider if patients are supposed to rely on commercial applications for everyday use.

Recently, the limitations and complications arising from rapid development and the lack of scientific studies and publications within the area of mHealth have been addressed in numerous papers [23–28, 77–79]. Due to the rapid development of mHealth solutions and scant evidence supporting the effectiveness of mHealth solutions, it was even suggested that it might be time for methodological changes, such as the abandonment of RCTs as the primary method of scientific evaluation and an increased use of iterative participatory research and single-case design [80, 81]. However, as argued by others, given the unique potential of mHealth solutions, these solutions should not be examined with less rigorous scientific approaches than would be used to investigate new pharmacological treatments [23, 24, 75, 82]. Several authors have suggested guidelines for defining, detecting, and reporting harms related to these types of interventions to facilitate this process and increase quality and evidence of future mHealth studies and interventions [24, 83–87]. mHealth solutions often consist of multiple domains, and standardized reporting guidelines for mHealth interventions could provide tools to clearly define the content and context of the interventions and interpret how the interventions were implemented in the trials. In addition, the use of standardized guidelines could facilitate the replication of study findings within the area of mHealth.

Limitations

Limitations on a Study Level

The trials that were included for evaluation in this chapter were overall assessed to be at high risk of bias or reasons to be concerned. Several concerns regarding the individual studies and outcomes limit the overall findings.

Limitations on Chapter Level

This chapter is a systematic review but did not employ meta-analyses as this was not feasible due to the huge variation between studies in study aims, designs, and methods. Thus, the results presented are merely present by vote-counting. Also, there may be trials, which have been conducted and published, which we did not identify during the process. In addition, we only included patients with a clinically validated diagnosis.

Recommendations for Future Trials

Future trials should investigate potential positive, neutral, and negative effects of smartphone-based interventions in carefully designed large RCTs. Furthermore, trials should to a higher degree include observer-based blinded ratings in addition to patient-reported outcome measures and carefully consider multiple levels of the statistical analyses, including predefined clinically relevant primary and secondary outcome measures, a predefined statistical power analysis, and inclusion of potential confounding factors.

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Chapter 6
Digital Therapies for Insomnia

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Abbreviations

CBT	Cognitive behavioral therapy
CBT-I	Cognitive behavioral therapy for insomnia
dCBT	Digital cognitive behavioral therapy
dCBT-I	Digital cognitive behavioral therapy for insomnia
dMBT-I	Digital mindfulness-based therapy for insomnia
MBCT-I	Mindfulness-based cognitive therapy for insomnia
MBI	Mindfulness-based interventions
MBSR	Mindfulness-based stress reduction
MBTI	Mindfulness-based therapy for insomnia
RCT	Randomized controlled trials

Insomnia Disorder and Current Treatments

Insomnia is a common and costly condition. Approximately 10% of the population experience chronic difficulties with insomnia (insomnia disorder) which are characterized by difficulties falling asleep, staying asleep, or waking too early that lead to

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significant impairment in daytime functioning and/or cause distress [1]. Insomnia takes a huge personal toll on an individual's quality of life, but also costs the U.S. economy $USD 30–70 billion annually in lost productivity, workplace absenteeism, and healthcare related costs [2]. Insomnia is frequently comorbid with other mental health conditions, such as anxiety or depression, and left untreated, insomnia can worsen the severity and duration of a mental health condition episode (e.g., major depressive episode) [1, 3–7]. Despite the high cost of insomnia and the reciprocal relationship with mental health difficulties, insomnia is often left untreated with significant implications for public mental health (Table 6.1) [8].

The most commonly accepted framework with which to understand the development and maintenance of insomnia is Spielman's 3-P model of insomnia, later elaborated by Morin, which emphasizes predisposing, precipitating, and perpetuating factors [9]. Factors such as a family history of insomnia [10], female sex [11], and anxiety and depressive symptomology [12] can predispose an individual to develop insomnia. Family, health, work, and school-related stressors can then precipitate the onset of insomnia [13]. In response to poor sleep, individuals often engage in maladaptive cognitions and behaviors, excessively worry about sleep, experience heightened physiological arousal, and attend to sleep-related threats, all of which contribute to increased sleep-related hyperarousal. A vicious cycle is then created which acts to maintain insomnia even when the initial stressor has resolved. Behavioral and psychological interventions for insomnia therefore target the hyperarousal, dysfunctional cognitions, and maladaptive behaviors that maintain insomnia [14].

Cognitive behavioral therapy for insomnia (CBT-I) is recommended as first line treatment for insomnia disorder worldwide [15–18]. CBT-I is a multicomponent treatment, which includes sleep restriction therapy, stimulus control, cognitive therapy, sleep hygiene, and relaxation training (see Cunnington and Junge [19] for review). Briefly, sleep restriction therapy involves curtailing the time spent in bed to consolidate sleep and then lengthening this time spent in bed as sleep efficiency improves. Stimulus control is aimed at creating positive associations between the bed and the bedroom with sleep and re-establishing a consistent sleep–wake schedule; consequently, a person should avoid wakeful activities in bed (e.g., reading,

Table 6.1 Overview of the components and goals of CBT-I

CBT-I components	
Technique	Aims
Stimulus control	Strengthen bed and bedroom as sleep cues
Sleep restriction	Restrict time in bed to increase sleep drive and consolidate sleep
Relaxation, buffer zone, worry time	Arousal reduction
Sleep hygiene	Address substance use (e.g., caffeine intake), exercise, eating, environment
Cognitive restructuring	Address thoughts and beliefs that interfere with sleep and adherence to CBT-I
Circadian rhythm entrainment	Shift or strengthen circadian sleep/wake rhythms

eating, watching television (sexual activity excepted)). Cognitive therapy is used to change unhelpful thoughts about sleep. For example, it may be used to assist the individual in reducing catastrophic beliefs about the consequences of insufficient sleep or to manage other worries which may interfere with sleep. Relaxation training involves methods aimed at reducing somatic tension (e.g., progressive muscle relaxation, breathing techniques). Sleep hygiene education provides information about health practices and environmental factors that may either be detrimental or beneficial for sleep. CBT-I has level 1 evidence as an effective treatment for insomnia, leading to significant improvements in sleep quality [20, 21]. Treating insomnia in people experiencing comorbid insomnia and mental health conditions has also been shown to be effective for improving sleep, but also improving mental health symptoms like depression severity [21, 22].

Despite strong treatment efficacy, access to CBT-I is limited due to a lack of trained CBT-I healthcare providers, impeding the translation of this effective treatment into clinical practice [23, 24]. Digital CBT-I (dCBT-I) treatments provide an innovative way to improve access to insomnia treatment. By digitizing treatment, CBT-I has become accessible to millions of people around the world who may never had the opportunity for face-to-face insomnia care [25–28]. Initial data suggests that dCBT-I may be a more cost-effective approach compared to therapist-delivered CBT-I [29]. Comparison data between guided dCBT-I and CBT-I has shown similar treatment effects, but the total healthcare and societal costs tend to be lower for dCBT-I [30, 31]. Today, there are a number of dCBT-I programs on the market that have been validated as effective treatments for insomnia [27, 28, 32–38]. It is important to note that these tools can vary in the way they are used, ranging from dCBT-I as support (therapist delivers the therapy with some specific digital elements used to support therapy, such as a sleep diary app); therapist-guided dCBT-I (combination of an automated program with clinical support); and fully automated dCBT-I [39]. Table 6.2 presents some of the validated guided and fully automated programs currently on the market. These programs all provide the core CBT-I components, yet differ in platform accessibility (e.g., available via mobile phone application or internet browser), country access (e.g., worldwide or country specific), program duration, automation, interactivity, data export functions, and probably most importantly, cost.

An alternative treatment for insomnia, receiving increasing clinical interest in recent years, incorporates mindfulness. Mindfulness refers to a state of conscious, intentional, and nonjudgmental awareness of present moment experiences [40]. Mindfulness is often taught and cultivated through meditation, which is the act of purposely paying attention to one's internal experiences or surrounding environment as they occur in the present moment in a nonjudgmental manner [41]. The goal of mindfulness within a psychotherapy framework is to improve one's awareness of, and response to, mental processes that can contribute to the development and maintenance of emotional and behavioral problems [42]. From a theoretical perceptive, mindfulness-based interventions (MBI) would therefore improve insomnia by helping individuals cultivate a more accepting and nonjudgmental relationship with these mental and physiological processes that impede sleep. Research examining

Table 6.2 Comparison of validated, publicly available digital CBT-I programs (English language options only)

CBT-I program	Sleepio	This way up—managing insomnia	Somryst (based on the research program SHUTi)	CBT-I coach	Dr Lullaby	RestEd	Go! To sleep
Website	bighealth.com/sleepio	thiswayup.org.au/courses/managing-insomnia-course	somryst.com	ptsd.va.gov/appvid/mobile/cbticoach_app_public.asp	drlullaby.com/	myrested.com	clevelandclinicwellness.com/Pages/GoToSleep.htm
Country access	UK, and USA based. Other countries worldwide may access Sleepio through research trials (e.g., Australia)	Australia only can access self-help option	USA	Worldwide	Worldwide, US based	Canada	Worldwide, US based
		Worldwide access available if supervised by a clinician					
Access/distribution Platform	Internet browser (full functionality)	Internet browser	Tablet	iPhone App	iPhone App	All browsers	Internet browser
	Tablet	Mobile friendly so can be viewed on tablet or smartphone	iPhone App	Google Play App	Google Play App (coming soon)		
	iPhone App		Google Play App				
	Google Play App						
Population	Adults	Adults	Adults 22+ years	Designed for use by people who are participating in CBT-I treatment guided by a healthcare professional	Infants	Adults	Adults
					Toddlers		
					School-aged kids		
					Teenagers		
					Adults		

Cost distribution	No out-of-pocket costs for patients—payers are health plans, employers, or healthcare systems	Free	Cost for most users	Free	Cost for users	Cost for users	Cost for users
	Free research program	90-day access	$$$	Unlimited access	$$ for simple membership with dCBT-I	$$ for 6 months	$ one off payment
	NHS staff and patients in the UK are covered under NHS contract		Some financial assistance is available to cover costs		$$$ for premium membership with dCBT-I + telehealth with PhD trained psychologists	Some help available to cover cost	
	In the USA, covered benefit by some health insurers		Some health insurers may help to cover the costs in the US		Telehealth may be reimbursed by insurance in the US or out-of-pocket options are available	Some health insurers may help to cover the costs in Canada	
			Other discounted options or payment plans may be available				
Program duration	6 weeks minimum	4 lessons ideally completed every 1–2 weeks	6 lessons over 9 weeks	Not structured lessons	4–8 lessons completed weekly	6 lessons over 6 weeks	6 lessons over 6 weeks
Level of support	Fully automated dCBT-I	Fully automated dCBT-I	Fully automated dCBT-I	dCBT-I as support	Offer fully automated dCBT-I alongside telehealth—dCBT-I is completed by older children or parents of younger children	Fully automated dCBT-I	Fully automated dCBT-I
	Therapists can support and monitor patient progress with dCBT-I	Therapists can prescribe, support, and monitor patient progress with dCBT-I		Designed to be used in conjunction with a healthcare provider			
Validation studies	Yes [27, 43–54]	Yes [35]	Yes [34, 55]	Yes [36, 56]	Yes [37]	Yes [32, 57–59]	Yes [38, 60–62]
Export data available (e.g., sleep diaries)?	Yes	No—healthcare provider can view sleep diary entries via patient dashboard at appointments	Yes	Yes	No—healthcare provider can view patient dashboard at appointments	No	Yes—healthcare providers can sign up for a provider code which allows program users share program participation/outcomes

(continued)

Table 6.2 (continued)

CBT-I program	Sleepio	This way up—managing insomnia	Somryst (based on the research program SHUTi)	CBT-I coach	Dr Lullaby	RestEd	Go! To sleep
Unique features	Can link with sleep tracking devices such as Fitbit	Affordable self-help option for individuals in Australia	Program has FDA approval—therefore requires a prescription from healthcare professional (which can be facilitated by Pear Therapeutics)	Intended to be used alongside face-to-face care with a healthcare professional. However, it can be used by an individual with insomnia on its own (or individuals can download alternative VA App, Insomnia Coach)	Options for video coaching with qualified psychologist (paid)	CBTi delivered via a series of modules, videos, written content, and exercises	Affordable option
	Access to Sleepio Community online	Clinicians can prescribe a course to patients to support them through the program	Detailed scientific explanations of CBT-I principles and strategies	Automatic calculation of the sleep prescription (SRT) with therapist adjustment options	Graphics tailored for children	Graphs provided to monitor sleep quality and efficiency	Daily sleep improvement recommendations
	Healthcare professionals can access for free via Sleepio Clinic	Other evidence-based CBT programs are available through website for a low cost (or no cost when prescribed by a clinician)	Interactive and tailored to the user based on online sleep diary data and other user entered information		Incorporates family into treatment		Daily e-mails and articles from a program coach
							Personal progress charts
	Completion certificate						Six specially crafted relaxation practices
			Over 30 RCTs have now been conducted using SHUTi, including translated versions in Dutch, Norwegian, French, and soon a Spanish version of Somryst				Focuses on promotion of sleep health and general stress management focus in addition to CBT-I

Note. Annual cost for users: Free = no cost; $ = price range $USD1–100; $$ = price range $USD101–399; $$$USD400+. Only English language publicly available dCBT-I studies with at least one peer-reviewed study published are reported here. This list may not be exhaustive and programs in languages other than English are not included here—however there are validated CBT-I programs available in Dutch (i-sleep—i-sleep.nl/over-ons/; Minddistrict—minddistrict.com/catalogue/sleep-well)

the effectiveness of MBIs for insomnia has increased over recent years. Promising results have been found for the use of mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy for insomnia (MBCT-I), and integrated mindfulness and CBT interventions for insomnia (MBTI) in treating insomnia symptoms. Specific characteristics of insomnia that appear to benefit from mindfulness-based interventions include subjective sleep quality, pre-sleep arousal, insomnia severity, and dysfunctional cognitions.

Self-help mindfulness tools for sleep are also becoming increasingly available to the general public with the advent of smartphone applications dedicated to mindfulness practice. A cross-sectional survey in the USA which examined preferences for the modality by which mindfulness meditation is delivered showed that internet was the first choice format for 42% of respondents, suggesting that, for many individuals, online MBIs may be an acceptable alternative to face-to-face formats [63]. Table 6.3 presents some of the validated MBIs for insomnia on the market. A review of mindfulness-based mobile applications indicated that many applications were free or required a relatively small fee, which may be of particular benefit to those who are unable to access or afford traditional face-to-face interventions. As with dCBT-I programs, MBIs for insomnia vary with regard to the degree of clinician

Table 6.3 Digital mindfulness programs designed to improve sleep

Mindfulness program	A Mindful Way	Headspace	Calm
Website	amindfulway.com.au	headspace.com	calm.com
Access/ distribution program	Internet browser	Internet browser	Internet browser
		Tablet	Tablet
		iPhone App	iPhone App
		Apple Watch	Google Play App
		Google Play App	
Cost distribution	$$ for 3 months access to a 6-week course	Cost $ to $$ depending on billing cycle (monthly billing is more expensive over 12 months than an annual subscription)	$ to $$ depending on billing cycle (monthly billing is more expensive over 12 months than an annual subscription)
		Monthly subscription comes with a 7-day free trial period and annual subscription comes with 14-day free trial	The Calm app is free to download with limited free content available. 7-day trial period available. Users need to pay the annual subscription to get full use of the app. Monthly payment options are available but fiddly to activate

(continued)

Table 6.3 (continued)

Mindfulness program	A Mindful Way	Headspace	Calm
Program features	Six weekly lessons of guided online CBT for insomnia and mindfulness meditation instruction	Meditation/audio based, with some educational articles available	Meditation/audio based, with some educational articles available
Time commitment recommendations	Approximately 2 h/week to complete lessons and meditation practices	10 min/day (1 h 10 min/week)	10+ min day (1 h 10 min / week)
Validation studies	Yes [64]	Yes [65, 66]	Yes [67, 68]
Sleep specific meditations	Mindfulness meditations are recommended to be performed during the day to develop general skills, not to meditate oneself to sleep. Mindfulness principles are applied to sleep difficulties	Yes—Sleep by Headspace pack with meditations that focus on applying principles of mindfulness to sleep and also provides Sleepcasts (bedtime stories)	Yes—Sleep stories min/ week meditations
Unique features	Learn core CBT for insomnia content coupled with mindfulness meditation	Can set reminders to practice meditation	Great graphics
	Structured and easy-to-navigate course which builds on skills learned in previous weeks	Great graphics	Winner of several App awards
	A Short Guide to Better Sleep can be downloaded for free	Informative sleep articles with content developed by sleep professionals	Free meditation resources available with discount codes to reduce the cost of the app

Note: This list may not be exhaustive and programs in languages other than English are not included here. Only includes programs that have been evaluated. Annual Cost $ = price range $USD1–100; $$ = price range $USD101–399; $$$USD400+

support required and level of integration with other cognitive and behavioral components. For example, *A Mindful Way* is a formal MBTI program, offering a combination of mindfulness-based practices with CBT-I components. In contrast, Headspace offers guided meditations focused on improving sleep (e.g., a 30 day "Sleep Pack" to explore how people think about sleep and change their relationship with insomnia) but no formal CBT-I lessons (e.g., sleep restriction therapy) are included.

Current Evidence for the Efficacy of dCBT-I and dMBT-I

Support for the use of dCBT-I is well-established, with a large and growing literature base. A recent meta-analysis of 11 randomized controlled trials (RCTs) of dCBT-I found a large post-treatment effect size for insomnia severity (Hedges' $g = 1.09$), a medium effect size for sleep efficiency (the time spent in bed asleep; Hedges' $g = 0.59$), and small effect sizes for reductions in time taken to fall asleep and the number and duration of nighttime awakenings as well as a small effect size improvement in sleep quality (Hedges' $g = 0.21–0.49$) [69]. Averaged across studies, at the end of treatment, participants who received dCBT-I slept for 38 min more on average each night, took 21 min less to fall asleep, and were awake for 28 min less during the night. The most recent meta-analysis, including 33 RCTs of dCBT (11 of which included follow-up assessments) showed that improvements in insomnia symptoms are maintained at follow-up of up to 1 year [70]. There is promising evidence that dCBT-I may also enhance health resilience years after completing therapy. A study by Cheng and colleagues found that people who had completed a dCBT-I program in 2016–2017 reported lower levels of insomnia symptoms, stress and depressive symptoms, and better general health during the COVID-19 pandemic, compared to those who received sleep education [71]. This suggests that the skills learned through dCBT-I may have long-lasting protective effects on sleep and well-being.

Changes in insomnia symptoms, as well as total sleep time, time taken to sleep, and duration of nighttime awakenings, resulting from dCBT-I appear to be comparable to the improvements seen in face-to-face CBT-I [69]. Soh et al.'s [70] analysis concluded that dCBT-I is "non-inferior" to face-to-face CBT-I. However, only three trials have directly compared dCBT-I to face-to-face CBT-I. A trial of group CBT-I and a trial of individual in-person CBT-I found the treatments, compared with dCBT-I, to be equally efficacious [72, 73]. A separate study, however, found that face-to-face CBT for insomnia was superior to online CBT-I [74]. A fourth trial comparing telehealth (video conferencing) delivered CBT-I to online CBT-I found both treatments to be equally effective [57]. As such, more direct comparisons between these formats are needed.

Digital platforms of MBI have been found effective for improving mental health outcomes [75]. However, very few mindfulness-based applications have been empirically evaluated within the area of insomnia. Initial evidence for improvements in self-reported sleep quality in older adults with sleep disturbance was demonstrated using a partially online MBI program compared to a sleep hygiene education control (Cohen's $d = 0.89$) [76]. Low and colleagues [65] examined the effectiveness of the Headspace *Sleep Pack* compared to a progressive muscle relaxation program in adults with both subclinical and clinical symptoms of insomnia. Improvements in self-reported total wake time, insomnia severity, cognitive

symptoms of pre-sleep arousal, and daytime positive and negative affect from baseline to follow-up were observed across both intervention groups. These findings suggest that digital MBI and progressive muscle relaxation interventions both have the potential to improve insomnia severity and mood.

More recently, a more formal digital MBTI program was evaluated through a pilot study of community participants experiencing insomnia symptoms [64]. The program involved 6-weekly modules incorporating CBT-I and mindfulness-based practices. Relative to a waitlist control group, the digital MBTI program showed significant reductions in insomnia severity (Cohen's d = 1.49) and both cognitive (Cohen's d = 0.35) and somatic (Cohen's d = 0.24) pre-sleep arousal after the 6-week intervention. Importantly, 75% in the intervention group achieved remission, compared to only 8.3% in the control group. Based on the currently available evidence, digital MBTI has the potential to be a viable treatment option for those with subclinical and clinical symptoms of insomnia; however, further RCTs are needed to confirm these findings. Future research would benefit from a continued investigation into the use of digital MBIs as an effective intervention for insomnia and to determine their effectiveness relative to dCBT-I.

Using dCBT-I in Real World Settings: Evidence from Effectiveness Trials

While RCTs are the gold standard for the assessment of novel interventions, effectiveness studies are also extremely important as they provide information about how these treatments work when disseminated into "real world" settings. To date, there have only been a handful of effectiveness trials of dCBT-I. In a guided trial of dCBT-I in a community setting, Luik and colleagues found good adherence for the *Sleepio* program (73% of participants completed the program) and significant reductions in insomnia symptoms at post-treatment [77]. In that trial, users received six support calls throughout the program. As entirely automated, self-help interventions are far more scalable than those requiring guidance from a clinician or technician, Grierson and colleagues examined the effectiveness of an unguided, four-module dCBT-I program in community users. In that trial of the *This Way Up Managing Insomnia* program, large effect size reductions in insomnia symptoms were observed; however, adherence was moderate (~37% treatment completion rate), which is consistent with adherence in other evaluations of self-help, unguided, online interventions outside of RCT settings for other common mental health conditions such as anxiety and depression (e.g., [77, 78]). These findings have been replicated since, including in a sample who completed the course during the COVID-19 pandemic [79]. Importantly, although these studies only included users who lived in Australia, they had no other exclusion criteria, which adds further weight to the generalizability of these findings to diverse populations, including those with comorbidities, as is frequent with insomnia [80].

As with face-to-face CBT-I, there is good evidence from RCTs that dCBT-I is efficacious for people with mental and physical health comorbidities. The positive effects of dCBT-I have been observed in adolescents [31], breast cancer survivors [81], asthma, and hypertension. Beyond these conditions, dCBT-I appears to not only reduce symptoms of insomnia, but also to reduce symptoms of comorbid anxiety and depression [46, 55, 82, 83]. Moreover, there is preliminary evidence that when insomnia is comorbid with depression, the treatment of choice may be in fact dCBT-I. Specifically, Blom and colleagues [84] randomly allocated individuals with comorbid insomnia and depression to receive online CBT for insomnia or online CBT for depression. They found that the dCBT-I group had better outcomes in terms of insomnia symptoms than the dCBT for depression group but that both groups experienced equivalent improvements in depression symptoms. Put another way, dCBT for insomnia was as effective at reducing depression symptoms as dCBT specifically designed to treat depression. We (Mason and colleagues) have recently completed a similar study examining individuals with comorbid insomnia and anxiety disorders and found comparable results [85]. That is, individuals who received dCBT for insomnia had better outcomes in terms of insomnia symptoms than those in the dCBT for anxiety group, but both groups experienced equivalent improvements in anxiety symptoms. These findings have exciting public health implications given that stigma is a key barrier to accessing treatment for anxiety and depression [86] and that individuals appear to be much more willing to access treatment for sleep difficulties than for anxiety or depression [87]. The benefits of mindfulness may also extend beyond sleep, by influencing other domains of healthy functioning, such as mood, physiological arousal, and somatic symptoms [64]. Therefore, effective, scalable treatment for insomnia could be a powerful way to reduce the burden of disease associated with anxiety and depressive disorders and to improve general well-being.

What Factors Influence the Effectiveness of dCBT-I and MBTI?

There are a number of potential factors that may predict improvement or influence the effectiveness of digital CBT-I and MBTI, including sex, age, and insomnia severity. In an effectiveness trial, Grierson and colleagues found that females and older adults were more likely to complete the online CBT-I course than males and younger users. However, Vincent, Walsh, and Lewycky [58] found that age did not impact treatment outcomes at post-treatment or follow-up. Others have also found that comorbid sleep disorders as well as less severe levels of insomnia, higher sleep efficiency, and longer total sleep time predict worse outcomes or lower completion rates (as reviewed by 28). Conversely, higher education has been shown to be a positive predictor of improvement in sleep [58]. There are likely to be other factors that also influence treatment uptake and adherence, such as motivation and personal

preference. For example, patients who experience significant fatigue may not engage as well with some of the components of CBT-I, such as sleep restriction. The acceptance-based approach that mindfulness offers may appeal more to some patients compared to cognitive restructuring. On the other hand, some patients may prefer cognitively focused therapy over mindfulness-based therapy. For example, Garland 2014 found much higher dropout rates in the first 3 weeks of therapist-delivered MBSR (52%) vs. CBT-I (15%), when participants were not aware of which group they would be randomized to [88]. Further research on factors that influence adherence and outcomes in digital therapies for insomnia would certainly be valuable.

Of course, difficulties with adherence are not unique to digital interventions for insomnia and other mental health conditions. Indeed, it has been shown that only 50% of individuals are adherent to antidepressant medication (i.e., half of patients discontinue earlier than recommended by their doctor) [89]. For dCBT-I, treatment adherence (defined as completion of all treatment sessions) is estimated to be around 64% [90]. Nevertheless, it is pertinent to investigate strategies to improve adherence as it seems that there is a dose–response relationship between the number of modules completed and symptom outcomes for patients undergoing online CBT for anxiety and depression [91], though it should be noted that data on this for dCBT-I is still lacking [29]. It is established that the inclusion of support/guidance improves adherence in digital CBT interventions for anxiety and depression [91], and this appears to be true of digital interventions for insomnia also. Indeed, a higher degree of personal support in dCBT-I is associated with larger improvements in insomnia symptoms [69]. Of course, however, the requirement of support increases the cost of an intervention and reduces scalability. Zachariae et al. [69] suggested that it would be beneficial to determine which patients are likely to require additional support and who are likely to benefit from fully automated interventions to improve the efficiency and cost of digital interventions. In fact, there is already some research that suggests that individuals with comorbid depression are likely to benefit from support [92].

In addition, further research on the minimum amount of support necessary to increase engagement in dCBT-I while maintaining a scalable and cost-effective model of service delivery is needed [35]. For example, Luik et al.'s [82] guided effectiveness trial included a support call of 20–30 min for each of the six modules of the dCBT-I program and it may be the case that shorter and/or less frequent calls are sufficient to maintain high adherence rates. Indeed, previous research on online interventions for anxiety and depression demonstrated that patients contacted at least once were more likely to complete their online CBT course than patients who were not contacted at all [91]. Patients who were contacted in that study were only contacted twice on average by their clinician suggesting that even modest support is sufficient to increase adherence rates; however, the ideal amount of support required to optimize outcomes while reducing clinician time remains unknown. Moreover, there is also evidence from the dCBT for anxiety and depression literature that support need not be provided by a specialist clinician. In two studies, researchers found that whether a clinician or technician supervised patients through the online course,

treatment outcome was the same [93, 94]. It seems likely that this will apply to dCBT-I also. Using technicians, who just check in with the patient, providing encouragement and technical support, rather than specialized clinicians (of whom there are fewer) may be a way of increasing scalability while still providing support to the patients who require it.

Some research indicates that payment for the course increases completion rates [91]. Drawing from the field of behavior change, it may also be that incentives can improve adherence and outcomes. For example, providing a refund of costs upon program completion for a weight loss program has been shown to increase adherence and outcomes [95]. To the best of our knowledge, this incentive approach has not yet been trialed as a way of improving adherence to digital CBT. This approach may appeal to health insurers or government funded programs given that dCBT-I is likely to reduce future health care costs and indeed has been shown to be cost-effective [96]. There is growing interest in persuasive e-health technologies which are design elements used to influence behavior and improve engagement. They include *primary task support*, such as tailoring or personalizing the intervention toward a particular user or individuals; *dialogue support*, such as using reminders and rewards; and *social support*, such as using discussion boards and peer support [97]. Inclusion of these elements can influence and improve adherence to digital health tools. Further development and integration of persuasive technology elements and other digital elements such as gamification in the context of dCBT-I and dMBT-I will be an important next step.

To date, investigations of mediators and moderators of dCBT-I and dMBT-I are sparse. However, as reviewed by Seyffert et al. [98], studies of dCBT-I have found a significant decrease in dysfunctional beliefs about sleep (e.g., "I need 8 h of sleep to feel refreshed and function well during the day.") relative to waitlist controls. One study found that reductions in sleep-related behaviors (such as clock watching) were a key mediator of the improvements resulting from dCBT-I. This reduction in sleep-related behaviors was even more important than changes in dysfunctional beliefs [99]. Understanding mechanisms of symptom change in dCBT-I will allow for the development of more effective treatments and potentially lead to more personalized approaches in which key maintaining factors for an individual are able to be directly targeted.

Integration of Digital Tools for Insomnia with Standard Care

Digital interventions for insomnia can be used as standalone interventions as well as in stepped-care and blended care models. Digital interventions have particular appeal in stepped-care models, whereby individuals first undertake less resource intensive interventions (e.g., dCBT-I) and only non-responders progress to receive more resource intensive interventions (e.g., face-to-face therapy). This approach is intended to result in more efficient allocation of scarce therapeutic resources. Given lengthy waiting lists to access face-to-face therapy [100], dCBT-I may be also

valuable to use with patients on a waitlist for face-to-face treatment. Whether used in this way or in a conventional stepped-care approach, upon completion of the course, the patient can be reassessed to determine whether remission has occurred or whether further face-to-face treatment may be beneficial [101]. Further treatment can be helpful to assist patients in tailoring skills to their specific circumstances and may be particularly useful in assisting patients to implement more challenging skills, such as sleep restriction therapy. Additional treatment may also be needed to target other concerns not addressed in the course (e.g., symptoms of other psychiatric disorders).

As a standalone intervention, dCBT-I has been shown to be efficacious for individuals across different severity levels. dCBT-I may also be used as an adjunct to face-to-face treatments in a blended care model. In this approach, patients can obtain the core CBT content from the dCBT-I course and revisit this information repeatedly to assist with learning, while precious session time may be used to troubleshoot any difficulties in the implementation of skills or to address issues that have not been covered in the dCBT program [101]. In a case series study examining a stepped-care approach to treat insomnia in a public health setting using dCBT-I (return2sleep.com) as the first step, service efficiency increased by 69% [102]. In that study, patients were more likely to progress to more intensive steps for insomnia (single session consultation, group treatment, and then individual therapy) if they were older, unemployed, and had more severe symptoms of insomnia. In line with this, Meaklim et al. [103] found that older outpatients to repatriation clinic were hesitant to trial a dCBT-I while waiting for face-to-face treatment, due to limited internet access, language barriers, and a preference for face-to-face treatment [103]. In the only published RCT to examine a stepped-care approach to the treatment of insomnia, Savard et al. [104] found that a stepped-care approach, using web-based CBT-I as the first step was non-inferior to a standard face-to-face CBT-I approach in a group of patients with cancer experiencing insomnia. These studies provide useful preliminary evidence to support the use of dCBT-I in stepped-care models to improve service delivery within public health settings; however, adaptive or blended stepped-care models targeting the patients that would benefit the most from digital interventions are needed to facilitate program implementation.

Conclusions: What Are the Next Steps for Digital Therapeutics for Insomnia?

The number of digital therapies for insomnia is growing. The evidence to date is supportive of both the efficacy and effectiveness of this treatment modality for improving insomnia severity, as well as other daytime outcomes. In addition, these positive benefits have been observed across a number of populations and medical and psychiatric conditions. There are however a number of questions that still remain, that will need to be addressed in future research. We are still in the early

stages of understanding both the mediators of treatment effectiveness and the mechanisms of action for dCBT-I and dMBT-I. Future studies are needed to determine who responds best to treatment and why, so that we can better tailor these digital treatments to improve both outcomes and adherence. One of the most promising findings from the current literature is that effectiveness of dCBT-I goes beyond sleep, with a number of studies demonstrating parallel improvements in depression and anxiety outcomes. Digital treatments for sleep therefore not only improve accessibility for patients, but may also reduce the stigma associated with seeking treatment for mental health conditions.

The extension of CBT-I and MBTI to online platforms has widespread clinical implications by increasing the scalability and accessibility of these interventions, for which access is challenging due to lack of both knowledge and trained practitioners [23]. As with many medical treatments, adherence to digital therapies for insomnia remains a challenge. Having therapist guidance may help with adherence and treatment outcomes, but will impact on scalability and potentially cost-effectiveness. These digital therapies can potentially reduce costs to the individual and the health service, increasing accessibility, decreasing isolation, and increasing convenience and time efficiency [105], all of which are particularly critical during the time of the COVID-19 pandemic. Given the high prevalence and negative implications of insomnia [15], exploring more effective ways to treat the millions of people experiencing this public health problem is urgently needed.

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Chapter 7
The Efficacy of Smartphone-Based Interventions in Bipolar Disorder

Gerard Anmella, Diego Hidalgo-Mazzei, and Eduard Vieta

Abbreviations

app	Smartphone application
BD	Bipolar disorder
CBT	Cognitive-behavioral therapy
EMA	Ecological momentary assessments
ISBD	International Society for Bipolar Disorders
mHealth	Mobile health
PROMS	Patient-reported outcome measures
PTSD	Post-traumatic stress disorder
RCT	Randomized controlled trials
SIMPLe	Smartphone-based psychoeducational program for bipolar disorder
SM	Self-monitoring
SMS	Short message services
TAU	Treatment-as-usual
UEIs	User-engagement indicators

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Bipolar Disorders

Bipolar disorders (BD) are chronic and recurrent major affective diseases with onset during youth, a lifetime prevalence estimated at 2.4%, and a course of disease that entails fluctuations between mood phases—depressive, (hypo)manic, or mixed episodes [1, 2]. Higher recurrences of mood episodes in BD have been related to reduced response to psychological and pharmacological treatments, progressive neuroanatomic brain changes, and cognitive dysfunction, which, in turn, leads to a worse clinical course and functional disability [3, 4]. The progressive, recurrent, and sometimes severe nature of BD, along with high rates of morbidity and mortality [5], translates into a 8–12 years shortened life expectancy [6], reduced quality of life, and a huge burden of disease, making BD one of the main causes of disability among young and working-age people [7, 8].

The prognosis may be improved with maintenance pharmacological treatments, which have proven effective in preventing mood recurrences in BD [9], especially in early phases of the disease [10]. However, people with BD often lack insight about their symptoms and the need for treatment, especially in manic phases [11, 12]. In addition, common psychiatric clinical monitoring through routine medical visits mainly consists of periodic cross-sectional symptoms assessments that rely on self-reports, posing several limitations due to confirmation bias and misinterpretations [13]. Hence, more effective strategies for the clinical management of BD are imperative.

The Digital Revolution and the Growing Interest and Use of Mental Health Tools

The digital revolution has made possible to capture behavioral, cognitive, and mood information in an objective, continuous, passive, unobtrusive way by using ubiquitous devices, such as smartphones and wearables [14]. The connection capabilities of smartphones and their embedded sensors allow to unobtrusively collect active information from subjects on their natural environment (ecological momentary assessments (EMA)) using tests or questions. Moreover, smartphones allow the automatic and continuous collection of passive objective data from the device usage patterns and/or sensors, either measuring activity or location (indirect markers of socialization), keyboard interactions (indirect markers of neurocognition), or voice and speech (indirect markers of the thinking process). Altogether, this new type of objective information that could reveal objective individual fingerprints has been denominated “digital phenotyping” [15].

Digital phenotyping limits the possibility of subjectivity and psychological heuristics to which traditional methods are exposed [13] and avoids the possibility of recall bias in comparison to standardized scales and questionnaires which asses at a specific time point the presence of symptoms over the last previous weeks or

months. The data collected by smartphones is automatically transmitted to cloud servers over the Internet preventing loss of data integrity in the process and can be analyzed through different techniques. Even though smartphone technology promises to transform many aspects of health care, no area of medicine is likely to be changed more by this technology than psychiatry.

Smartphones are among the most rapidly adopted innovations in recent history, and its ownership continues to increase in developing and developed countries. Through providing the capacity to download and run externally created applications ("apps"), along with ubiquitous Internet connectivity, smartphones could provide global, cost-effective, and evidence-based mental health services on demand and in real time [16]. This huge therapeutic potential has triggered a wave of interest and investment in mental health apps from governments, technology companies, advocacy groups, and international research groups [17]. As a result of the increasing affordability, accessibility, and user-friendliness of smartphones, people with mental health problems are also increasingly adopting them for a wide variety of purposes, including the management of their mental health [18, 19].

People suffering from BD and other affective disorders own and use smartphones similar to the general population [20]. A survey among people with BD in the UK revealed that more than 50% had used an app intended to treat or monitor their condition. Moreover, they are also interested in using smartphones to receive support and treatment. For instance, in another survey, almost 80% of respondents with BD showed interest in using an app to monitor affective symptoms and receive advice on how to cope with their condition. These surveys reflect an increasing demand among people with BD for the appropriate digital health apps [21].

Digital Phenotyping in Bipolar Disorder

BD represents the ideal diagnostic framework for digital phenotyping, as its biphasic nature overtly translates into altered emotion, speech, and behavior. For instance, BD patients usually show overactivity, euphoria, racing thoughts, and increased self-esteem—during a manic episode—in contrast to low energy, depressed mood, inability to concentrate, and feelings of worthlessness—during depressive episodes [22]. These biphasic abnormalities in motor, social, and speech activity reflect the mood state very accurately and their digital quantification (i.e. digital phenotyping) using smartphones has been correlated to different mood states [23–25].

Smartphones offer unique capabilities for monitoring depressive and manic symptoms through automatically collected data, such as speech and activity, but also real-time self-reported data [26, 27]. Smartphones even have the potential to provide early detection of prodromal symptoms between outpatient visits in BD [28] and, therefore, potential for facilitating timely and contextual care delivery for patients with BD. This could improve the diagnosis and provide options for early cost-effective interventions in people with BD [16].

Smartphone-Related Research in Bipolar Disorder: State of the Art

Over the last decade, several studies have been conducted exploring the feasibility, validity, efficacy, and cost-effectiveness of mobile health (mHealth) with promising results. These studies involved a diverse array of mobile technologies, such as SMS (short message services), wearables, and smartphone-based interventions (including smartphone apps) intended at monitoring symptoms and delivering interventions for BD [29, 30].

Smartphone-based interventions have been the most investigated aspect of mHealth in affective disorders, including BD. These interventions, although diverse in design, aimed to cost-efficiently extend and facilitate monitoring and therapeutic services [31–33].

In addition, since smartphones are becoming nowadays a generalized method for communication, socialization, shopping, and entertainment among other activities, they hold the potential to collect continuous digital behavioral footprints, including the smartphone daily usage and voice patterns. Up to date, most of the studies assessing the validity of digital behavioral patterns through mobile technologies sought at comparing standardized self-reported or clinician-administered scales to the data generated by smartphones. In general lines, the results extrapolating social and circadian rhythms [24, 34–37], as well as specific illness activity from smartphone generated data seem encouraging, although still not conclusive enough to replace standardized scales [38]. Even if this may seem a disappointing fact, there is a growing belief that differences between smartphone-collected data and scores of already imperfect subjective scales, might actually represent a whole new type of information and an opportunity to complement the limitations of traditional scales to comprehensively reflect BD and their inter-individual diversity [14, 39].

Despite the aforementioned growing evidence and novel insights that smartphones have been contributing in the understanding of BD, few major clinical trials have integrated them as complementary methods to measure outcomes, with only a few exceptions to date [40–45]. The pharmaceutical companies have shown little interest in incorporating smartphone-based interventions in their clinical trials to monitor symptoms despite the growing evidence about data integrity and their cost-effectiveness in collecting continuous and granular data about illness course and symptoms.

The Dissociation Between Private Corporations and the Academic Field

Notwithstanding the huge number of smartphone interventions for BD already available through Apple or Google marketplaces, very few meet evidence-based medicine quality standards (they do not have any scientific evidence about their validity or efficacy in the field of BD), so that finding a useful app supported by robust evidence is clearly a challenge [46, 47]. Furthermore, the data privacy of users of many of these apps might be compromised, according to recent reports [48].

Even though national committees have been working on regulations and frameworks to assess the validity of mental health apps have been proposed, the functioning of app stores and their commercialization processes make it difficult to manage [49, 50]. People with BD and other mental health disorders are generally offered with smartphone-based interventions without any warning, guarantees, or instructions [19].

The Efficacy of Smartphone-Based Interventions in Mental Health Disorders

Smartphones can provide not only the afferent limb of assessment (through automatically collected data or self-report) but also the efferent limb of intervention, which can be precisely titrated through continuous feedback from digital phenotyping [51]. In other words, smartphones allow cost-effective psychological interventions which can be personalized according to each individual course and be available to individuals remotely and with no time constraints. In fact, people with BD are generally predisposed toward smartphone-based interventions, according to recent studies [52].

So far, smartphone-based interventions have shown positive mild/moderate efficacy for anxiety [53], depression [33], and symptoms of post-traumatic stress disorder (PTSD) [54]. Yet, the efficacy of smartphone-based interventions for BD needs to be established.

Smartphone-Based Interventions in Bipolar Disorder

A recent meta-analysis compared the effect of smartphone-based interventions and monitoring with control methods in BD [55]. This study concluded that smartphone-based interventions in BD are effective in reducing manic and depressive symptoms. However, the analyses included studies that assessed the efficacy of phone calls of therapists to facilitate psychotherapy [56, 57], web-based platforms [58], as well as the effectiveness of phone/mail-delivered self-rating feedback [59]. Moreover, the meta-analyses were performed including not only participants with BD, but with other diagnoses [44, 45]. Hence, part of the main conclusions of this study may be biased.

Considering the limitations of the aforementioned study, the International Society for Bipolar Disorders (ISBD) Big Data Task Force has been working on a position paper aiming at examining the efficacy and user-engagement indicators (UEIs) of smartphone-based interventions in BD [60].

Up to January 21, 2021, six randomized controlled trials (RCT) [40–45] had been published providing data on smartphone-based interventions in people diagnosed with BD.

According to the RoB 2 tool, all RCTs showed low risk of bias. All RCTs were randomized single-blind trials. One RCT included 3 arms (one intervention and two control groups: one active and one inactive) [44], and five RCTs included 2 arms

(intervention vs control groups) [41, 43, 61]. Their duration ranged from 10 weeks [43] to 9 months [61].

The Efficacy of Smartphone-Based Interventions in Bipolar Disorder (RCTs)

The majority of RCTs assessing the efficacy of smartphone interventions in BD compared differences in depressive and manic symptoms assessed with clinician-administered scales between groups [40–45].

Four smartphone-based interventions from the included RCTs did not show efficacy in reducing depression outcomes [40–42, 45], and two did: one only including people with BD in which the comparator was paper-and-pencil monitoring [43] and another study measuring depressive outcomes with the brief psychiatric rating scale and only when comparing the intervention with treatment-as-usual (TAU), but not when comparing the intervention with the active control group [44].

None of the smartphone-based interventions from the included RCTs showed efficacy in reducing mania or improving function outcomes [40–45].

Quality of life was improved in one [42] out of four RCTs, and perceived stress was reduced in two [40, 42] out of three RCTs.

Regarding affective relapses, one RCT [42] showed a reduction in manic relapses, but an increased risk of depressive relapses, whereas another study did not show significant differences in affective relapses of any polarity [40].

Regarding psychiatric readmissions, one RCT [40] did not show reduction in rate or duration of readmissions.

In sum, most RCTs did not show efficacy in any outcome regarding affective symptoms (mania or depression), function, or quality of life when comparing with active controls, but only when compared with inactive controls (paper-and-pencil monitoring [43] or TAU [44]). In this regard, it should be noted that the RCTs were highly heterogeneous, including general design, characteristics of the interventions, compared groups (including diagnoses and baseline symptoms), as well as considerations regarding user-engagement with the app. All those concepts may have influenced the efficacy results and are discussed below.

Smartphone-App Characteristics and Type of Interventions

Smartphone-based interventions ranged from self-monitoring (SM) [40–43], to app-delivered personalized cognitive-behavioral therapy (CBT) plus SM [44], to SM plus app-delivered interventions, including CBT, skills training, psychoeducation, medication reminders, and/or coping strategies [45].

The apps of only two studies collected passive data [40, 42]. Five apps included psychoeducation: one app in a direct way [45] and four of them indirectly through a feedback loop [40–42].

Participants were contacted by text message, phone call or e-mail in three studies if there were signs of deterioration of depressive or manic symptoms [40–42].

When trying to identify specific aspects of smartphone interventions and subpopulations with BD associated with the efficacy of the intervention, the heterogeneity in the design of the studies and the lack of uniform registered variables and definitions precluded those analyses. The mechanism of change in smartphone interventions is poorly understood, such as whether SM by itself may affect change or if therapeutic elements that draw from evidence-based interventions such as CBT are impactful beyond SM.

The Potential Influence of Baseline Affective Symptoms

Most patients included in the RCTs were euthymic or with mild affective symptoms [62]. It is known that the magnitude of affective symptom reduction increases with the initial severity of symptoms, and may be minimal or nonexistent, on average, in patients with mild or moderate symptoms, both for depressive [63, 64] and manic symptoms [65]. Probably for this reason, the expected reduction in depressive and manic symptoms scales was nonexistent to minimal in RCTs including only euthymic or subsyndromal BD patients. This was the case in a post-hoc analysis of one of the included RCTs, in which participants with moderate-to-severe depression did have significant reductions in depression symptoms at posttreatment compared to participants with minimal or mild depression [66]. However, this was not consistent in other RCTs, in which participants with more severe baseline depressive (HDRS⩾7) or manic symptoms (YMRS⩾7) experienced higher levels of depressive/manic symptoms compared with the control groups [40–42].

Active or Inactive Control Groups

Active control groups varied widely, ranging from the use of a smartphone for communicative purposes [40–42], clinic-based group self-management interventions [45], smartphone self-monitoring plus face-to-face psychoeducation sessions [44], to paper-and-pencil monitoring [43].

Comparisons in the RCTs ranged from inactive controls (normal use of smartphones [40–42]) to controls with highly active interventions (face-to-face intensive psychoeducative sessions plus smartphone self-monitoring) [44].

The highest efficacy was found when the difference between the smartphone intervention and the control comparison was most marked (e.g. CBT + SM smartphone intervention versus TAU [44]) and lowest when differences between the smartphone intervention and the control comparison were less marked (e.g. smartphone-app versus intensive group intervention [45]). Moreover, the control groups in the included RCTs were highly heterogeneous, thus precluding a uniform comparison.

User-Engagement Indicators of Smartphone Interventions

UEIs of the smartphone-based interventions from the RCTs included information on the concepts of "usability, satisfaction, acceptability, and feasibility" of the apps, as suggested by a review of user engagement in mental health apps [67]. However, studies reported other UEIs such as "adherence, retention, dropouts, or fidelity." The definitions and outcomes of UEIs have been summarized in Table 7.1.

Other UEI evaluated were "patient-reported outcome measures (PROMS)," which have been proposed as valid indicators of effect [40], "fidelity," with positive evaluations in the active groups of one study [44], and "confidentiality," which was positively evaluated according to participant's statements in [42].

Table 7.1 User-engagement indicators

UEI	Definitions	Outcomes
Adherence	(a) "Compliance" and objectively measured as "number of days completing a survey or an entry into a mood chart" [43] (b) "Adherence to self-monitoring" [40–42] and measured as daily completed self-monitoring [41, 42] (c) "Mobile-device interactions mean adherence" and objectively measured as the "% of surveys responded during the monitoring period" [44]	Outcomes of "adherence" ranged from 93% [42] to 26% [45]
Usability	None of the RCTs defined usability	Some RCTs reported positive feedback on the use of their app, such as: (a) "A system easy to use, and user-friendly with a high usability" [42] (b) "A useful intervention to address moderate-to-severe depressive symptoms" [45] (c) "Acceptable to use" [41], or (d) "Usable and useful" [40]
Satisfaction	None of the RCTs defined satisfaction, but measured it as: (a) Self-reported satisfaction scales [43] (b) Self-report ratings [45] (c) The Verona satisfaction scale-affective disorder (VSS-A) [40]	Outcomes of satisfaction ranged from a median value of 9/10 [43] to a mean value of 25.7 out of 35 [45]

Table 7.1 (continued)

UEI	Definitions	Outcomes
Acceptability	None of the RCTs defined acceptability, but measured it as: (a) Self-reported questionnaire of specific acceptability of mobile devices [43] (b) A subjective evaluation from several statements, in a previous study [45, 68]	Most RCTs reported positive feedback on the acceptability of their apps, such as (a) "Acceptable to use" [41] (b) "The patients expressed that the self-monitoring system was supportive, useful, quick, and easy to use with a low level of intrusiveness" [42] (c) Positive ratings such as "I would use this device again in the future" [43] or (d) "The intervention was acceptable and usable" [45, 68]
Feasibility	(a) An unspecific term combining satisfaction and adherence [43] and (b) An amalgam of objective parameters of the app use [45]	Many studies reported positive feedback on the feasibility of use of their apps, such as (a) "Feasible and acceptable" [43] (b) "A feasible intervention" [45] and (c) "A single intervention augmented by mobile intervention was feasible" [44]

All RCTs concluded that their app reported positive evaluations for UEIs. Nevertheless, it should be highlighted that most UEI were usually conflated (i.e. concepts and definitions used with high heterogeneity among studies and sometimes interchangeably within studies). Furthermore, some outcomes to measure UEIs varied from self-reported scales (utterly subjective and usually non-validated) to objective parameters regarding the use of the app, but with arbitrary thresholds (defining positive/negative outcomes) never stated before the study, but rather "a posteriori." These inconsistencies in the UEI evaluation process question the studies' capacity to claim that their app showed positive "engagement." [67]

Besides the aforementioned review [67], in which the process by which this review defined each UEI was not specified, no expert consensus has ever been reached to establish consistent and replicable definitions for UEI in smartphone-based interventions for BD.

The Effectiveness of Smartphone-Based Interventions in Bipolar Disorder (Observational Studies)

Apart from RCTs, up to January 21, 2021, two observational pre-post studies assessing the effectiveness of smartphone-based interventions in BD had been published [69, 70].

The duration of the studies was 3 [70] and 6 months [69]. Both studies used a smartphone-based psychoeducational program for bipolar disorder (SIMPLe). The SIMPLe app included SM through EMA and provided adapted psychoeducation messages according to the clinical states, risk situations, and potential relapses. The

first study was conducted with the original version (SIMPLe 1.0) [70], in a clinical setting, and the second study was conducted in a web-based 100% online setting worldwide with the upgraded version (SIMPLe 1.5) [69]. The upgraded version incorporated some features including personalized prodromal symptoms register, medication reminders, and gamification modules.

The two pre-post studies showed effectiveness of their smartphone-based interventions comparing baseline versus the end of the intervention: one in reducing manic and depressive symptoms and improving biological rhythms and medication adherence [71], especially in participants with more use of the app [70], and the other in improving self-perceptions of disease, well-being, and functioning [69].

One study included participants at any phase of the disease [69], and the other only euthymic patients [70]. No sub-analyses were made according to baseline affective symptoms.

Limitations of the Studies Assessing the Efficacy of Smartphone-Based Interventions and Potential Solutions

Most studies involving the use of smartphones in people with BD did not assess the efficacy of the interventions, but focused on the correlation between smartphone automatically collected or self-reported data with clinician-assessed scales [72–75], or the assessment of UEIs [76].

There are several limitations of smartphone-based interventions for BD that should be acknowledged. BD is a disease with a high neurobiological component [2], which requires biological drugs (e.g. lithium) to control the fluctuating course of the disease [77]. Psychological interventions, always adjunct to pharmacotherapy have proven beneficial in reducing affective relapse, particularly depressive in BD [78–81], and in improving cognition [82] and functioning [83, 84].

However, in acute episodes of mania or depression, adjunctive psychotherapies in most studies did not improve the rate of recovery when compared with pharmacotherapy alone [85, 86]. Psychological interventions alone cannot change the natural biphasic course of an illness with such a high biological load. The same limitations as psychotherapies may be present in smartphone-based interventions for BD: they may be useful to increase the patient's insight, and secondarily their adherence to medication [87], as well as provide the capacity to identify prodromal symptoms, so that full-blown affective episodes may be prevented. This way, smartphone-based interventions may improve the patient's stability indirectly, but on their own they may not be able to reduce symptoms' intensity or change the natural course of BD. Hence, the aforementioned RCTs may have been imperfect in design—by mirroring traditional clinical trials aimed at assessing the efficacy of drugs—and therefore targeting misleading primary outcomes.

In this direction, the measure of "mood instability" as outcome of effectiveness instead of symptom reduction has been proposed [39]. "Mood instability" supports that

a substantial proportion of patients with BD experience subsyndromal mood swings on a daily basis. In other words, that many patients with BD remain subsyndromally symptomatic during inter-episode periods [88]. Increased mood instability has been associated with decreased quality of life and functioning, increased perceived stress, [89, 90] and increased risk of affective relapses and psychiatric hospitalizations [91–93].

Since smartphone-based interventions are unlikely to change the natural biphasic course of BD or to reduce depressive or manic symptoms, they may be effective to detect mood swings in inter-episodic phases and promote an early intervention to avoid affective relapses and hospitalizations [40, 42]. Therefore, the quantification of mood instability and the risk of affective relapses may be more sensitive outcomes to measure the effectiveness of smartphone-based interventions in BD. The latest RCTs on smartphone-based interventions in BD have embraced this idea and assessed the risk of affective relapses [40, 42] and psychiatric readmissions [40] during the studies. The results so far have been conflicting, so that further evidence is required. Moreover, most studies analyzing digital data, including smartphones-obtained data, have used classical statistical methods with many inconsistencies and variability, thus precluding a generalization of results and limiting their interpretability in a clinical setting. Novel machine learning models may help with the analysis of digital "big data" by considering their changing and continuous nature and integrating different parameters measured. These methods may aid at providing a more precise clinical interpretation and identifying potential real-time digital predictors of clinical relapse [94].

Evidence-Based Smartphone Interventions Still Trapped in Lab Cages

There is one common factor across research projects regardless of the approach and the mental health disorder targeted: most of the apps developed and tested in research projects have not been released or available for users to access neither freely nor commercially. They have remained mostly restricted to research projects with few making their way to real-world implementation studies. This may be due to the lack of regulations, guidelines, or requirements for being deployed, or a combination of the prior. Moreover, even when capturing active and passive smartphone data to identify digital behavioral biomarkers and delivering tailored interventions seems appealing, there are several technical embedded cross-platform limitations in smartphone operating systems as well as unexplored interindividual variability and engagement issues when these platforms are scaled up in real-world conditions [69, 95, 96]. Whatever the reason, while people suffering from mental health disorders, including BD, are exposed to totally untested apps which multiply every week in app stores, mHealth solutions developed and tested in the academic field (many with positive results) are still trapped in cages at our labs.

Long-term maintenance of smartphone-based interventions (e.g. server maintenance, security patches, regular bug fixes with the updates of OS, etc.) as well as the

maintenance of the digital platforms that support those (e.g. data storage facilities) involves significant costs which are difficult to assume within the context of academic projects, in which there is usually limited funding. In this regard, alternative options should be explored, such as releasing the code to open-source repositories or establish a partnership with commercial companies, patients' associations, or non-profit organizations. Nonetheless, most of the academic efforts in the last years have been concentrated in assessing, reviewing, discussing, and commenting on the apps available instead of investing funds and time in developing, testing apps, and producing original research from clinical trials. For instance, a quick search on PubMed at the time of writing this chapter yields half the number of original research in comparison to letters to the editor, review, systematic review, and meta-analysis both for mental health (133 vs. 266) and bipolar disorder (18 vs. 36).

Future Directions

The heterogeneity of studies assessing smartphone-based interventions in BD so far fostered the development by the ISBD Big Data Task Force of an expert consensus to establish how studies assessing the efficacy of smartphone-based interventions for BD should be designed and report UEIs objectively [60]. The goal of this consensus was to allow clinicians to compare and replicate studies and reach higher scientific rigor, qualitatively and quantitatively classify and rank smartphone-based interventions, and have accurate and reliable UEI to evaluate smartphone-based interventions in BD.

Many of the recommendations of the aforementioned consensus may be extrapolated to smartphone-based interventions in affective disorders or even other mental health disorders or symptoms. In this regard, apps targeting transdiagnostic symptoms in mental health disorders rather than aspects of a particular disorder have shown promising results [66]. This might be an interesting path worth exploring that could optimize accessibility and globalization. It has been highlighted that the field of digital health, and especially digital mental health needs a set of standards for quality that will include measures of efficacy, engagement, and privacy [51]. Frameworks on shared decision-making on how and when to use smartphone apps in the clinic have been proposed [97]. However, probably due to the market heterogeneity, the information about apps may not always be available, so that it is not possible to assess them with current frameworks.

Smartphone-based interventions have the potential to revolutionize both the monitoring and assessment of BD. By allowing for remote monitoring and management, these platforms would be able to assist clinicians in managing patients beyond simply meeting them during routine clinical appointments [28]. A key potential limitation of the success of these approaches will be the physician's and healthcare system's ability to integrate these data into clinical practice in a way that is ethical, legally permissible, and respectful of patient privacy. Clinicians already suffer from an overload of data, so that smartphone-derived data should be incorporated in a

value-added way. New tools to help interpret and simplify data for use in everyday clinical decisions will be vitally important. In this part, data curators may help manage the digital data from the patient by creating a more friendly view for clinicians [98]. However, care must be taken to ensure the privacy of patient information, and there is a need for large-scale randomized-control trials on more diverse patient populations, such as those with comorbid mental illnesses, to determine if these applications are truly useful for the majority of the patient population with BD [28].

Nowadays, there is no point in suggesting that we should ignore and prevent the use of smartphone-based interventions by people suffering from BD and other mental health disorders until we have convincing evidence. People are already using them, and evidence suggests an increasing interest and latent demand that cannot be overlooked. However, in the case of commercial and non-validated smartphone-based interventions, it is important to let users know that it is not possible to rely exclusively on them, and their use should be discussed with their clinicians. Governments and stakeholders are constantly working on digital health regulations. However, in most countries, those are far to be reached and generalized. Future steps in this direction may include working side by side with leading players in smartphone operating systems to include on their app stores and products including a basic classification for smartphone-based interventions. This could be the result of consensus between health regulation agencies and private companies. This classification could be based on the availability of studies and their results and also include information for users about privacy, security, and confidentiality of the data collected through an understandable scoring system. The generalization of this classification would facilitate users and clinicians relevant information to consider smartphone-based interventions in their shared decision-making process and might encourage companies to evaluate their interventions before releasing them to the market [99].

Smartphone-based interventions for BD have sufficiently demonstrated their potential. However, there are many challenges still to be addressed that need the cooperation of multiple and distinct parties involved. Hence, it is important to reach consensuses, work collaboratively, and establish future strategies on the future of smartphone-based interventions, but also affective and other mental health disorders. This will finally allow high-quality and evidence-based digital tools to be finally available for clinicians in real-world settings to recommend or prescribe with confidence safe and efficacious smartphone apps to people with BD.

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Chapter 8
Chatbots in the Field of Mental Health: Challenges and Opportunities

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ELIZA shows, if nothing else, how easy it is to create and maintain the illusion of understanding, hence perhaps of judgment deserving of credibility.
A certain danger lurks there. Weizenbaum (1966)

Human–Computer Interaction and Social Rules

From the early stages of the technological development of computers and the internet, researchers have tackled the phenomenon of social responses to technology [1–3]. What are the norms that regulate computer–human interaction? Moreover, how does this interaction occur when the computer is able to use conversational language to interact with humans?

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In 1964, MIT researcher Joseph Weizenbaum developed ELIZA, a simple natural language processing software that allowed for scripts to be built directing how the program should construct a response in English to a user input. At the time, a popular script for ELIZA was DOCTOR, which was designed to act as a Rogerian psychotherapist [4]. ELIZA was not able to understand speech, but Weizenbaum noticed that people would get emotionally attached to it, in what he called a "powerful delusional thinking" [3, 5]. These *chatterbots*, or simply *chatbots*, as they are commonly referred to, more recently became widespread, and with the rise of virtual assistants such as Alexa, Cortana, and Siri a similar phenomenon has arised: these conversational agents are becoming much-loved companions in millions of households worldwide [6].

From experimental evidence, it seems like individuals apply social rules and expectations to computers, overusing social categories (such as gender and ethnicity) by applying them to digital conversational agents [2]. This, however, does not result from users' or social dysfunctions or from ignorance [1]. Actually, social cognition literature suggests that people tend to use knowledge that is most accessible to them to attribute characteristics to nonhuman objects [7]—thus, the knowledge of human interaction is applied, anthropomorphizing these objects [8]. Additionally, individuals also seem to perceive a mind—with intention, consciousness, and goals—in nonhuman targets such as chatbots [9].

Therefore, interactions with chatbots can be deeply social—and for this reason we frequently thank (and care for) them, even knowing they are not human. Additionally, the elicitation of social responses and the perception of a mind highlight the possible applications of chatbots in clinical practice and mental health settings. These perceptions make having a conversation more meaningful, and inferring mental states from chatbots can produce desirable cognitive and emotional responses in users [8]. Even though chatbot research has been ongoing for nearly sixty years [10] and that, over the last two decades, a solid body of evidence has shown the potential benefits of using conversational agents such as chatbots for health-related purposes [11], its applications in mental health are still scarce, but promising [5].

For that reason, the purpose of this chapter is to present an overview of the use of chatbots in mental health settings, highlighting its potential contributions to clinical practice in the field. Therefore, by building upon transdisciplinary literature, we start by introducing operational definitions and key terms in the chatbot field, including a brief historical overview and presentation of the taxonomy of chatbots (Fig. 8.1). Then, its current applications in the mental health field are presented, followed by a discussion of its benefits and possible concerns on patient safety. Finally, we present recommendations and future applications of chatbots in mental health research and practice.

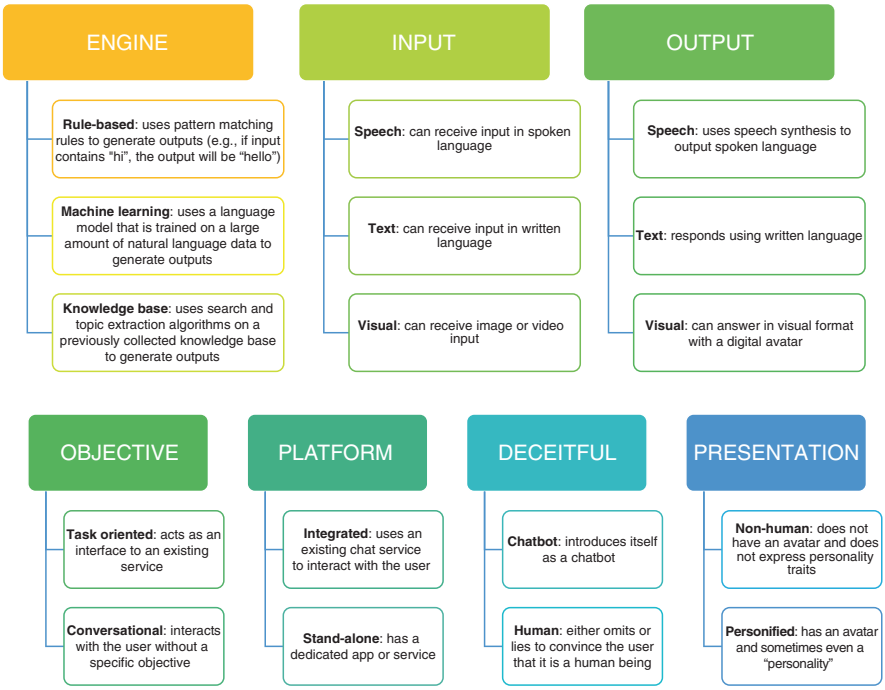

Fig. 8.1 Taxonomy of chatbots. Note that chatbots may display a combination of the types mentioned on each characteristic

What Is a Chatbot?

The term *chatbot* is a compression of *chatterbot*, the latter term having first appeared in 1992 [12]. A chatbot is commonly referred to as a digital system that provides an interface for interaction with users that is based on natural language—the language commonly used by humans to communicate with other humans. Although chatbots can be an end in themselves, where creating and maintaining interactions are the sole goal [13], it is more common that they act as a user interface, much as a mouse pointer, to underlying services [14]. Therefore, instead of clicking through menus or icons on a screen, or typing predefined commands on a keyboard, a chatbot allows for users to access a service by communicating through text or speech. Chatbots allow interactions in a more natural setting, one where the interface is both made simpler, by having a single communication channel, and more complex by allowing the richness of language.

As the name implies, a chatbot is required to have natural language both as input and output. In contrast, a Google search may accept natural language as input (e.g., one may type "what is the tallest building in the world?") but the output is *structured* as a list of documents. Chatbots mimic human conversations, aiming to provide most of the outputs in natural language.

Traditional user interfaces require the user to learn how to use the interface before accomplishing any task. Chatbots instead allow the user to communicate in ways that are natural to them, deferring the learning requirement to the interface itself. This enables for a standardization of interfaces to many different types of services; they all provide a single communication channel. Of course, this is not desirable for all types of services—arguably, it still is more effective to drive a car using a steering wheel than issuing voice commands.

The advantages of this standardization became more pronounced due to the proliferation of instant messaging applications in smartphones and other digital devices [15], such as WhatsApp, Facebook Messenger, Telegram, and WeChat. Originally designed to allow human-to-human communications, these applications have now become platforms for chatbot interactions. The main advantage is that the user is not required to install or learn to use anything different from what they already have on their devices.

Chatbots can be presented in a variety of ways. The communication medium is a central element in the design [14]. Text is the most common medium, as textual input and output are widely available in computational devices. More recently, speech has become more popular due to advances in speech recognition [16] and speech synthesis [17] and is now central in virtual assistants such as Apple's Siri and Amazon's Alexa (both were initially *exclusively* speech-based). Some more recent chatbots also accept visual input in order to interpret sign language [18].

Internally, virtually all currently available chatbots work with text both as input and output. A speech-to-text layer is added to allow for spoken inputs, but that is often completely independent from the chatbot algorithm—i.e., the algorithm will only receive the textual output of the conversion layer. Typically this means that nuances in speech, such as urgency or anger, that may convey useful information, are lost in the process. Likewise, a text-to-speech layer can be added, which solely converts the textual output of the algorithm to speech. Narrow exceptions include Amazon's Alexa, which is able to recognize when a user whispers commands and switches to a whispered speech as a result. Likewise, visual input can add a layer of information that is not present in text and there are proposals where facial expression recognition is used to build chatbots.

Chatbots may be built to have an identity with a specific personality and/or gender. This is most common when an avatar (a graphical representation of the chatbot) is present or speech synthesis is involved since these elements are part of the design, but even purely text-based chatbots may present themselves with an identity as it can lead to improved engagement. An avatar is often used to facilitate the anthropomorphization of the bot, helping to define an identity and personality.

Bots can also display some level of *autonomy* and actively take actions that go beyond simply responding to users' inputs. For example, in supported locations one can ask Google Assistant to make reservations at some restaurant and it will take a series of steps, and make decisions, to solve the problem, which include calling the restaurant and negotiating to find an open time that fits the user's preferences.

Autonomy is also connected to *initiative*. While a question-and-answer chatbot will only answer when prompted by the user, in many cases it is desirable for the bot

to initiate an interaction. A chatbot using a calendar system as interface may send a message to the user when an event is approaching. More complex behaviors include asking for information when required (e.g., "you recently visited Restaurant X; how was the meal?") and create an intervention when some conditions are met (e.g., "you seem to be trying to accomplish task Y, do you want to see a video about it?")—Microsoft famously introduced in 1996 the Office Assistant which continuously monitored users' actions and offered help, which turned out to be more annoying than helpful and was withdrawn.

This concept of autonomy ties with that of an *intelligent agent* and indeed chatbots can sometimes be called *conversational agents*, a way to denote both the requirement of some autonomy and the conversational nature of its interface. The reference to the concept of intelligence goes back to the work of Alan Turing in the 1950s, in which chatbots were proposed as a method to evaluate artificial intelligence in general, in what is now known as the Turing Test.

In a popular version of the Turing Test, human judges make use of a computer to communicate, exclusively using text, with either another person or with a computer (a chatbot). The task consists of the judge deciding whether they are communicating with a human or not. Turing postulated that if people cannot tell the difference, then the machine's behavior ought to be considered intelligent or, at least, indistinguishable from human intelligence. The test allows for the problem of asking whether a machine can think to be decoupled from that of asking whether a machine can *act* as if it is thinking.

Chatbots often draw from the area of artificial intelligence, which studies how to make machines act intelligently. ELIZA [4] used a rule-based approach to map user inputs to responses and was arguably the first one that could participate in engaging conversations. In rule-based chatbots, a developer programs the bot with strict rules on what to answer for possible inputs. A rule could be as simple as "if the input contains the statement *how are you* then answer with *I'm great, how about you,*" but could also be arbitrarily more complex. Rule-based chatbots depend entirely on the creativity and effort of the developers and typically will require ample testing to catch cases that the bot is not working on, which will require having specific rules built for. This method provides a simple way to create chatbots that act on narrow and well-defined conversation domains such as customer service but can fail short on more general conversation. Arguably most chatbots still use this method.

In contrast, *machine learning* can be used to build automatic rules by letting the bot first observe a large corpus of desired interactions. For example, one can use movie dialogues to train a bot, which will try to learn patterns from the data that can be exploited for future interactions, replicating these patterns. This approach substitutes developers' direct effort to build custom-made rules with large amounts of data. In the last few years machine learning has become a more viable approach by leveraging the large amounts of natural language data available on the internet and digital mediums. With these large amounts of data, it is possible to train expressive language models which can in turn be used to create conversation chatbots.

Also, novel AI algorithms based on neural networks, such as GPT-3 [19], promise to spur new innovations around chatbot design. These algorithms were trained in

millions of documents from diverse sources and are able to parse and generate complex and long sentences and can be adapted to many different domains with fewer data. However, since these algorithms draw from large, unvetted, data sets, it becomes challenging to restrict their scope, leading to unexpected, and possibly highly undesirable, outputs. With more people using their phones to obtain health information, it is vital that chatbots acting on healthcare give appropriate and predictable responses on distressing situations such as heart attacks, domestic violence, and suicidal thoughts but at this point even conversational agents backed by large corporations such as Siri, Cortana, and Google Now can fail to give appropriate responses in these situations [20].

Hybrid implementation approaches aim to solve these problems by handcrafting a small number of rules to address critical situations but also leveraging machine learning to better engage with users on a wide variety of topics [21].

Mental Health Applications of Chatbots

Chatbots have been used for a variety of applications in the field of mental health. A recent scoping review of published studies identified screening/assessment ($n = 10$), training ($n = 12$), and therapeutic ($n = 17$) as common purposes, with autism and depression among the most frequently addressed mental health problems. In most cases, chatbots were implemented as stand-alone platforms (70%) and dialogues were led by the bots (87%) [22]. In almost all studies (93%), chatbots were built using predefined rules (with only 4 studies employing machine learning approaches to generate responses).

In terms of diagnostic assessment, embodied conversational agents have already been used to identify outpatients with major depressive disorder using DSM-5 criteria, with sensitivity against gold-standard psychiatric assessment increasing according to the severity of the presentation and exhibiting good acceptability [23]. Good discriminative ability was also observed in the use of embodied conversational agents for the screening of tobacco and alcohol use disorders [24]. These applications have shown adequate rates of engagement by patients, as indicated by high levels of trust and acceptance [25].

An increasing number of studies have been published investigating the use of chatbots as interventions for mental disorders. A randomized controlled trial (RCT) indicated that the use of an automated conversational agent (Woebot) based on cognitive-behavioral therapy principles was associated with a reduction in symptoms of depression among young adults in comparison to an information-only control group [26]. More recently, another version of the Woebot also showed to reduce problematic substance use [27]. An RCT also suggested the role of an integrative psychological chatbot (Tess) in the reduction of symptoms of depression and anxiety [28]. Another RCT failed to show significant difference for a chatbot intervention (Gambot) targeting problem gambling [29]. Initial evidence also suggests that a CBT-based chatbot is feasible and effective in the treatment of panic disorder [30].

A further CBT-based chatbot, Todaki, was effective in reducing attention-deficit/hyperactivity disorder symptoms among adults [31].

In a real-world assessment design, participants with a high level of usage of an empathy-driven conversational agent (Wysa) showed a greater reduction in depression scores in comparison with low intensity users [32]. An automated chatbot app (Shim) has also been tested in a nonclinical population for the delivery of positive psychology-based intervention, indicating engagement in the 2-week intervention, with effects on well-being and stress in comparison to a waiting list control group [33]. A pilot study using unguided CBT delivered by an embodied conversational agent also suggested feasibility and acceptability, with indication of positive effects on mental health [34].

Notwithstanding all these initial, mostly promising results in favor of the use of chatbots for mental health promotion and care, there is an urgent need to expand and consolidate the evidence base in the field. Most studies still include only a relatively low number of participants (usually $n < 100$), and there is a marked lack of research on the use of chatbots with children and adolescents. The vast majority of published research up to now has been performed in English-speaking countries, most frequently using written text. Challenges ahead include the use of voice assistants, as well as improved metrics to assess (and remediate when required) issues related to adherence and engagement. Further research in the field of mental health should also address the hybrid use of chatbots and in-person approaches.

Benefits of Using Chatbots

Even though chatbot applications in the field of mental health—either by aiding patients, clinicians, or data collection—are still in its early stages, the definition of psychiatric chatbots or their role in the clinic is becoming widely discussed [5]. Chatbots can increase access to mental health interventions [22] and have several other benefits that can positively impact mental health prevention, promotion, and treatment. Therefore, this section will describe and discuss the benefits of using chatbots in mental health settings, such as clinical practice and/or research, highlighting areas for future development.

Increasing Access to Mental Health Care

Access to mental health care is, possibly, one of the biggest challenges in the field. While the demand for care is high, the current clinical workforce is insufficient to meet these rising needs. This is especially troubling in lower-income countries, where there are as few as 0.1 psychiatrists for every 1,000,000 people [35]. It is important to notice, however, that accessing care involves a number of different factors, including individual-level ones (beliefs and characteristics of the individual),

system- and process-level factors (policy and structural factors), and resource-based or practical factors (transportation and childcare issues, for example) [36].

Therefore, the option of technology, and more specifically chatbots, can contribute to decrease this problem [5]. Chatbots could potentially increase access to healthcare—both in situations where the person is unable to access the provider or when they are reluctant to [5, 37]. Chatbots are feasible solutions for delivering mental health support [38], and some studies suggest that this also applies to the support of children [39] and adolescents—there is evidence that, especially to this age group, online conversations can be preferred over in-person interactions when teens are dealing with difficult situations [40].

Additionally, it has been argued that chatbots can be used to augment the provider's time by increasing the patients' understanding of and compliance with instructions [37]. In this sense, chatbots can be a tool for managing the increasing demand for health services. This can be done either by means of aiding clinicians in the delivery of therapy [26, 41], providing referral management to clinicians [11], and/or even by screening and diagnosing mental disorders [23, 42]. Lastly, the insufficiency of workforce mentioned above can also be alleviated by the potential of chatbot use for encouraging and monitoring treatment adherence and compliance [37] and promoting self-care and psychoeducation in both clinical and nonclinical populations [5, 43].

Data Collection and Management in Research and Clinical Settings

Chatbots, in addition to increasing access to mental health care and disclosure, can be useful for data collection in diverse mental health settings. First, they can increase standardization in clinical questionnaires and interviews [42]. Therefore, applying standardized well-accepted clinical instruments and interviews through chatbots may increase the fidelity between different face-to-face diagnostic procedures, improve quality of care, and diminish demands on practitioners [23].

The application of chatbots can also extend to data collection in management and research settings. The diverse possibilities of delivering chatbots to patients may be a tool to promote collection of clinically relevant data (such as data on behavior or mood) in real-word contexts. This is consistent with Ecological Momentary Assessment (EMA) methods, in which psychological phenomena are assessed through the day within patients' natural environment [44], diminishing problems related to recall bias [45]. These data can be useful for clinical purposes—such as assessment of change during treatment or even to promote treatments [46]—as well as for the development of research. One of the main questions within EMA is the response burden of self-report, which can lead to inaccurate portrayal of behaviors. Therefore, allying EMA collection within chatbot development may be a way of diminishing this perceived burden, drawing on the perceived interactivity of chatbot interaction as a way to increase respondent engagement.

Promoting Disclosure

In addition to increasing access to mental health care and improving data collection, the use of chatbots in clinical practice may increase disclosure. In mental health contexts, especially in initial encounters, patients can be reluctant to respond honestly [47]—and this may be due to stigma, discrimination, or fear of negative reactions, rejection, and loss of privacy [48]. Interestingly, studies have shown that people tend to disclose more in computer-mediated interviews because they are felt as more anonymous [5, 42, 47, 49, 50], and these interviews often are marked by a lower fear of self-disclosure and more intense display of the interviewee's feelings [47].

Conversational interaction in chatbots may even decrease respondents' satisficing behavior, producing data with higher quality. It is worth noting, however, that this is only produced when the conversational interface creates an exchange between chatbot and user in a friendly, humanlike manner, generating a sense of higher interactivity [51]. This seems to be based on the assumption that chatbots are perceived as social actors, and that conversations are ruled by the same rules of human interaction and dialog, including the occurrence of reciprocity [52]—chatbot self-disclosure promotes deeper participant self-disclosure [53].

Recent work also shows that chatbots can be used to facilitate self-disclosure to a mental health professional [8]. This can be achieved by the chatbot design—it can either inquiry users answering questions and encourage them to share information with supporting professionals [54] or mediate disclosure (participants grant access to their chatbot records to mental health practitioners) [8]. The latter may help professionals gain more knowledge about the patients and their behaviors by using data collected during daily life to more accurately portray patterns and inform treatment decisions [55].

There is, however, no consensus on this matter—research has shown that there are important differences between chatbot and human interaction depending on the type of conversation [56]. Therefore, the use of chatbots for public health interventions is still an area in need of further exploration, since additional research is needed to examine the full effects of self-disclosure to chatbots on different populations.

Ethical and Safety Concerns

Even though there are several possible applications and benefits within the field of chatbot use in mental health research and practice, concerns regarding the ethics of the process have also arisen. Patient safety, privacy and confidentiality of data, and the management of emergencies are relevant in this context, but due to the novelty of the field, many of these aspects remain without clear solutions.

Privacy Breaches and Confidentiality of Data

While one of the strengths of using chatbots in the field of mental health is people's increased compliance and lower fear of self-disclosure, data management arises as a relevant factor for discussion. Privacy concerns regarding the use of the data collected by chatbots, therefore, are a relevant topic, especially due to the type of information gathered that includes sensitive data on users' mental health and well-being.

Until recently, chatbots were under limited regulation regarding the privacy of collected data or the implications of its uses. This has markedly changed since May 2018, when the General Data Protection Regulation (GDPR) went into effect—although with a geographical coverage focusing on the European Union, similar legislation has increasingly been adopted in other global contexts. The GDPR is based on the principle of private data as propriety of the holder and has created some ground rules for the development of chatbots. First, companies should state clearly the purpose and duration of data collection and storage, giving the user permission to exclude data as easily as possible. Moreover, chatbot developers should strengthen the cryptography and control of the access to data, assuring users' data safety [57]. The goal of GDPR is to increase the level of transparency among customers and users, including the necessity of warning users that they are speaking with a bot and not a real human [58]. Additionally, it is worth noticing that these regulations can respond to issues regarding the liability of using such tools [37].

Privacy and transparency, therefore, seem to be two of the core ethical aspects regarding chatbots. While lack of transparency may deter the use of chatbots, it can also change the balance of risk and benefits for the user, arising as central in the decision-making process of using a chatbot [40]. Moreover, there is a need for clarity in the disclosure of how users' data will be used by platforms. It has been speculated, also, that increasing compliance to GDPR and to the disclosure of ethical statements can increase the number of people willing to share information about their mood and well-being and the quantity of information shared by single users [27].

Serious Health Concerns and Adverse Incidents

In addition to privacy and confidentiality, another important aspect regarding patient safety in the use of chatbots is their response to serious health concerns. First, it is vital to assess how chatbots can—and will—respond to guide and offer help when the users are in need. A study including the most common smartphone-based conversational agents showed that, when asked questions about mental and psychical health, as well as interpersonal violence, these agents responded "inconsistently and incompletely" [20], showing important gaps in responding fully and effectively to health concerns. This is especially important since the response from conversational agents is critical—the conversational style of software can influence behavior [59].

Moreover, approaches using machine learning are becoming more common, and more chatbots are using unconstrained natural language processing to generate dialogues. The use of flawed or biased data for machine learning may carry the risk for reckless behavior on the part of chatbots—and this has been shown in cases such as Microsoft's Tay, a Twitter bot described as an experiment in "conversational understanding," that, in short time, became extremely aggressive and biased [60]. This raises the question of liability, but also about the safety and accuracy of advice and/or interventions carried out by chatbots, especially if they are not being monitored closely by health care providers [11, 37].

Finally, it is also important to acknowledge that using chatbots to deliver interventions to people with serious mental health concerns can also raise the question of adverse incidents, its monitoring and handling. In a recent systematic review of the use of chatbots in the mental health field, the overall safety of chatbots was assessed in two RCTs, and both reported no harm, distress, or serious adverse events (such as worsening of symptoms, suicide attempts, death or serious violent incidents) [61]. Another review also concluded that the risk of harm in using chatbots in mental health is extremely low, with 1 adverse event in 759 recruited participants [5]. The adverse event reported by Bickmore et al. 2010 was of a participant who developed paranoia and withdrew from the study [37].

Therefore, while studies suggest that risks in the use of mental health chatbots are extremely low, caution is still advised to mental health practitioners and researchers who want to develop a chatbot. This is due to the relational aspects that are entangled with the use of bots in mental health and will be described in the following section.

Attachment to Bot and Developmental Concerns

Concerns regarding attachment to chatbots have also arisen in the field. This is mainly due to the social nature of relationships with programs—studies have shown that feeling close with a nonhuman partner is possible if the partner possesses humanlike features [62]—but also to the opportunity of assistance in the frequency and setting the user wants. Some authors suggest that users can become overly attached, codependent, or even too credulous of the capacities of the bot, which leads to an increased expectation regarding their abilities [5, 37].

Moreover, the application of chatbots for mental health promotion and care seems to be more susceptible to such occurrences, especially since the disclosure of personal and sensitive information is known to create a sense of attachment [63]. While some level of attachment is positive and may result in more effective interventions, negative feelings may arise due to technical mistakes when a chatbot does not respond—people may become worried about its well-being when there is a technical failure [62]. Therefore, such concerns should be taken into account when using chatbots in mental health.

Additionally, there are concerns regarding the use of chatbots by children and adolescents—it is worth noting that even when chatbots are not designed for this age group, they are interacting with them [64]. Therefore, understanding how chatbots can affect development is another important point in this matter. Overall, children seem to perceive chatbots as friendly and trustworthy and try to understand them as a person—they often acknowledge these agents as actors from which they can learn [65]. There are, nonetheless, increasing concerns on the long-term effects of raising children in a context where conversational agents—often perceived as know-it-alls—are ubiquitous. It is especially important to highlight that children often turn to chatbots for answers to questions. While specialists highlight the importance that parents are present and help the children make sense of explanations, rephrasing when necessary [66], more serious concerns regarding the failure to properly handle reports of abuse or provision of inadequate advice have to be taken into account. According to UNICEF, "when not designed carefully, chatbots can compound rather than dispel distress" which "is particularly risky in the case of young users who may not have the emotional resilience to cope with a negative or confusing chatbot response experience" [64].

Future Directions

Since ELIZA, studies on the application of chatbots for mental health promotion and care have been regarded as a promising new area for clinicians and other healthcare professionals. As in many emerging fields, there are different ways to define and conceptualize the main concepts of the area—there are different approaches to defining and differentiating chatbots, conversational agents, and other embodied digital agents. Therefore, the field still lacks a consensus to unite different concepts and approaches to the employment of these digital systems. Investing in the further exploration and definition of a common conceptual framework for the chatbot field is necessary to guide future interventions and studies.

Additionally, there are ethical considerations that need to be further discussed. The ideal response to serious health concerns and adverse incidents for chatbots is still in a matter of debate. On one side, developers and clinicians should have the responsibility of minimizing possible negative events and responses from chatbots. With the widespread use of giant databases for the training of systems, however, unexpected and undesirable outputs may be inevitable, which entails a need for human validation and monitoring of the responses of chatbots as a way of mitigating possible negative consequences. This creates a dilemma: to create better chatbots, human supervision is needed, but this jeopardizes the privacy of human–chatbot communication.

To that extent, the development and implementation of chatbots pose important questions that need to be further discussed. While digital systems offer a variety of possibilities for development of new tools and applications, there is a need for close evaluation of the decision of creating new chatbots. New mental health

apps—perhaps one of the most common ways of implementing a chatbot—are created almost on a daily basis, especially since tools and expertise to create them are becoming mainstream. While these apps have a great potential in enhancing mental health care, most of these apps have not undergone rigorous evaluations of its benefits, posing another relevant challenge in the implementation of chatbots. Moreover, close evaluation of the benefits and shortcomings of creating new apps should be considered, especially as leveraging on existing tools could also be prioritized in a more frugal innovation approach.

Lastly, there is a need for understanding what makes these digital systems acceptable to its targeted audience, possibly using strategies such as co-design with potential users. As we have seen, human interaction with chatbots is deeply social and it is inevitable to refrain humans from attributing meaning to interfaces and conversations. Therefore, the meanings that are elicited from these interactions should be further explored, accounting for unintended consequences. Nonetheless, users themselves need to be included in this conversation—involving stakeholders in the concept development is crucial to ensure that the created systems match the needs and preferences of users [67].

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Chapter 9
How to Evaluate a Mobile App and Advise Your Patient About It?

Timothy Dy Aungst

Mobile applications (apps) are a ubiquitous feature of smartphones that have become a societal standard of engagement across the whole spectrum of consumer needs. Factors that have led to their growth include the release of the Apple iPhone in 2006 and mobile operating systems (such as iOS and Android) and the rise of the app store in 2008. Mobile devices have expanded from the smartphone to tablet device and the now converging trend for tablet computer merge. Alongside improvements in hardware and touch-based interface devices, it includes burgeoning access to the internet through mass Wi-Fi access and LTE and now 4G/5G cellular services.

In the United States of America (USA), 85% of adults own a smartphone, despite ownership of home computers remaining stagnant or dropping in certain socioeconomic groups [1]. As of 2019, there are almost four million apps available across the iOS and Android marketplace [2]. The largest segments of mobile apps used include gaming, social media, and entertainment [3]. The transformative power of mobile apps serves as the front door to new services such as online shopping, transportation, and social engagement platforms with upended legacy platforms. For instance, transportation is subsumed with on-demand gig workers via companies like Uber and Lyft and food delivery with Uber and DoorDash. The COVID-19 pandemic highlighted the use of these virtual tools, with online shopping and other digital services leading to $143 billion spent in the mobile app market. 2020 saw users download over 218 billion apps compared with 204 billion in 2019, demonstrating a year-over-year increase [3]. In turn, average screen time has also increased by 20%, with users spending up to 4.2 h a day on a mobile device.

While the transformation of consumerism through mobile formats has matured to a certain point, the health care space has only relatively recently evolved to a level

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of acceptable use. There are currently 300,000 health-related apps on the market, with 10,000–20,000 related to the mental health space [4, 5]. The utilization of these apps saw a surge during the pandemic, especially in healthcare, with a 25% increase in health-related app downloads and over 200% increase in mental health app downloads during the pandemic [6, 7].

The digital health environment has significantly evolved in the 2010s leading to novel means of engaging patients in their care [8]. Novel technologies are gaining further attention, such as the use of VR technologies for treatment in patients with psychological diagnosis, the use of digital biomarkers via wearables and digital tools for tracking disease progression and symptoms, which can lead to the pathway of digital phenotyping patients with certain chronic conditions, such as mental health [9–14]. Intermittent clinical assessments are being subsumed by real-time care modalities empowered by the use of remote patient monitoring tools and devices alongside health apps that can synchronize health data and then be shared with caregivers and providers. Coupled with the deficit of trained psychiatrist staff in the USA and the growing issues of mental health disorders, digital health has become a focal area for health innovators and companies to fill in these gaps of care [15].

This perhaps was most closely seen with the COVID-19 pandemic that allowed cross-state line telehealth services to be provided for patients seeking help with mental health. In addition, significant utilization of apps for mindfulness, depression, and anxiety self-treatment demonstrated a parallel growth with the rise of mental health concerns in the population during the same time period. It then comes as no surprise that payers, health systems, and providers are gravitating to utilizing mobile health apps and related technology to engage and empower their patients with tools and services that were not available in the past. The ability to scale services to a larger population, automate certain services, provide coaching, and identify patients at risk of possible relapse and in the most timely need provides the clinical toolbox more dexterity for use if used correctly.

Despite the gravitating attention toward mobile apps for health, there have been multiple issues in the mobile health and broader digital health space that has created criticisms by the medical professional field and worry by patient groups. In many ways, mobile apps have proved divisive with the pros and cons that have arisen in discussions about patient care. However, with a decrease in mental health services and availability across the USA due to a lack of health professionals, digital services and the integration of mobile health apps will be integrated to address current access issues. Nonetheless, how to use these services and at what scale needs to be identified and evaluated.

Despite the large premise of mobile health apps providing improved medical and health insights and benefits to patients, there have been substantial issues identified over the past 13 years. This has been problematic due to the nature of the mobile app stores, which have traditionally had little clinical oversight in their initial creation and management, and sale of apps. A developer who wished to create a mobile app that could influence medical decision-making by a provider, or give health recommendations to patients, did not have any requirements aside from the technical

ability to program and create an app. As such, early apps attracted the attention and wariness of early adopters of mHealth technologies as a wild west phase of utility.

This can be seen in several cases over the years that have attracted both media attention and regulator intervention. Interestingly many early cases of medical apps that were retracted or forced off the market were done so by the FTC, who received alerts from consumers and clinicians and not by the FDA. In 2011, for instance, the FTC fined two app developers who purported their app could treat acne based on the blue light from the screen, and they were eventually removed from the app store [16]. The FTC would go on to conduct further interventions, such as apps that purported to identify melanoma via the smartphone camera, fine a vision improvement app developer $150K for false claims, a company ordered refund for a smartphone attachable device to detect blood alcohol content, and a settlement for a fertility app sharing data-sharing privacy concerns [17–20]. The FDA, in turn, has had several notable instances, as well, such as alerting a urine test app that they did not have 510(k) clearance for their product but has tended to pursue companies that move a product to market before getting clearance for medical use [21].

These issues represent the ongoing issues that have faced the mobile app stores since their inception. Early research of the app stores demonstrated that multiple apps did not cite or state what clinical evidence was being utilized, with scientific accuracy ranging greatly [22, 23]. Other noticeable issues early on were that apps did not disclose whether a person with medical knowledge was involved in the app creation or curation of knowledge, such as one study evaluating vascular medical apps finding only 27% of the apps had medical professional involvement [24]. These issues led to early provider hesitancy to utilize mobile medical apps in patient care and aid in medical decision processes.

Within the psychology space, mobile apps have seen steady growth and are now estimated to make up 5% of the mobile health app market but have also seen their share of issues. For instance, the FTC charged a “brain training” program for false advertising that its program could perform better at work or delay cognitive impairment with no scientific data to support those claims [25]. The company settled with the FTC and paid $2M in a settlement. Other barriers include a recent report that found several popular mental health apps terms of usage and privacy policies do not clarify how user data is collected and shared, which could undermine public trust in these tools [26]. Independent researchers have also noted issues, such as apps for bipolar disorder finding a lack of evidence-based and clinically usable apps on the market [27].

Given the nature of concern related to the availability of mobile health apps that consumers and providers may utilize and not recognizing possible clinical flaws, there was a movement by multiple parties to intervene. These include a multitude of informal groups, regulatory bodies, start-ups, and clinical associations that all developed their own working bodies to sort through the mobile app store to identify possible apps of use and screen them for use. Reviewing these apps also was a significant undertaking, with objective mechanisms of rating apps for viability consuming much clinical investigation in the 2010s.

Table 9.1 Notable mobile app evaluation stakeholders

Organization/ stakeholder	Description
National Health Service	Created a government sponsored app library in 2017 that is open to developers to submit for review to be included after review, whereby they will be NHS approved, under test, or nonviable for use
Xcertia	Consortium of health technology organizations (e.g., AMA, HIMSS, CTA) to curate mobile health apps focused upon operability, content, security, and privacy
Digital Therapeutics Alliance	Non-profit organization working with digital health and biopharma stakeholders invested in developing and bringing digital therapeutics to market
Digital.Health	Resource designed for clinicians by exponential medicine, focused on digital health, digital medicine, and digital therapeutic products. Currently establishing methodology to review apps and then curate them for others to utilize
Orcha Health	Review digital health products and apps using multiple measures across clinical accuracy to data privacy and security. Have reviewed over 6000 apps and allow providers to prescribe apps directly through the platform
Rx.Health	Digital health formulary platform developed by physicians to enable providers to cloud-based service that allows digital health products to be prescribed for patient care
AppScript	Introduced in 2013, this is a digital app curation, prescribing, and studies platform available on the Epic App Orchard

In terms of relevant organizations, Table 9.1 highlights several key stakeholders' past and present. Notably, there have been several setbacks early on that are worth emphasizing the tribulations of this industry to evaluate and certify health apps for general use. For instance, one for-profit organization sought to evaluate and certify mobile health apps in the early 2010s. They initially certified 16 apps in 2013, but several digital health experts, upon closer investigation, found significant security issues with several of the "certified" apps leading to them being pulled from the program, and the organization ultimately abandoning this strategy in favor of a different health app curation program in the late 2010s [28, 29]. Even the NHS had difficulty in their initial forays to identify and recommend possible apps with early analysis of their initial library of health apps demonstrating gaps in compliance with data protection principles and developer disclosures [30]. Given the issues in the USA with independent organizations' initial forays meeting difficulties and rapidly changing tech that required novel assessments, regulatory bodies took it upon themselves to give guidance on what digital health technology would fall under their purview.

In the USA, the FTC released a tool for developers in 2016 to aid developers in understanding if their app would fall under their review, and FDA in 2013 released a document related to medical apps and what they would review [31, 32]. The FDA defined a "mobile medical app manufacturer"as any person or group "creating an app or software system that providers users' access to medical device function… or creates a mobile platform that is intended to be used as a medical device." However,

this initial stance caused some issues, as the FDA stated they would not look at the majority of health-related apps (such as those that provided medical information, general patient information, allow patients to log or track health information, those that behavioral suggestions on general wellness) on the app stores due to their scope only covering those apps that were "…to be used as an accessory to a regulated medical device; or to transform a mobile platform into a regulated medical device," which is in the minority of apps on the store. The FDA in 2017 launched its "Digital Health Innovation Action Plan" to take a further oversight in the digital health field such as with digital therapeutics and other therapies that would need review [33]. Currently, in 2021, the FDA created the "Digital Health Center of Excellence," whose objective and goal are to empower stakeholders to advise care through digital health and build partnerships and innovate regulatory approaches [34]. It can be surmised that the FDA will take a more proactive approach going forward but will have to closely work with companies given their inherent lack of human resources in this new sector that has recently become cemented as a firm reality.

Aside from regulatory bodies and companies seeking to help establish the fundamental level of expectation for mobile health apps, other clinicians and researchers have sought to delineate what makes a "good" or "bad" mobile health app. There have been many approaches for the past decade, with multiple scoring tools currently published [35]. Some like the Mobile App Rating Scale (MARS) were launched in 2015 and underwent validation for five years [36, 37]. There are significant issues related to these tools ranging from question item length, subjective versus objective score measurements, the inclusion of technology and security assessments, and overall clinical accuracy measurement. One issue that has appeared includes the interrater reliability of mobile app measures, where using multiple reviewers using scoring tools still led to varying rankings of appropriateness, which underlies the subjective nature of conducting such rankings [38]. Nonetheless, these app assessment tools offer the door for a fundamental approach to identifying, categorizing, and rating apps for use, but caution is being raised on a possible overload of frameworks to assess apps coming to the market, which will also pose a barrier [4].

Evaluation of mobile apps for mental health has also posed some more nuanced issues than the global health app market and has led to the further delineation of specific evaluation frameworks. Several researchers have identified related issues to reviewing mobile apps for mental health and variation across the numerous frameworks currently available and a need for standardized behavioral app quality measures with guidance for clinicians and consumers [39]. Relying on the app stores themselves to eventually address their internal issues or reliance on a review system will not yield the results needed [40]. As such, as in other health areas, the mental health space will need to turn toward its own internal knowledge base and experts to help guide the way forward, such as a psych-related app evaluation framework [41].

Clinical organizations and associations have risen to the challenge to approach their individual areas of interest, and the mental health and psychology space has seen significant work. Over the past five years, the American Psychiatric Association (APA) has put together an initiative called the "App Advisor" to rate mental health

Table 9.2 APA app evaluation framework overview

Areas of focus	Description
Access and background	Determine useful information about an app before evaluating it to determine context of its purpose. Areas include, but not limited to, who owns and operates the app, is it for medical purposes, what operating system does it function on, how often is it updated
Privacy and safety	Assess how the app manages data (patient, user) and what security is used to protect stored or shared data and for what purposes. At this point what is "acceptable" levels of data security and sharing is subjective to those that choose them to decide a minimum level of acceptance
Clinical foundation	Evaluate the app for benefit, based upon either direct clinical evidence or personal review of the app to determine if you feel the app may be beneficial based on your personal experience. This may include gauging the clinical utility of the service provided by the app, whether it appears to follow best-practice care models or comes from a foundation of clinical validity. At this time, there is no set standard for what a "good" app should contain and will be up to the clinician to determine acceptance
Usability	Determine if the app will be usable among patients and end-users, taking into account the apps user interface and experience and ability to customize for the users need (e.g., visual, audio) and personalization
Data integration toward therapeutic goal	Consider how the use of the app may either feedback into current clinical data infrastructure (i.e., EHR) or could possibly fragment care with the need for additional portals of data access points from the app to prove meaningful. Determine how easy data can be shared and integrated with your clinical workflow and also how it may be transferred and not lost over time, and lastly how the data can improve the therapeutic endpoints desired between patient and provider

apps [42]. The initiative is led by an expert panel of leading mental health and digital health experts, who have created a comprehensive app evaluation model seen in Table 9.2. As seen in the model, the five key themes are meant to guide the evaluator to determine the app's background and assess the clinical applicability to achieve its desired therapeutic goal. The APA, through this work, has identified multiple benefits and risks associated with mental health apps, ranging from supplementing the therapeutic relationship between patients and providers and increasing patient connection between sessions allows better practice management support, but also the issue of a lack of research in many of these mental health apps and issues around inappropriate use that could lead to adverse therapeutic outcomes and the underlying questions still related to data collection and use by developers [43].

The APA framework to evaluate health apps has led an individual group to create the "mHealth Index and Navigation Database [Mindapps]," (Mindapps.org), which allows others to rate apps through 105 different questions related to said features, privacy, clinical information integrity [44]. The database allows a user to search for mental health apps and utilize up to 88 filters such as, but not limited to, cost, developer type, evidence level, privacy. In addition, other features can be used as well by a user to search for apps such as those that track symptoms, sleep, medication use, biofeedback, cognitive behavior therapy, and more. This work demonstrates the

application of a guiding framework to spur the development of individual databases for apps of potential use in the mental health space. However, Mindapps is not the only group focused on the mental health space, with One Mind PsyberGuide also offering an online database based on an independent expert panel to review mental health apps for use. They have also collaborated with another group to create a guide on mental health apps that employers can use [45].

Considering the significant inroads of these stakeholders to identify apps of potential use, it comes as no surprise that medical institutions, health systems, and payers are now looking to integrate apps into their clinical care processes as digital health matures. This includes creating the so-called digital formularies that include not only apps but devices and other digital health tools. As it stands, digital health companies that seek to create and bring to market mobile apps for consumers face not only getting patients to utilize their products but also financial coverage. This, in turn, has also led to the creation of "prescribable apps."

These prescribable apps have been a topic of discussion for many years but recently have gained further interest based on the growing digital therapeutics field. These digital therapeutics (DTx) are defined as delivering "…medical interventions directly to patients using evidence-based, clinically evaluated software to treat, manage, and prevent a broad spectrum of diseases and disorders" [46]. The value of DTx over current apps on the market is that they can increase patient access to health outcomes, allow clinicians to have more tools for treatment, and give payors an opportunity to reduce costs associated with traditional care by supplementing digital interventions. Areas of focus for DTx have included mental health, chronic pain, cardiometabolic disease, pulmonary disease, and oncology.

Digital therapeutics within the mental health and psychology clinical space have seen increasingly high growth, and the first FDA-approved DTx in 2017 was focused on substance use disorder and opioid use disorder [47]. Initially, the FDA had a precertification program where they worked with early adopters, including the DTx space. This work was essential for further DTx being able to come to market. Even the COVID-19 pandemic spurred the FDA to recommend the streamlined review process of digital health devices to address psychiatric disorders, which helped multiple digital health products come to market, including DTx [48]. Several DTx companies have published innovative research regarding their products which led to clearance for certain mental health conditions. Several noteworthy products cleared by the FDA include the use of electrical direct-current therapy for depression which uses an app-guided hardware device, those for sleep improvement, and a videogame platform for ADHD as an adjunctive treatment with stimulant use [49, 50]. There are currently multiple DTx under investigation and evaluation by the FDA, and it can be expected that clinicians and patients will have multiple possible solutions to utilize in the next few years. However, this field is still rapidly advancing, and early trials still have not shown all positive results [51].

It is more than likely that DTx and the nature of their scientific validity will pave the way for new mechanisms to gauge the utilization of mental health apps. If a clinician is presented with an opportunity to recommend or prescribe an app for a patient, questions will arise about suitability and clinical outcome desired for their

utilization. Payment models for reimbursement for the use of such apps will also be questioned, similar to how current pharmacotherapy is currently utilized in the treatment of psychological conditions. If payors create digital formularies and are adopted by insurance companies, DTx may become a default tool over other mental health apps on the field due to a more streamlined utilization like pharmacotherapy. However, this still requires an infrastructure in place which is only beginning to come to fruition.

Given the inevitability of a framework whereby mobile health apps to different levels of clinical utility will come to market and receive uptake, the clinician and patient relationship regarding these interventions comes into question. Several issues are currently paramount for utilizing mobile apps effectively [52]. The AMA has been focused on utilizing and delivering digital health tools in clinical practice and has created two playbooks thus far, including a telehealth and remote patient monitoring (RPM) playbook [53]. The RPM is quite analogous to the utilization of mobile medical app selection with or without the hardware attached and can serve as a framework on global issues to consider when selecting what mobile health app to use in mental health. Table 9.3 highlights questions to consider when looking to integrate apps into practice.

It can be established that within the foreseeable future there will be a definitive pathway where apps will likely be either prescribed by providers or recommended for use, due to variability in the clinical outcome associated with the app and liability limits assumed by providers and companies. Nonetheless, getting apps into practice beyond questioning validation of use is still of a large concern [54]. While employers and health benefit platforms and insurers are offering health apps for their members, digital formularies are coming to the forefront, and the FDA is clearing apps for direct clinical outcomes, payment models and reimbursement is being explored, clinicians must now address the clinical concerns of their utilization aside from those mentioned in Table 9.3.

Table 9.3 What should be done to integrate mental health apps into clinical practice?

Possible issues	Items to consider
Why do you want to prescribe an app?	• Determine if the use of an app can help offer scalable services or increased level of care for your patient • Assess if the use of apps is something that is desired by your patient groups • Determine if you want to evaluate apps on your own, use a society guide, or subscribe and purchase a digital formulary service to help you
Which therapeutic conditions could benefit from the use of an app?	• Ideate on if mental health apps could help improve outcomes for your patients and in which therapeutic areas or in general health • Evaluate whether an app is targeted toward general health areas, comorbidities, or specific mental health concerns • Consider the use of the APA framework clinical assessment on apps that may be available

Table 9.3 (continued)

Possible issues	Items to consider
How much oversight do you want with an app?	• Review current practice and determine if apps are to be recommended as adjunctive to care or directly lead to a clinical endpoint • Evaluate apps that allow personalization for individual patients if desired • Determine if apps allow providers to be notified, how the notifications are received, and if notifications can be customized for therapeutic areas of concern (e.g., medication nonadherence, negative survey result, or mood notification)
How do you train yourself and staff to handle apps in our workflow?	• Consider whether you or your staff have the training and tools to integrate mobile apps, especially if data sharing and interpretation are entwined, into your patient care process • Evaluate if certain staff (e.g., nursing, front desk) will be responsible for triaging patient alerts or evaluating patient data • Evaluate who will manage communication with patients using apps and through which processes
How do you onboard patients to use an app in care?	• Determine who will be responsible for training patients on using the app and navigating it • Assess if patients or caregivers will want to share the data with you or other providers • Evaluate individual patient capacity to use the app or have the necessary hardware (e.g., smartphone, tablet computer) • Establish when patients should contact the app developer or related third party for technological support or reach out to their providers for clinical guidance or concern related to the app
How do you implement an app service into our infrastructure?	• Identify if the app will transfer patient related data if you have the infrastructure setup to receive and access the data • Data may be stored directly on a patient device, in a cloud-based server, or transferred to your system and then require management • Evaluate how app updates or portal needs are reviewed and staff are kept informed of possible data lapse or downtime
How do you review outcomes and create value?	• Review what clinical endpoints related to patients using the app should be established • Pilot or conduct preliminary internal testing of the app and get feedback from patients and staff on how to improve rollout • Identify when treatment failure or success is met with an app or when to utilize another app or treatment • Collate data for internal review to determine if continued use is warranted or pivoting to another similar product should be considered

Within the mental health space in particular, the APA and others have propositioned items to consider when clinically choosing apps to use in patient care [55, 56]. Compared to other apps on the market for chronic conditions, like high blood pressure or pulmonary problems that have objective measurements to track outcome, mental health may fluctuate over time. Providers will need to gauge when to recommend the app for chronic use, as an adjunctive to current standards of care, or

even as independent treatment. Further decisions will need to be discussed if these interventions will be chronic or self-initiated by the patient or recommended for reinitiation by the provider on an as needed basis. Clear communication between patients regarding their mental health app usage whether recommended by other providers or the mental health provider or by self-choice by the patient will need to be part of the patient care process going forward.

For instance, if a patient is under treatment for a psychological problem such as depression, and receiving therapy by a provider and medication treatment, but chooses to use an app they choose to follow, there could be a potential interaction in provider directed care and self-treatment. This could be analogous to issues with other conditions where patients may receive treatment via mediation but utilize alternative medications or herbal supplements that may interact causing a medical misadventure. Since this digital age is now present, conducting an "app reconciliation," similar to medication reconciliation processes, should be considered.

Tracking progression should also be assessed. Does the patient like the app or platform, does the provider find the data valuable, and is progress being observed should be considered at all times. The key aspects will be a movement away from intermittent care models that rely on patients having infrequent touchpoints with their mental health provider and now through an app a potential real-time assessment of a patient. This may then lead from relying on patients reaching out when they may be experiencing issues, and providers may instead use digital biomarkers or relevant data to initiate changes to patient care prior to a mental health exacerbation. As such, changing the workflow between the patient, staff, and provider to work within this new paradigm of care should be explored further, especially in a growing move toward telehealth as a possible default of care in some conditions.

Lastly, choosing which app to use will ultimately likely follow a semi-evidence-based approach whereby it will rely on provider comfort, patient choice, and scientific evidence. This will include studies that may compare apps outcomes, especially in the DTx space, alongside integration into clinical guidelines. It will likely be that the 2020s will see further exploration of best practices using digital health technologies and in the mental health space differing levels of gauging what may work best in different patient groups. For mental health providers, keeping abreast of the growing body of evidence on what apps can be used, and determining which patients to use these interventions in will be paramount. Ultimately, these interventions will be another tool in providing care, as we eventually move on from calling it digital health and just health care.

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Chapter 10
Telepsychiatry

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Telepsychiatry and the COVID-19 Pandemic

Telepsychiatry is a useful tool and a promising alternative during the COVID-19 pandemic when face-to-face meetings are unavailable or undesirable. It can be considered a critical tool to cope with the growing needs for mental health care while allowing for social distancing practices [1]. Furthermore, telepsychiatry could play an important contribution to the decrease of the inequitable access to psychiatric care everywhere, reaching people in need in different places where psychiatrists, psychologists, and other mental health professionals are not available [2].

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Mental health treatment is not available for everyone. For instance, two-thirds of primary care physicians in the USA reported that they could not access outpatient mental health services for their patients. Rural areas have even more difficulties in accessing mental health professionals [2]. Apart from this, mental health is one frequent challenge for primary care physicians. Even prevalent disorders are difficult to be identified by primary care professionals. One meta-analysis evaluated how accurate the depression diagnosis performed by the primary care physician was and found that depression is more frequently detected in those who are not depressed than in those who are [3]. Hence, telepsychiatry can be seen as one possible solution to the shortage of mental health professionals worldwide and may enable these professionals to conduct psychiatric evaluations and consultations, access psychoeducation, provide telepsychotherapy, and perform follow-up evaluations from different places [4]. Thus, telepsychiatry is an important field that could fill the gaps in mental health care.

There are some important reasons to use telepsychiatry in patients who do not have access to face-to-face psychiatry care for any reasons, such as (1) decreasing the failure to follow-up after inpatient discharge; (2) using psychoeducation to improve compliance to medications; (3) avoiding readmission and ER visits in high risk patients; (4) avoiding the increase in suicide rates [5]. Some studies have shown that these virtual care systems had a positive reception by patients and were associated with decreased admissions or readmissions to psychiatric hospitals, being considered cost-effective [6].

Despite all the advantages of telepsychiatry, this was not a frequent treatment in use until the SARS-CoV-2 pandemic outbreak. In 2009, only about 2% of the psychiatrists had ever used telepsychiatry in the USA. Although telemedicine care had increased from 2005 to 2017, its use was still infrequent by 2017 [7]. This approach was even less common in other continental countries. In China, telepsychiatry became regulated only in 2018 and in Brazil, there was no regulated use of telepsychiatry until 2020. Therefore, it can be observed that the use of telepsychiatry increased substantially during the SARS-CoV-2 pandemic [8]. The reasons for increasing the availability of this modality of treatment might be due to the emotional distress caused by fear and loss, but also due to the unavailability of face-to-face meetings. However, it was very well perceived among mental health care providers, and many would like to continue using it. Access to technology and training in this different treatment modality raises concerns, so professionals should receive training in this modality of treatment and it should be included in the residency training [8].

For patients, telepsychiatry improves access to care, reduces the waiting time for appointments, as well as travel time and costs. Although some patients still prefer in-person encounters, comfort and satisfaction usually increase after patients get used to telepsychiatry [7].

Applying Telepsychiatry in Real Life

The American Psychiatry Association Work Group considered telemedicine and telepsychiatry well-established across different cultures and preferable to face-to-face in many areas, such as older adult, child, and adolescent psychiatry [9]. There are concerns about developing a therapeutic alliance and relationship through the internet in the absence of nonverbal cues, but a systematic review evaluated the therapeutic alliance in e-therapy and it seems to be equivalent to traditional therapy [10]. Furthermore, some studies have shown that telepsychiatry is associated with lower transaction costs, high satisfaction, and no difference in outcomes to face-to-face treatment [11–14].

The utility of virtual mental health care includes assistance for the immigrants' and refugees' populations [15]. These groups are at risk of mental disorders, since during forced immigration they could have experienced traumas like torture and loss of relatives, while non-forced immigration can cause adjustment difficulties such as displacement challenges, cultural differences, separation from family, and financial losses [16, 17]. Telepsychiatry is a gap-filling strategy that increases access across borders [15], and the acceptance of telepsychiatry for these groups is already well-established [18].

Some institutions have organized guidelines for online medical services [8]. First of all, legal aspects should be respected: confidentiality, providing an appropriate environment for care, explicit consent for recording the session if necessary, and the use of a secure and trusted platform with encrypted transmission. So, if a patient lacks the capacity to make a decision, consider whether remote consultation is appropriate [8]. Table 10.1 depicts general recommendations for the use of telepsychiatry.

Some techniques of interview can facilitate communication between health professional and patient. It is possible to stimulate the patient's communication with posture and words: lean forward, make eye contact, and use expressions like "Hum hum," "Continue" or "I'm listening," to help the patient to maintain the narrative [19]. To demonstrate attention and understanding, summarizing the participant's narrative

Table 10.1 General recommendations for care in telepsychiatry

Before the consultation	– Scheduling can be made easier when software is used to set the date and time zone of the virtual appointment [19] – The patient needs to check their internet access and the skills to use the platform [8] – The physician needs to be familiarized with the video consultation platform. Unnecessary programs and applications should be closed, volume of the video should be adjusted. Use comfortable distance from camera to allow patient to see and to hear clearly. Avoid sensitive and personal details in the background [8]

(continued)

Table 10.1 (continued)

During the consultation	– Perform the intervention in a private location where you will not be interrupted; tell the patient that you are alone; prefer using headphones to ensure privacy and try to make your face visible [19] – Instruct the patient to also seek a private location and convenient time to avoid interruptions [19] – Allow nonverbal communication, including head, neck, upper body, and arms on the screen; tailor information and check the patient's understanding, mainly for those with lack of digital literacy; look at the camera [not at the patient's eyes]; check the patient's telephone number to contact in the event of a lost connection [8] – Keep your attention focused on the patient, avoid other attentive focus, like annotations [19] – Evaluate patient safety: Level of agitation and the potential for harm to self or others and clinical symptoms. Be aware of where the patient is located. An emergency service should be available and the telephone number of a collaborator to immediately contact patients at risk [7, 8]
After the consultation	– Document appropriately: Time, date, remote site location, time spent with the patient, the location and personnel, clinical history, mental state examination, diagnosis, treatment plan [8]

throughout the interview and repeat some words from the patient's speech [19]. Transmitting empathy is essential when caring for people in emotional distress, ask about emotions felt by the patient, show that you understand the patient's feelings [19].

Special Populations

The psychiatric care of children and adolescents has some particularities that need to be considered. Youth are dependent upon adults to access health care, so the psychiatrist should establish a therapeutic alliance with all participants [20]. It is important to incorporate the caregivers in the consultation, asking them to introduce themselves and explaining the symptoms and treatment in a way that is easy to understand. Some elements can be included in the session for a better evaluation, for example, crayons and simple toys to assess fine motor skills, communication, and attention [20]. Besides that, it is important to minimize overdecorating the physician's room to minimize distractions during the consultation [20].

Among the geriatric population, telepsychiatry has shown benefits even in cognitive screening, with the strongest evidence for tests that rely on verbal responses [21]. In psychotherapy with older adults, the involvement of caregivers is often necessary, with benefits for the treatment with CBT for insomnia, depression, care-giver support, depression, and quality of life [21]. However, due to the "digital divide," geriatric population might need teleconsultation by phone instead of video call. There is evidence of the positive impact of telephone befriending on older people's well-being [22]. Besides that, CBT over the telephone compared with face-to-face resulted in equivalent improvement in depression among primary care patients [23].

Barriers of Telepsychiatry and Strategies to Overcome it

Despite many studies reporting the benefits of using telepsychiatry, there are some limitations to be considered when applying this model. The main concerns mentioned by psychiatrists are: the lack of studies on the applicability of this modality and its effects in long term; the poor training support in the use of telepsychiatry; reimbursement/financial, legal/regulatory, and licensure/credentialing issues; and safety of patients suffering a crisis [7, 18].

The most important barrier found in the literature is the fear of physicians that internet based assistance is less personal and more difficult to establish rapport, because of the decreased ability to detect nonverbal cues, making eye contact and picking up nuances and emotions, and also difficult when using silence as a therapeutic tool [7]. Clinicians also worry that patients could be uncomfortable, especially the older ones, those with cognitive, visual, or hearing impairments, and those with psychotic disorders. Aspects that can difficult rapport are especially the technology's limitations, which include poor visual images, pixilation, "drops' 'of conversations, turn-taking in discussion all due to low bandwidth [7, 8]. Studies evaluating patients' satisfaction with telepsychiatry, compared to face-to-face consultation, report the same levels of satisfaction, comfort, and acceptance, while clinicians report to perceive patients less satisfied with telepsychiatry [9]. Moreover, studies that evaluated the therapeutic alliance in face-to-face setting versus telepsychiatry models did not find differences between the intervention types, which is in accordance with patients' perceptions about telepsychiatry [10, 11]. Strategies to improve the online rapport include having a good internet connection with stable audio and video, allowing a correct assessment of the patient's facial expressions. It is important to note that nonverbal communication is also impaired by the use of masks [8].

Another important issue that can be a barrier is the privacy of the patient and their data. With the dissemination of technology, patients use different devices to perform online consultation, varying from computers, tablets, and smartphones. It is important to consider that especially smartphones are vulnerable to hacking and data leakage, so it is recommended to use a safe platform [7]. Also, privacy in both patient and psychiatrist location is important, ensuring an environment in which other people cannot access the consultation. The clinician should explain it to the patient and also advise that they do not multitask during the consultation, avoiding distractions from the environment, such as eating or exchanging messages on their cell phone during the consultation [11].

The use of telepsychiatry with patients going through a crisis requires special attention. Crisis is defined as a relatively sudden situation, in which a patient has an imminent risk of harm to the self or others and judgment is impaired [16]. The literature highlights how telepsychiatry in the emergency context can increase patients' access to psychiatrists, especially in rural and remote areas where the specialist may not be present [16]. In this context, a support staff must be present at the location of the patient and the psychiatrist needs to have the patient's family contact,

in case of need for immediate intervention. Also, potential problems with technology and network (like loss of connection) can occur, so the psychiatrist needs to know the exact location of the patient and have a local collaborator or another method to contact the patient immediately if needed [7]. When such care is taken, even patients with psychotic conditions benefit from the use of telepsychiatry [24].

Another potential barrier to telemedicine refers to legal and administrative aspects, such as payments of the consultation fees, prescription of medications, laboratory requirements, as well as regulatory laws [17]. With the COVID-19 pandemic, regulatory health agencies removed some of those barriers. The main ones were the regulatory changes in the payment of telepsychiatry consultations by health insurance and adoption of telehealth platforms able to create prescriptions for controlled substances and laboratory requirements [13]. Another important change refers to the licensure of clinicians—in the majority of countries physicians can be accredited to work within their state, limiting the use of telemedicine to patients who are residents of the same province, but at the beginning of the COVID-19 pandemics some countries have authorized doctors to be able to treat patients from all states of the country, regardless of their accreditation status, increasing access to telepsychiatry, especially in remote regions with few psychiatrists [7]. Where the rules have been made more flexible, telepsychiatry has grown more [18].

Some patients may have greater difficulty in accessing telepsychiatry, especially those with lower socioeconomic status and the elderly, which have lower access to electronic devices, lower internet quality, and often little privacy at home, showing a disparity in access to this modality, called the "digital divide" [13, 14]. Although digital access increased during the COVID-19 pandemic, the digital divide might also have increased, so it is important to make efforts to train patients with greater limitations in the use of technology, thereby increasing universal access to telemedicine [12]. A suggestion is for health services to offer guidance to their patients before the implementation of telepsychiatry [15]. The use of telephones by these patients can be preferred, with studies showing that interventions delivered by telephone can be effective and well-accepted especially by older people, thus overcoming the difficulties of this population with technology devices. Professionals should preferably use a professional telephone, but if using a personal one, it is recommended to deactivate the caller identification [23, 25].

Patients Experiences and Future Implications

Telepsychiatry has been shown to be equivalent to in-person care in diagnostic accuracy, treatment effectiveness, and patient satisfaction. Psychiatric diagnoses are reliable with good inter-rater reliability. Telemedicine could also facilitate language and cultural matching [9]. A few studies showed that clinical outcomes with telepsychiatry are as good as those achieved with face-to-face treatment [26]. Regarding cost-effectiveness, it seems that telepsychiatry saves time, travel, and money for patients and providers.

Telemedicine and telepsychiatry are well-established fields and are preferable in many areas such as for patients on the autistic spectrum and those with severe anxiety symptoms [9]. Patients with severe anxiety disorder may avoid care because it could be difficult to get transportation or feel safe outside. Not surprisingly, children and teens that have been raised in the internet era find that telepsychiatry is preferable to in-person care [7]. Telemedicine can also facilitate medical encounters with subspecialty expertise and nursing home assessments more rapidly and efficiently.

Future perspectives include studies that have been focused on asynchronous telepsychiatry. Asynchronous telepsychiatry is a psychiatric interview performed in collaboration with other professionals and the psychiatrist evaluates the interview to perform diagnosis and recommend treatment to primary care physician. Studies hypothesized that this approach could improve access, quality, cost, and care over the usual care. Asynchronous telepsychiatry has been studied to be used in collaboration with the primary care in nursing homes, in order to diagnose psychiatric comorbidity and implement treatment [27]. A few studies are also evaluating different approaches to telepsychotherapy in face of COVID-19, including low-intensity psychosocial interventions in a population at risk to develop a psychiatric disorder. Studies using smartphone applications have also been conducted, with initial results finding benefit from digital intervention applied by application in improving dysfunctional personality traits [28]. Telepsychiatry has also been studied as a short-term intervention and after a few sessions, the PCP resumes care of the patient in ADHD patients and bipolar disorder. Also, studies are evaluating whether telecommunication tools, web pages containing online screening instruments and real-time video chat, will be an efficient way to screen psychiatric disorders [27, 29].

Conclusion

Telepsychiatry was underused until the beginning of the COVID-19 pandemic but became an important tool since then [5, 30]. It is capable of overcoming several difficulties such as the absence of professionals in remote areas, the risks associated with face-to-face care during COVID-19 pandemic, and the difficult commute for people living in remote areas, also having a good cost-effectiveness [1, 31]. Although some professionals are afraid of using this modality, it is well accepted by most patients [7, 32].

Using telepsychiatry requires some precautions, such as following the country's current legislation, using a safe and well-connected digital platform, and maintaining a therapeutic environment [8]. Special care is needed for special populations, such as children and adolescents, in which parents must also be included in the care, and geriatric patients, who may need assistance from young people to deal with digital divide [20, 21].

Telepsychiatry has some limitations to be considered, the main ones being: the absence of eye contact in the therapeutic relationship; absence of physical

examination; technological difficulties; distance from patients at potential risk; difficulty accessing populations with less internet access and legal aspects [7].Many of these barriers can be overcome by adopting some practices, such as a good internet connection, privacy at the place of care, adequacy to the rules of the country, and emergency contacts with the place where the patient lives [7, 8, 32]. Hybrid care models can also be adopted, as the outcomes of long-term remote care are poorly known [33].

Telepsychiatry is an important and efficient tool, especially during COVID-19 pandemic, and its rapidly increased use was well accepted by patients and clinicians [9, 34]. The future of telepsychiatry after the end of the pandemic is still uncertain and the results of studies on its long-term application during the pandemic are expected to delineate this practice in the future [34].

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Chapter 11
Prediction of Suicide Risk Using Machine Learning and Big Data

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Introduction

Approximately 800,000 suicides occur each year globally, accounting for one death by suicide every 40 s, with around 80% of all suicides taking place in developing countries [1]. This phenomenon is present in developed countries as well,

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considering that suicide rates have not declined over the past few decades in the United States [2]. Despite the alarming nature of these statistics, there is evidence that suicide rates are underestimated. A considerable number of deaths by suicide are classified as either accidental deaths or as deaths with undetermined intent [3]. For instance, a study based on Israeli data reported suicide rates to be nearly 42% higher relative to the official reports of deaths by suicide [4].

In epidemiological studies, it was shown that suicide is more common in males, with global rates of deaths by suicide around 15 per 100,000 people per year, while the global rates of suicide are approximately 8 per 100,000 in females [5]. Nevertheless, empirical evidence suggests that women are at a greater risk of suicide ideation and attempts, relative to men [6, 7]. Importantly, a previous meta-analysis of psychological autopsy studies highlighted that almost 90% of individuals who died by suicide presented with a prior psychiatric diagnosis [8].

There are several factors known to be associated with suicide risk. Such factors can be divided as protective or risk factors depending on the influence they may exert on individual patients decreasing or increasing suicide risk, respectively [9, 10]. For instance, good social support, high levels of extroversion, effective coping strategies, optimism, strong reasons for living, religious involvement, regular physical activity, and exercises are some of the protective factors against suicidality [9, 11].

The number of risk factors associated with suicide, suicidal behavior, and self-harm increases each year, as subsequent literature continues to identify novel candidate risk factors [9, 10, 12, 13]. Considering exponential growth within the field, there is an increased need for explanatory models to combine and synthesize these complex risk factors at different biological and clinical levels [9, 10]. The model represented in Fig. 11.1 [9] called biopsychosocial approach is one of these theories. This approach considers that different variables can interact at the distal, developmental, and proximal levels. This explanatory model was influenced by the stress-diathesis model, in which an individual with a genetic predisposition (diathesis), when under an amount of stress that exceeds a specific threshold, may develop a psychopathological condition [14].

Importantly, external factors, such as income inequality [15], uncertain political conditions [16], and the COVID-19 pandemic [17] may precipitate the rise of suicidality and suicide attempts in young people. However, in the early months of the pandemic, it did not appear that suicide rates had increased in high-income countries. This picture is less clear in developing nations that lack a substantive safety net, however [18]. The pandemic is associated with psychological distress in levels which are yet to be measured, also contributing to increased vulnerability to mental health problems and suicidal behavior in the affected populations [19]. For instance, recent studies have shown increases in the prevalence of suicidal ideation in the USA [20] and Greece [21]. Additionally, it remains to be seen whether the broad negative economic effects of COVID-19 [22] precipitate an increase in post-pandemic suicide.

Considering this context, the aim of this chapter is to describe the use of big data and machine learning to predict suicide risk at an individual level, enriching the

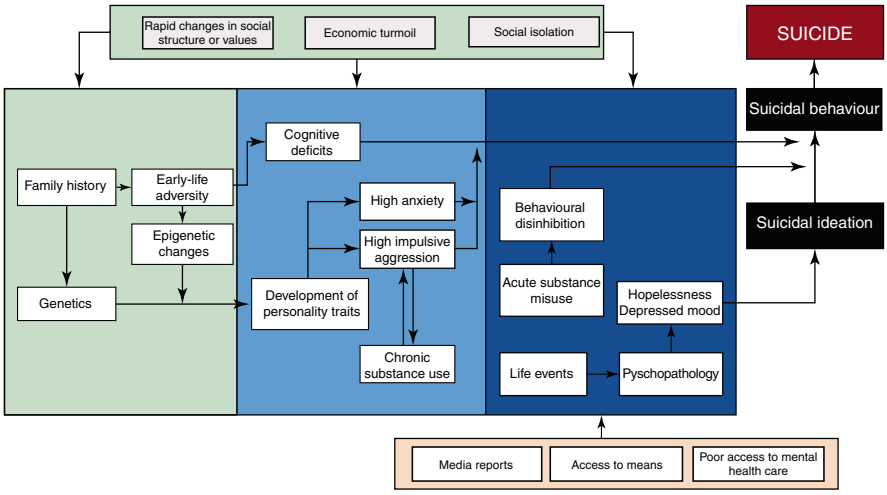

Fig. 11.1 Explanatory model synthesizing risk factors for suicide-related outcomes, adapted from [9]: Suicidality and suicide attempts may originate in the interaction of complex and multilevel factors, such as individual-level factors (in shades of blue, divided as predisposing, developmental, and precipitating factors) and population-level factors (including environmental factors, in pink; and factors associated with lack of social cohesion, in green). As highlighted in the model, predisposing factors increase the risk of death by suicide through changes in gene expression, which leads to effects on developmental factors. These developmental factors, however, lead to increased suicide risk through the promotion of specific traits such as impulsive aggression and anxiety; these traits may increase the likelihood of suicidal behavior in cases of suicidal ideation. Other developmental factors such as chronic substance use and cognitive deficits may also lead to the promotion of such traits. Precipitating factors, including acute substance misuse and other forms of psychopathology (any mental disorder associated with increased risk of suicide, as well as specific adverse life events which may lead to significant psychopathology), are associated with changes that ultimately lead to suicidal behavior and death by suicide

discussion with recent examples from contemporary scientific literature. In addition to the discussion of the revolutionary impact of these tools, potential ethical implications, current limitations and challenges will be acknowledged and debated.

Prediction of Suicide Risk

Frequently, the daily routine of psychiatrists, as well as other health professionals, is marked by the need to predict the risk of suicide-related outcomes for every individual patient [10]. However, the task of determining the suicide risk of any given patient is often performed subjectively. Recent data from Ontario [23] showed that over 67.4% of people who died by suicide saw their primary care physician prior to their deaths. Moreover, suicide risk assessments were reportedly conducted in 87.1% of physician visits. However, among those who actually died by suicide, 39.8% were classified by their clinicians as having no risk, and an additional 50%

were deemed low risk [23]. Unfortunately, these results clearly indicate that the clinical assessment of suicidal behavior largely fails to predict suicide.

In many fields of medicine, the majority of clinical interventions, including treatment, diagnostic and prognostic interventions, are based on an "average patient," where results from such studies are then generalized to the whole population [10]. In terms of treatment strategies, another limitation that needs to be acknowledged in randomized clinical trials is the use of overly restrictive inclusion and exclusion criteria, which compromise the generalizability of the results to real-world settings [24].

Considering the limitations of current risk prediction and group-based treatment plans, there is a need for a more individualized and personalized assessment of suicide risk. Within the framework of personalized medicine, "precision psychiatry" provides a way to predict patient trajectories, treatment response, and to guide prospective trials for individualized interventions [25, 26]. Precision psychiatry provides the path forward for a revolution in clinical psychiatry, aiming to make accurate individualized predictions of mental health outcomes, assessing each patient with multidimensional data of large magnitude and high specificity, and subsequently offering targeted clinical solutions (including diagnostic, prognostic, and treatment interventions) for each patient in an individualized and personalized manner [25–27]. A schematic example of the application of precision psychiatry in the prediction of suicide risk can be seen in Fig. 11.2.

However, in order to facilitate precision psychiatry, large-scale and high-quality multidimensional data is required. The concept of "big data" is generally defined by the five "Vs" [25, 28]. The first "V" is velocity, which corresponds to the increasing speed of data generation; volume, which is the second "V," describes the large amount of data, which only becomes bigger as the time passes; variety is the third "V" and describes the diversified nature of the data, which may come from different sources, levels, and distinct dimensions, and the data can be structured, semi-structured, or unstructured. Veracity, which is the fourth "V," represents the reliability we have on the data; lastly, the fifth "V" is value, which describes the applicability and practical value that these data will have on the lives of the individuals affected by it [28, 29]. Additionally, *big data* collects information from an entire system (n = all), with this information being produced continuously; in contrast to what could be called as *small data*, in which data presents a more static pattern and is collected from a population sample [30].

In order to analyze such a massive and complex amount of data, it is necessary to use sophisticated computational methods, such as machine learning [25, 28]. Machine learning is a method of data analysis and branch of artificial intelligence that aims to learn relevant patterns from given data, without being previously programmed by a human counterpart, thus mimicking the human process of learning, and subsequently using this learnt pattern to solve new problems [31–33]. The steps of developing a machine learning model is beyond the scope of this chapter and can be found in other sections of this book.

The use of big data and machine learning is widespread in several contexts of our daily life [33]. In addition, this is a growing field, with several studies exploring the

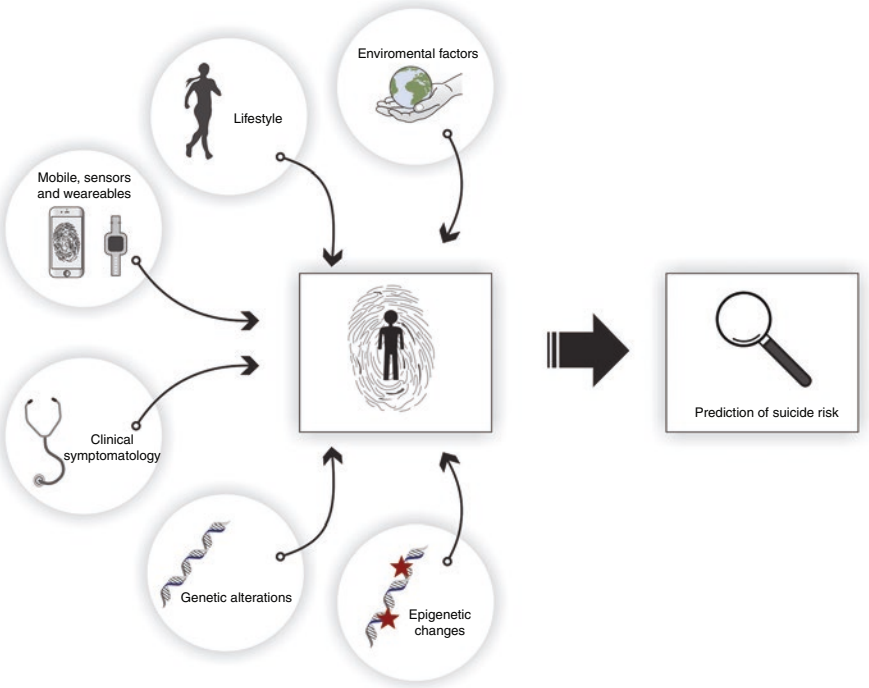

Fig. 11.2 (Adapted from [10])—Suicide risk stratification tool based on big data. In this model, each patient has an individualized phenotype, generated with the use of multidimensional and nonlinear data, combined with the use of sophisticated computational tools. This individual phenotype is the substrate for clinical decision making, including the prediction of suicide risk, in an individualized and targeted manner

use of such methods in psychiatry as well as other medical specialties; for instance, the number of published studies with the use of these methods in medical sciences more than doubled from 2016 to 2018 [34].

Having said that, one of the main challenges in predicting suicide risk is identifying the specific individuals who are at risk. However, a previous longitudinal study, based on data from the USA, described that nearly 50% of the individuals who died by suicide visited a healthcare institution within four weeks before their deaths [35]. A subsequent systematic review and meta-analysis showed that contact with medical services was common prior to suicide, and there appears to be an increasing proportion of individuals seeking inpatient or outpatient mental health services prior to making an attempt [36]. Altogether, this represents a significant window of opportunity to apply preventive and treatment strategies, in order to mitigate this risk and prevent such a devastating outcome as suicide.

Machine learning models, for example, could be translated into suicide risk calculators, which could then be used in primary care settings [29]. Therefore, patients predicted to have high suicide risk could benefit from more specialized assessments

of this risk, be referred to a specialty clinical follow-up, as well as benefit from treatment and preventive strategies, known to impact and decrease the risk of suicide [10].

Machine Learning Models for Prediction of Suicide Risk

The field of machine learning-based prediction models for suicide risk evaluation is in its infancy; nevertheless, several studies have highlighted promising results, which may have future implications in the management of patients at risk of suicide. For instance, a systematic review [37] recently summarized the evidence regarding studies investigating machine learning-based models in predicting self-injurious thoughts and behaviors, with suicidal and nonsuicidal intentions. In their results, the authors were unable to conclude on the overall performance of the models, due to high heterogeneity across studies. Even though the accuracy of the majority of the models described in the review did not surpass 90%, most models presented significantly higher accuracies in comparison with traditional statistical models.

One interesting study [38] explored the use of machine learning applied to functional MRI data, to investigate neural representations of concepts related to life and death in youths, with the aim of classifying individuals with suicide ideation. In their study, they used a *Gaussian Naive Bayes* algorithm, applying this method in a small sample with 17 participants with suicidal ideation and 17 healthy controls. Their model presented high performance, reaching an accuracy of 91%.

Another study [39] aimed to identify a textual signature of suicide risk using a machine learning algorithm called *Naive-Bayes*, for text classification of Virginia Woolf's letters and diaries, using texts within and outside the period of two months before her death by suicide. The final model presented good performance, reaching a balanced accuracy of about 80% in the prediction of suicidal behavior. These findings show the potential of linguistic-driven prediction models and may be applied to subjects with psychiatric disorders by means of data captured from social media, e-mail, among others.

A large longitudinal investigation [40] focused on developing machine learning models to predict death by suicide after psychiatric hospitalization, in a follow-up period of 12 months, using *regression trees* and *penalized regression* algorithms. Their analysis was based on administrative data from 40,820 US army soldiers, corresponding to a total of 53,769 psychiatric hospitalizations. Their models presented good performance, reaching AUCs of approximately 0.85. In addition, almost 53% of the post-hospitalization deaths by suicide occurred in a group identified as having high risk of suicide, corresponding to 5% of the initial number of hospitalizations.

Another large longitudinal study [41] of US army soldiers ($n = 23{,}854$) explored the combination of traditional statistical methods with machine learning (using an algorithm called *super learner*), with the aim of predicting non-fatal suicide attempts in a follow-up of 45 months. In their initial sample, they only included soldiers without previous suicidal ideation. In the first step of this two-stage procedure,

researchers used army administrative data to generate prediction models, using traditional statistical methods, with the aim of predicting a subsample with high risk for suicide attempts, from within the initial sample. Their best model reached good performance, with an AUC of 0.82 in this first stage. In addition, this high-risk subsample corresponded to 30% of the initial sample, which allowed investigators to exclude, before the second-stage procedure, the low-risk subsample, which corresponded to 70% of the total sample. In the second stage, using clinical data from a specific questionnaire, researchers used machine learning with the aim of predicting, from the high-risk subsample, a new high-risk subsample, which accounted for 10% of participants from the high-risk subsample obtained in stage 1, and 3% of the participants from the initial sample. In this stage, their best model reached an AUC of 0.83. After applying both stages, it was possible to identify a subsample with highest risk for suicide attempts (3% of the initial sample), which corresponded to 45% of the total suicide attempts in the follow-up. Another potential implication of this study was the possibility of saving resources, identifying a low-risk subgroup, which may not need to undergo costly assessments of suicide risk after being classified in an initial screening stage.

Populations at Higher Risk for Suicide

Several machine learning models have been created for specific populations that may be at higher risk of suicide. Passos and colleagues [42], for instance, used a set of clinical and demographic variables to test a set of machine learning algorithms and developed a clinical signature of suicidality in 144 patients with mood disorders. The study reported a balanced accuracy of 72% and an AUC of 0.77 in predicting suicide attempts. Prior hospitalizations for depression, comorbid posttraumatic stress disorder, cocaine dependence, and history of psychotic symptoms were the most robust variables in the model. Other studies predicted suicidality by using machine learning coupled with a combined genomic and clinical risk assessment approach and built models with an AUC of 0.98 [43] and 0.82 [44] in patients with bipolar disorder. Another prospective study [45] involved 6350 participants with lifetime major depressive episodes and developed a model with elastic net regularization that distinguished individuals who had attempted suicide from those who had not with an AUC of 0.89, balanced accuracy 81.64%, specificity 85.86%, and sensitivity 77.42%. Previous suicide attempt, borderline personality disorder, and overnight stay in hospital because of depressive symptoms in participants with lifetime major depressive episodes were the most important predictor variables.

Another population at increased risk for suicide is composed of medical professionals and medical students. A cross-sectional study [46] with data from 4840 undergraduate students generated an algorithm capable of differentiating participants that attempted suicide with an accuracy of 0.83. The main predictors for suicide attempts in students were female gender, homosexuality, low income, bullying

by university colleagues, trauma in childhood or adulthood, family history of suicide, suicidal ideation in the last month, daily use of tobacco, and being at severe risk of alcohol abuse. It is possible that algorithms with similar purposes will have a clinical and preventive utility in the near future, helping educational and health institutions in identifying students at risk.

Electronic Health Records as Source of Data

Medical records represent a useful source of data for machine learning models, offering invaluable clinical information known to be associated with suicidality. For instance, a longitudinal study [47] aimed to develop and validate machine learning models using electronic health records (EHR) to predict suicide attempts and suicide deaths after an outpatient visit. The data was obtained from 2,960,929 patients, corresponding to 19,961,059 specialty visits, in mental health or primary care clinics, with diagnoses of mental health. Potential predictors included 313 demographic and clinical characteristics extracted from the records for up to 5 years before each visit. For visits to mental health specialties, C-statistics (measure equivalent to the area under the curve) for prediction of suicide attempt and suicide death were 0.851 and 0.861, respectively. For primary care visits, C-statistics for prediction of suicide attempt and suicide death were 0.853 and 0.833, respectively.

Another longitudinal study [48] also explored sociodemographic and clinical data from EHR to create a machine learning algorithm capable of predicting suicide attempts. Participants were 5167 adult patients with self-injury, with 3250 patients attempting suicide (i.e., cases) and 1917 patients engaging in self-harm that was not suicidal, accidental, or unverifiable (i.e., controls). In this study, the authors compared the performance of a machine learning model (random forest) with a traditional method (multiple logistic regression). The machine learning model produced a more accurate prediction of suicide attempts than traditional methods (e.g., ML produced AUCs in the 0.80s, traditional regression in the 0.50s and 0.60s).

Importantly, EHR is a broad term that can be composed of data from several domains, including structured, semi-structured, and unstructured data types. Analysis of unstructured data may improve predictive performance, in comparison with models based on only structured data. A case-control study [49] sought to predict first-time suicide attempts using natural language processing and machine learning to unstructured (narrative) clinical notes and structured EHR data. The study included 45,238 patients (5099 cases and 40,139 controls) comprising 54,651 variables from 5.7 million structured records and 798,665 notes. Four machine learning models were evaluated using 2-year historical EHR data before suicide attempt or control index visits, with prediction windows from 7 to 730 days. Using both unstructured and structured data resulted in significantly greater accuracy compared to structured data alone (AUC: 0.932 vs. 0.901 $P < 0.001$). The best-predicting model utilized 1726 variables with AUC = 0.932.

Social Media and Other Sources of Data

Population databases have also been explored as sources of data for models aiming to predict suicide risk. A previous study [50] used national medical check-up data from 372,813 individuals in Korea from 2009 to 2015. In their model, the AUC to predict suicide risk was 0.849, sensitivity 81.7%, and specificity 75.4%, with an average overall follow-up period of 1.52 years. A prospective cohort study [45] with a nationally representative sample of the adult population in the USA built models to predict suicide attempts using machine learning approaches. The model developed with elastic net regularization distinguished individuals who had attempted suicide from those who had not with an AUC of 0.89, balanced accuracy 81.86%, specificity 89.22%, and sensitivity 74.51%. A diagnosis of borderline personality disorder, posttraumatic stress disorder, and being of Asian descent were the most important predictor variables. These approaches are important because they allow the implementation of these algorithms for the general population and not just for specific samples.

Another strategy that could be used in machine learning-based suicide risk assessment is the use of social media, an everyday user-generated behavior in a naturalistic environment. The popularity of social media platforms, such as Facebook or Twitter, has created opportunities to mine large datasets, with natural words and non-words language, and with data from non-treated or non-diagnosed individuals. A case-control study [51] trained a random forest model using twitter data and neural network outputs to predict binary suicidal ideation status. They used 512,526 tweets from 283 suicidal ideation cases and 3,518,494 tweets from 2655 controls and used twitter data queried against suicide-associated psychological constructs including burden, stress, loneliness, hopelessness, insomnia, depression, and anxiety. The model predicted 830 suicidal ideation events derived from an independent set of 277 suicidal ideators relative to 3159 control events from 2961 controls with an AUC of 0.88. The model also generated temporal prediction of risk such that peak occurrences above an individual-specific threshold denote about sevenfold increased risk for suicidal ideation within the following 10 days.

A group of researchers [52] detected suicide risk from textual Facebook posts using Artificial Neural Network and ELMo, a deep Contextualized Word Embeddings algorithm. The dataset included 83.292 postings authored by 1.002 authenticated Facebook users, alongside valid psychosocial information about the users and eight psycho-diagnostic measures collected directly with the participants. They used two models to predict suicide risk, the Single Task Model built from Facebook postings directly (Facebook texts→suicide) and a Multi-Task Model, which included Facebook postings and hierarchical, multilayered sets of theory-driven risk factors (Facebook texts→personality traits→psychosocial risks→psychiatric disorders→suicide). The average prediction performances of the single task model was significantly higher than chance level, with AUC around 0.62, and the multilayered prediction demonstrated substantial improvements in prediction accuracy, in comparison with the single task model and with the previous efforts in the literature to predict suicide risk without machine learning and natural language processing methods.

Interestingly, additional findings of this study [52] concern the most relevant words to the model developed. The results indicated that the most distinctive words of the true positive class consisted of negatively charged words such as “bad,” “worst,” including swear words as “bitch,” “fucking,” words referring to feelings of distress as “mad,” “cry,” “hurt,” “sad,” and to physical complaints as “sick,” “pain,” “surgery,” and “hospital.” In contrast, the most distinctive words of the true negative class consisted of positive words such as “great,” “happy,” “perfect,” including positive emotions as “loving,” “love,” “peace,” positive events as “wedding,” “thanksgiving,” positive experiences of belonging and friendships as “together,” “friends,” “mother,” “wife,” and positive attitude towards life as “blessed,” “gift,” and “wishes.” Another dominant theme in the postings of these true negative users was related to religion and spirituality, which can represent the protective factors associated with suicidal behaviors. In addition, suicide-related words, such as “kill,” “die,” or “suicide,” did not appear in this list and, of 73 mentions of these words, only in a single instance they appeared in messages directly related to suicide, which represent that the language may not be mentioned explicitly.

Predicting the risk of suicide at the individual level is essential for the application of adequate preventive strategies only in those who are in need of these interventions. For instance, a study [53] have tested the feasibility and acceptability of Proactive Suicide Prevention Online (PSPO), a new approach based on social media that combines proactive identification of suicide-prone individuals with specialized crisis management. They first located a microblog group online. Their comments on a suicide note were analyzed by experts to provide a training set for the machine learning models for suicide identification. The best-performing model was used to automatically identify posts that suggested suicidal thoughts and behaviors. A total of 27,007 comments were analyzed and 2786 (10.32%) were classified as indicative of suicidal thoughts and behaviors, with the detection model with high precision (0.86) and accuracy (0.88). Next, a microblog direct message containing crisis management information, including measures that covered suicide-related issues, depression, help-seeking behavior, and an acceptability test, was sent to users who had been identified by the model to be at risk of suicide. For those who replied to the message, trained counselors provided tailored crisis management. In a comparison of the frequency of word usage in their microblog posts 1 month before and after the consultation, they found that the frequency of death-oriented words significantly declined while the frequency of future-oriented words significantly increased.

Another growing area of study involves the acoustic-prosodic properties of a speech signal, which are modulated with a range of health-related effects [54]. In a prospective, multimodal, multicenter, mixed demographic study [55], machine learning algorithms were used with the subjects’ words and vocal characteristics to classify 379 subjects recruited from two academic medical centers and a rural community hospital into one of three groups: suicidal, mentally ill but not suicidal, or controls. By combining linguistic and acoustic characteristics, subjects could be classified into one of the three groups with up to 85% accuracy. Another study [56] was conducted to explore the feasibility of incorporating previous study procedures in the prediction of the level of suicide risk in adolescent mental health therapy

sessions, by capturing and classifying their language using machine learning methods. They collected 267 interviews from 60 students in eight schools, with 29 students indicating suicide or self-harm risk. During external validation, models were trained on suicidal speech samples collected from two separate studies. In their results, they found that the *extreme gradient boosting* model presented the best performance, with an AUC of about 0.78, concluding that voice collection technology and associated procedures can be integrated into mental health therapists' workflow.

Challenges and Limitations

Even though there are countless potential benefits of applying big data and machine learning tools in the prediction of suicide risk, including the potential of changing an extreme scenario, which is the rising trend in suicide deaths [57], there are some challenges and limitations that need to be acknowledged. Such limitations prevent the translation of this novel and revolutionary scientific knowledge into complex clinical settings, and policy making contexts [37, 58].

Machine learning models greatly benefit from large, representative and reliable datasets [28, 31]. Nevertheless, the collection of these high-quality and large datasets in medical sciences is time consuming, expensive, and a complex procedure [28]. In addition, there is a need for not only high-quality data but also homogeneous datasets from multiple sources, which will allow the generation of reliable and generalizable prediction models, as well as the generation of replicable results in published studies [28]. The sharing of datasets, with the creation of specific protocols for data collection and sharing, would help in addressing some of these challenges.

Another limitation, mainly in terms of translating the knowledge to clinical settings, concerns the understanding and interpretability of the models. Some sophisticated machine learning algorithms, such as *deep learning*, are inherently complex, working sometimes as a "black-box," in such a manner that the human counterparts will not be able to fully explain how the algorithm produced a specific model or result [31, 59]. However, new local explanation methods have been developed, including SHapley Additive exPlanations (SHAP), to explain variable contributions at the individual level. SHAP uses the variable contributions to generate a low-dimensional space with a dimensionality reduction technique, and then attempts to find clusters in an unsupervised way. Moreover, this method captures interaction effects between features and allows for directly monitoring the impact of individual features on model loss [60].

In addition, considering the relative novelty of this field in psychiatry, healthcare professionals and patients, who are not familiar with these concepts yet, are expected to have trouble understanding the models and initially react with skepticism regarding the use of these tools in clinical practice [31, 58]. Therefore, it is essential to invest in educational efforts, with the aim of facilitating the integration of these methods in practical settings.

Another limitation concerns the low positive predictive value of machine learning models in the prediction of suicide [61]. However, it is debated by some authors that a number of the current existing models for prediction of suicide attempts present predictive values equal to, or greater than, those of widely accepted risk prediction tools [62]. Besides that, it is important to highlight that several medical interventions are performed in clinical practice in spite of presenting a low positive predictive value [62].

The psychiatric categorical diagnosis is another limitation that is important to acknowledge. Most diagnostic categories are heterogeneous, lack scientific consistency, and are not based on solid evidence, and there is a considerable overlap among symptoms from psychiatric disorders of different nature [25, 28, 31]. Nevertheless, this is a limitation which may be addressed with the generation of more accurate explanatory models for each disease with the aid of machine learning tools; additionally, unsupervised algorithms may help in the clustering of symptoms and other clinical features into more data-driven diagnostic categories.

Ethical Implications of Machine Learning and Big Data Applications in Suicide Risk Assessment

In addition to the limitations and challenges, it is also essential to consider eventual ethical implications of using big data and machine learning models in the evaluation of suicide risk. For instance, considering the sensitive characteristics of the data related to suicidality, it is essential to create ethically adequate protocols and procedures for data access and sharing, also anonymizing the data so as to not expose sensitive data from individual patients [28]. In addition, it is of vital importance to consider how health insurance companies will handle these predictive models and their predictions, with the potential of stratifying health coverage prices according to machine learning-based classifications; these predictions, if not carefully regulated, have the potential of increasing social discrimination and inequalities [28, 58, 63].

Other two implications are even more relevant in cases of suicide risk assessment. The first one concerns a big challenge that will need to be addressed in clinical use of these tools, which is the eventual false positives and false negatives that may arise after these predictions [58]. Moreover, it is necessary to consider the eventual iatrogenic effect of an individual patient getting to know about his high predicted suicide risk. These predictions may affect negatively the patient's life expectations, increasing hopelessness, which ultimately may even increase the risk of suicidal behavior [28, 31].

Conclusion

Suicide remains a complex and urgent public health issue, accounting for hundreds of thousands of deaths each year around the globe. One of the main challenges to overcome involves the early identification of individual patients at increased suicide risk. Accurate detection of those at risk is needed to triage patients to specialized care in a targeted way. In this context, big data and machine learning models provide exciting avenues to potentially bridge these gaps and change this tragic scenario. While the field remains in its infancy, a standardization of ethical and technical considerations will be required prior to translation into clinical settings. Nonetheless, recent studies exploring these methods for the assessment of suicide risk have yielded promising results and present a great deal of potential in transforming this unfortunate scenario.

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Chapter 12
Electronic Health Records to Detect Psychosis Risk

Dominic Oliver and Paolo Fusar-Poli

Precision medicine tailors clinical recommendations and/or treatment to the individual, informed by data from sources that include sociodemographics, diagnoses and environmental risk/protective factors [1, 2]. Precision medicine approaches in psychosis are becoming increasingly relevant to improve outcomes, with only half of people with schizophrenia receiving care for the condition [3] and a lack of improvements in recovery rates and associated disability under standard care [4, 5]. While antipsychotic treatment can reduce the severity of symptomatology, they are unable to affect outcomes [6]. As such, early detection and intervention are imperative to affecting the clinical course of the disorder [7]. Leveraging the information available in electronic health records (EHRs) allows for prognostic models that can screen individuals at scale and aid early detection efforts in psychosis to improve outcomes. EHRs can contain diverse and detailed patient information across primary and secondary healthcare systems and can therefore offer unique opportunities to inform individual-level prediction of psychosis. This chapter will

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outline the current strategies to detect individuals at risk for psychosis and their limitations before outlining how prognostic models using EHR data have attempted to address this and the future of the field.

Primary Indicated Prevention and the Clinical High-Risk State

Over the past two decades, there has been increasing interest in the possibility of primary indicated prevention (i.e. targeting individuals identified as having signs or symptoms that indicate increased risk of developing a disorder) through the clinical high risk for psychosis state (CHR-P) [8]. CHR-P individuals are help-seeking, experiencing attenuated positive psychotic symptoms (unusual thought content, non-bizarre thinking, perceptual abnormalities and disorganised speech) accompanied by functional impairment [8]. Approximately 50% of first episode psychosis (FEP) patients retrospectively report experiencing a prodromal phase prior to the onset of their first episode [9–12], highlighting a clear clinical opportunity for indicated prevention in this population [7]. The CHR-P construct is now well-developed, with the National Institute for Health and Care Excellence (NICE) regarding assessment, treatment and monitoring of CHR-P individuals as an essential component of early intervention for psychosis [13]. Guidelines are similar internationally, leading to the CHR-P construct being well implemented with 47 specialist CHR-P services providing care to over 20,000 CHR-P individuals worldwide [14].

Preventing transition to a psychotic disorder is a key aim of CHR-P clinical services and the main clinical outcome that has been examined in CHR-P research [15]. The CHR-P state provides a unique opportunity to alter the trajectory of psychotic disorders before symptoms or pathophysiology becomes too severe and enduring [6]. Meeting CHR-P criteria is associated with a greatly increased risk of developing psychosis, with 22% of individuals transitioning to FEP within 3 years of presenting to services [16]. In addition to the long-term aim of preventing transition, in the shorter term, CHR-P services also aim to reduce the severity of the presenting attenuated positive and negative symptoms and to improve quality of life and impairments in social and vocational functioning. If an individual with CHR-P develops psychosis, early detection services can quickly refer them to FEP services and start antipsychotic treatment. The greater the length of time between psychosis onset and the provision of adequate antipsychotic treatment (the duration of untreated psychosis; DUP) [17], the worse the clinical [18–22], cognitive [21, 23, 24] and social outcomes in FEP [21, 23, 25]. CHR-P services can thus provide a very effective way of reducing DUP, thereby improving outcomes after psychosis onset [26].

Overall, the real-world impact of the CHR-P construct is dependent on three concatenated factors: (1) Efficient detection of individuals at risk of developing psychosis, (2) Accurate prognostication of clinical outcomes and (3) Effective preventative interventions.

This chapter will detail current strategies for detecting individuals at risk for psychosis, the limitations of those strategies and introduce potential solutions for these issues using EHRs.

Challenges of Detecting Individuals at Risk

Efficient detection of individuals at risk of developing psychosis is the first key rate-limiting step in permitting effective preventative intervention. The impact of preventative treatment will be modest if it can only be provided to a small proportion of those at risk. Unfortunately, current detection methods are suboptimal.

The first challenge associated with identifying individuals at risk is that the CHR-P state is not necessarily the prototypical pre-psychotic stage. While the majority of FEP patients have some form of CHR-P features, approximately one-third of FEP patients do not experience a CHR-P stage [27, 28]. This can often be attributed to a short-lived psychotic episode lasting a few weeks [29]. Therefore, if identification is entirely contingent on recognising the CHR-P state, then it is unlikely for all future FEP cases to be detected prior to psychosis onset. It is evident that to expand our approach to potentially identifying all FEP patients prior to psychosis onset, then CHR-P assessments will need to be supplemented with information from other sources.

The second challenge is that the current detection strategies for CHR-P services could be more efficient. Detection approaches vary widely between clinical services, with some relying solely on clinical referrals and others running intensive outreach campaigns. There have been various specific interventions within early intervention programmes to improve detection of FEP patients [30, 31] and CHR-P individuals [32, 33]. These were defined by the LYRIKS study: screening assessments and recruitment (outpatient and satellite clinics, armed forces, private hospitals, government organisations, internet gaming shops and youth hubs) [34]; workshops involving various community partners such as counsellors and mental healthcare professionals [35]; roadshows; student internships; print media (brochures and posters, articles and advertorials, newsletter) [34, 36]; and social media (Facebook, Twitter, blogs, websites) [34]. Regardless of the characteristics of the recruitment strategy employed, at present services are only detecting between 5% [37] (UK) and 12% [38] (Australia) of future FEP cases prior to psychosis onset. Thus, the vast majority of individuals who develop a first episode of psychosis will not have had access to help and support that might have either reduced their risk of transition or improved their prognosis after psychosis onset.

This, in turn, has a knock-on effect in terms of the utility of the CHR-P assessment. The probability of an individual developing psychosis after the result of an assessment is known (post-test risk) is dependent on the characteristics of the assessments (e.g. Comprehensive Assessment for At Risk Mental States [CAARMS], Structured Interview for Prodromal Syndromes [SIPS]) themselves, in particular their sensitivity and specificity. However, on the basis of Bayes' theorem, the

post-test probability is also dependent on the probability of the individual developing psychosis before the test result is known (pre-test risk) [39]. While the average pre-test risk in those referred to CHR-P services is 15% over 38 months, substantially higher than the 0.1% seen in the general population over the same time period, the heterogeneity of pre-test risk is high (95% CI: 9–24%) [40]. This heterogeneity can largely be explained by variation in strategies of recruitment. Pre-test risk is high when outreach campaigns are designed to recruit samples that are enriched for risk and are directed towards mental healthcare services. Among these samples, self-referrals are relatively uncommon [40]. However, pre-test risk is diluted when outreach efforts are extended to the general public (e.g. through social media), resulting in high numbers of self-referrals [40]. This reduction in pre-test risk (i.e. a reduced prevalence in the sample) has a negative impact on the positive predictive value (PPV) of CHR-P assessments, meaning that a larger number of individuals will meet at-risk criteria, be treated by services but will not develop a psychotic disorder.

Overall, these findings indicate that any intervention to improve detection of CHR-P individuals prior to the onset of their first episode of psychosis should be systematic and encompass strategies that do not dilute pre-test risk.

Detection Strategies in Primary Care

The potential for primary care as a setting for psychosis prevention is high with 60% of adolescents and young adults seen by GPs at least once a year, rising to 90% when individuals have at least one medical condition [41]. Recognising this, the Royal College of General Practitioners guidelines stress the importance of identifying the early signs and symptoms of psychosis. Primary care is a common referral source for CHR-P [42], and a greater number of primary care visits prior to a diagnosis of a psychotic disorder may result in a shorter DUP in FEP patients [43]. Despite this, a qualitative study found that GPs perceive that they may not have the relevant skills to identify individuals who may meet CHR-P criteria, with some not familiar with the CHR-P construct [44]. This emphasises the importance of outreach to primary care services to promote understanding of attenuated psychotic symptomatology. In well-funded healthcare settings, intensive outreach schemes to inform GPs and promote referrals are feasible [42]; however this may not be the case in all settings. Primary care-focused prognostic models could be extremely useful to aid GPs in identifying appropriate referrals to CHR-P services. However, efforts must be made to mitigate against potential dilution of pre-test risk enrichment.

Prognostic models using clinical EHR variables could be a useful aid for GPs, with the early stages of developing a prognostic model for psychosis in primary care having already been completed by Sullivan et al. using data from the Clinical Practice Research Datalink (CPRD) [45]. These data are high quality with limited missing data [46] and are therefore an ideal source for developing and validating a primary care model. Candidate predictors were selected a priori based on

associations in the literature [45]. A sample of n = 11,690 FEP patients and n = 81,793 matched controls was used to assess associations for each of these symptoms with psychosis onset. Bizarre behaviour, suicidal, cannabis-associated problems, depressive symptoms, blunted affect, ADHD-like symptoms, OCD-like symptoms, social isolation, role functioning problems, mania, sleep disturbance and smoking-associated problems were all significantly associated with psychosis onset [45]. This study also found that cases consulted their primary care physician more frequently compared to controls, but there was an increase in the rate of consultations per month as psychosis onset grew closer [45]. These variables could be key in future prognostic models in primary care settings.

Similarly, Chen et al. [47] used latent class analysis on UK primary care EHRs to classify three distinct clusters of FEP patients prior to their diagnosis: (1) no or minimal symptoms; (2) affective symptoms and (3) multiple symptoms. In particular, those in the multiple symptoms cluster present with a range of morbidity prior to FEP and have high rates of consultations [47]. The median time of the earliest recorded symptom in the multiple symptoms cluster was around 4 years prior to FEP, highlighting that this group may be patients who could be identified sooner [47]. Contrasting to this, those in the no or minimal symptoms cluster suggest either insidious psychosis onset or limited use of primary care. Early identification of individuals in this cluster would require information from other sources. Supporting the findings of Sullivan et al. [45], the research team found that many patients who later go on to receive FEP diagnoses are generally actively help-seeking, consulting their GPs more frequently, particularly in the 12 months prior to diagnosis. This is a missed clinical opportunity that prognostic models may be able to take advantage of, providing GPs with information to identify at-risk patients early when they increasingly attend appointments seeking help.

Development and Validation of a Transdiagnostic Risk Calculator for Psychosis in Secondary Mental Health Care

Current methods of detection are unstructured and idiosyncratic, with a resultant dilution of pre-test risk enrichment [40]. This is particularly prescient in South London and Maudsley NHS Foundation Trust (SLaM), where 95% of individuals developing a FEP have not been detected during their potential CHR-P stage [37]. This is a clear missed clinical opportunity for preventing psychosis in individuals who are already under the care of mental health services. To rectify these limitations in detection while maintaining enrichment of pre-test psychosis risk, a transdiagnostic risk calculator for psychosis was developed and externally validated in SLaM [37]. SLaM is a mental health trust that provides secondary mental health care for 1.3 million people in four discrete London boroughs (Croydon, Lambeth, Lewisham and Southwark) [48]. The trust is paper-free with all clinical records available and maintained digitally. Patients' records are continually updated throughout their

care, regardless of referral to other services or discharge from SLaM care. A Clinical Record Interactive Search (CRIS) function was implemented in SLaM to allow for searching and analysing real-world, real-time, anonymised routine clinical information from mental health care for research purposes [48]. This also enhanced implementation potential as the transdiagnostic risk calculator could easily transition from being applied to retrospective CRIS data to prospective use in clinical routine, systematically screening the local EHR system.

The core characteristics of the risk calculator emphasise the strengths of this approach (Table 12.1). Being transdiagnostic, the approach allows for the use of this calculator outside of CHR-P samples, across different psychopathological domains. This approach can be applied to any patient receiving an ICD-10 index diagnosis of a non-psychotic mental disorder, thus overcoming the above limitations. The tool is also clinically focused, using predictors that are widely available and rarely missing in EHRs, thereby reducing additional burden on clinicians and patients. Furthermore, the model is lifespan-inclusive, meaning it can work across all ages (including the age range of peak of risk for psychosis). As the model leverages information from EHRs, screening can be automated. This automation has a number of benefits: it allows for screening on a large scale, it allows for standardised screening and reduces costs associated with use. This transdiagnostic risk calculator aimed to use clinical and sociodemographic variables routinely collected as part of clinical care, and therefore available in CRIS, to enhance implementation potential. Predictor selection was supported by a priori clinical knowledge and meta-analytical [49] evidence, as advised by model building guidelines [50, 51]. Age, gender, age × gender interaction, ethnicity and ICD-10 diagnosis were used in the model [37]. The model is presented in Table 12.2 below.

Table 12.1 Core characteristics of the transdiagnostic psychosis risk calculator

Lifespan-inclusive	Works with any age
Clinically based	Predictors selected through a priori clinical knowledge
Transdiagnostic	Works across all ICD-10 diagnostic spectra
Individualised	Individual subject-level risk estimates
Cheap	Predictors routinely collected by clinicians
Automated	Electronic health records as well as manual entry of predictors
e-Health	Implemented online
Scalable	Screens electronic health records at scale
Optimisable	Further refined by the inclusion of other predictors
Sequential testing	Can be used as part of a staged assessment framework
Implementable	Can be integrated with existing structures for use in clinical settings

Table 12.2 Statistics for individual predictor variables in the transdiagnostic risk calculator in the derivation data set

Predictor	HR	95% CI
Age (years)	1.011	1.001–1.017
Gender		
Male	1.764	1.298–2.399
Female	1	Reference
Age × gender (male)	0.988	0.981–0.995
Ethnicity		
White	1	Reference
Black	2.823	2.438–3.268
Asian	1.671	1.215–2.298
Mixed	1.839	1.276–2.626
Other	1.504	1.210–1.869
ICD-10 index diagnosis		
CHR-P	1	Reference
Acute and transient psychotic disorders	2.682	1.981–3.631
Substance use disorders	0.146	0.105–0.202
Bipolar mood disorders	0.839	0.598–1.178
Nonbipolar mood disorders	0.152	0.109–0.210
Anxiety disorders	0.107	0.077–0.148
Personality disorders	0.213	0.141–0.231
Developmental disorders	0.031	0.015–0.064
Childhood/adolescence onset disorders	0.039	0.025–0.061
Physiological syndromes	0.085	0.052–0.137
Mental retardation	0.086	0.049–0.151

CHR-P clinical high risk for psychosis, *HR* hazard ratio

A Cox proportional hazards model was used to assess the effects of these prespecified predictors on the transdiagnostic development of non-organic psychotic disorders and time to psychosis onset. The overall SLaM sample was split between development (Lambeth and Southwark; n = 33,820) and external validation (Lewisham and Croydon; n = 54,716) datasets in a non-random fashion to mitigate overfitting [37]. Significant sociodemographic differences between SLaM boroughs meant that validation in this fashion would allow for a more generalisable model. Model performance was good in the development dataset (Harrell's C = 0.80) and fair-to-good in the external validation dataset (Harrell's C = 0.79) (Fig. 12.1) [37].

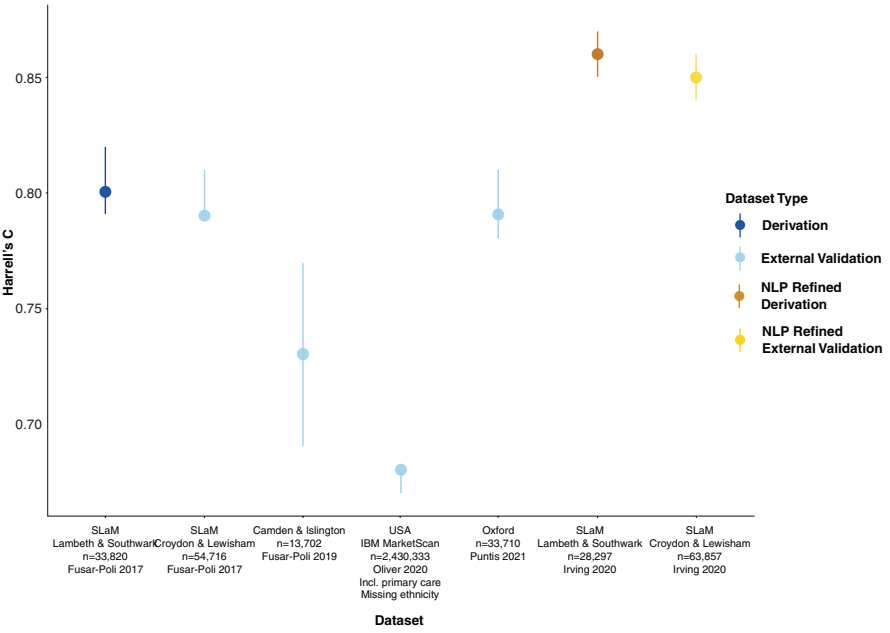

Fig. 12.1 Performance (Harrell's *C* and 95% CIs) of the original transdiagnostic risk calculator for psychosis in secondary mental health care and natural language processing (NLP) refined model in derivation and external validation datasets. Harrell's *C* is a measure of discrimination performance indexing the percentage of a model estimating a higher risk score to a case when a case and control are randomly drawn from the sample. Values near 0.5 indicate predictions are no better than chance; a value of 1 indicates perfect prediction in the sample

Replication of the Transdiagnostic Risk Calculator in Other Settings

While development of prediction models is extremely important, there is a large discrepancy between the number of published models and the subset that go on to be implemented in clinical care, both in psychiatry and in physical health. The transdiagnostic risk calculator was developed with clinical implementation in mind; it is, therefore, important to consider the barriers that impede other models. Successful translation of a model depends not only on its prognostic accuracy but also on its independent replication, and then an implementation process.

Precision psychiatry has enormous potential to improve patient care and outcomes. Although a relatively large number of individualised diagnostic and prognostic models for CHR-P individuals have been developed [52], very few of the initially positive findings from these have been replicated [53]. While discovery of new prediction models with strong discrimination remains important, replication has arguably become even more critical than discovery, particularly due to the scarcity of replications [54].

Replication is integral in psychiatric research for two key reasons. Firstly, published science has a statistical power issue at its core that results in a likely high

false report probability [53, 55]; therefore a replicated model is a more reliable model. Moreover, replication can provide evidence of clinical transportability [56] through demonstrating evidence of prognostic accuracy in different populations with different case mixes in settings with different care configurations. Despite these benefits, replication in early psychosis research is rare [57], and this dearth of replication restricts the possibility of clinical translation [54].

UK Replications

The transdiagnostic psychosis risk calculator has been replicated in two other UK settings, Camden & Islington (C&I) [58] and Oxford Health [59], which had key differences in populations and service configuration compared to SLaM.

Similar to SLaM, C&I (n = 13,702) is a large mental health provider in an urban environment in London; however, C&I does not have any CHR-P or child and adolescent services. Due to the lack of these services, the average age in C&I was 6.5 years older than in SLaM [58]. There were additionally fewer males and a lower proportion of patients of black ethnicity [58]. In terms of diagnoses, there were more substance use disorders, nonbipolar mood disorders, bipolar mood disorders and personality disorders in C&I compared to SLaM; however, anxiety disorders and physiological syndromes were less prevalent [58]. The cumulative incidence of psychosis was also higher in C&I compared to SLaM. Despite these differences in sociodemographics and cumulative risk, the risk calculator retained acceptable performance with a Harrell's C of 0.73 [58] (Fig. 12.1).

Meanwhile, Oxford Health (n = 33,710) is a secondary mental healthcare provider serving a more rural area compared to SLaM and C&I [59]. Similar to C&I, Oxford Health does not have specialised CHR-P services and additionally lacks substance misuse services. The Oxford Health dataset was composed of patients with lower average age, more likely to be female and white compared to SLaM [59]. In terms of diagnoses, there were a higher proportion of bipolar mood disorders, nonbipolar mood disorders, personality disorders, developmental disorders, childhood/adolescent disorders and physiological syndromes compared to SLaM; however, acute and transient psychotic disorders, substance use disorders and anxiety disorders were all less prevalent [59]. In addition, the cumulative incidence of psychosis was lower in Oxford Health compared to SLaM [59]. Despite these differences in sociodemographics and cumulative risk, the risk calculator retained adequate performance with a Harrell's C of 0.79 [59] (Fig. 12.1).

These validation studies have demonstrated the reproducibility and transportability of an individualised, clinically based transdiagnostic model for the automatic screening of EHRs and the detection of individuals at risk of psychosis. Despite key differences in case mix, service configuration and urban and rural geography, the model retained its performance in other UK settings, suggesting the risk calculator would be appropriate for use throughout the UK in routine secondary mental health care to improve detection of at-risk cases.

International Replication

Following these domestic replications, an international replication was completed in a US commercial insurance dataset [60]. A successful replication result in a US dataset would be encouraging for expanding the clinical utility of the transdiagnostic risk calculator to enable other countries with EHR infrastructure to improve detection of individuals at risk for psychosis through cheap, automated screening at scale. The US replication was the first replication of the transdiagnostic risk calculator outside of the UK and the largest replication study of a risk prediction model in psychiatry. The external validation dataset was from a commercial insurance database with several key differences from the derivation dataset, in particular country (US vs UK), care pathway (combination of primary and secondary care vs secondary care alone) and case mix. In addition to this, individual-level ethnicity data, one of the key predictors in the model, were not available. Instead, a composite ethnicity score was imputed on the level of the Metropolitan State Area (MSA) of each patient. Despite these differences, the transdiagnostic risk calculator performed significantly better than chance (Harrell's $C = 0.68$; Fig. 12.1), highlighting the transportability of the model.

Implementation of the Transdiagnostic Risk Calculator

Similarly, the gap between publication and clinical use of prediction models highlights the clear importance of implementation research: the scientific study of methods translating research findings into practical, useful outcomes. Implementation research seeks to understand and work pragmatically within real-world conditions, rather than trying to control for them [61–63]. Many methods of predicting psychosis risk are unlikely to be implemented into clinical care in the near future, partially due to pragmatic concerns relating to high costs (e.g. neuroimaging modalities), labour (e.g. cognitive tasks) or applicability (e.g. genetics). Implementation research aims at solving a wide range of practical problems relating to the real-world usability of precision medicine and digital health in clinical practice. For example, prediction models are unlikely to impact clinical pathways unless they are used by clinicians in day-to-day practice [64]; therefore clinicians' compliance with the recommendations made by a prediction model represents the first key barrier to implementation [65, 66]. Showcasing clinician adherence to the recommendations of the transdiagnostic psychosis risk calculator is an imperative step for it to be used effectively in clinical routine.

Previous research has shown that the transdiagnostic risk calculator has shown good-to-moderate prognostic performance in its external validations [37, 58] and theoretical clinical benefit by decision curve analysis [37]. Assessing the real-world clinical utility of the transdiagnostic risk calculator in clinical routine was therefore imperative. The first feasibility implementation study of a risk prediction model in

psychiatry demonstrated the potential for systematic detection of psychosis risk at scale [67]. Firstly, an in vitro phase involved clinician and service user engagement to identify and overcome implementation. Following this, the transdiagnostic risk calculator was integrated into the local EHR. In the in vivo phase, 3722 individuals accessing secondary mental health care with non-organic, non-psychotic disorders were automatically screened by the transdiagnostic risk calculator [67]. One hundred fifteen individuals were detected as being at risk, defined as ≥5% risk of developing a psychotic disorder within 2 years of index diagnosis by the risk calculator, and their responsible clinicians were contacted to recommend referral for a refined psychosis assessment [67]. Seventy-seven per cent of clinicians responded to alerts sent by the risk calculator and 85% with outreach [67]. Fifty-five per cent of these responses resulted in a referral for a refined psychosis assessment [67]. Further to this, the incidence of psychosis in those detected by the risk calculator was 12% within 6 months of individuals being detected, comparable to the level of risk seen in CHR-P individuals (10% at 6 months) [16, 67]. It is also important to note that the incidence of psychosis at 6 months was 14.7% in those not referred by clinicians, comparable to those referred. These findings add further support for the use of the transdiagnostic psychosis risk calculator in clinical routine as an automatic approach to systematically screen large-scale datasets and improve the detection of individuals at risk of developing psychosis.

In addition, the system of detection and alerting has been improved since the study through the migration to the CogStack system [68]. This permits real-time detection that updates every 10 min [68], compared to a once-per-week basis with the previous system. Additionally, whereas previously a member of the research team had to manually send alerts via email, CogStack can send alerts to clinicians automatically, reducing the logistical demands. This will be further enhanced with planned improvements to the existing EHR interface in SLaM, which should enable direct alerts to the relevant clinician on their personal dashboard. These advances can help further increase clinician adherence to the recommendations made by the transdiagnostic risk calculator and increase referrals of individuals detected to be at risk for psychosis. Prior work has laid the foundation for a prospective longitudinal study assessing the impact of the transdiagnostic risk calculator on the total number of FEP cases, early identification of FEP cases and the DUP in those detected to evaluate its real-world clinical utility.

Updating and Refining the Transdiagnostic Risk Calculator

Research in the field is continually developing, both in terms of statistical methods and evidence base, which provides us with the opportunity for improving prognostic models. As well as developing new models with revised information, it is also important to update existing models either by adding new predictors or refining existing predictors before re-validating the model [50].

For example, Natural Language Processing (NLP) can be used to extract data from free text within EHRs instead of pre-set categorical variables [69, 70]. This allows us to retrieve more detailed information from EHRs (e.g. symptomatology, prescribed medication, suicide attempts) and potentially use these as new predictors for psychosis onset. The transdiagnostic psychosis risk calculator has been refined through the addition of NLP predictors (agitation, appetite loss, cannabis use, cocaine use, delusions, disturbed sleep, guilt, hopelessness, insomnia, irritability, loss of insight, paranoia, tearfulness and weight loss) [70]. As the addition of large numbers of predictors can result in overfitting, a Least Absolute Shrinkage and Selection Operator (LASSO) penalty was implemented to shrink the coefficients of redundant predictors towards zero. This revised model was developed in an updated dataset from the same geographical area as the original model (Lambeth & Southwark, SLaM; n = 28,297) and similarly externally validated in the same geographical area (Croydon & Lewisham, SLaM; n = 63,853). Performance of the NLP-refined model was greater than the original in both development (Harrell's C = 0.86; Fig. 12.1) and validation (Harrell's C = 0.85; Fig. 12.1) datasets [70]. Using NLP applications to derive information on symptomatology, substance use and clinical details could be extremely useful in developing future prognostic models for psychosis.

Further to this, existing factors can be refined. In the original transdiagnostic psychosis risk calculator, age was represented in a linear form, i.e. the older the individual, the greater their risk. However, the relationship between age and psychosis is non-linear with a peak in risk between the ages of 15 and 34 [71]. A refined model was developed with non-linear modelling of age that may more accurately represent the time course of psychosis risk over the lifespan, and improved the discrimination (Harrell's C) of the original model from 0.79 to 0.81 [72].

Dynamic Risk Prognostication

Contrasting with these models that have adopted a static prognostic approach, dynamic approaches are able to update their individual-level risk estimates when new information becomes available. Dynamic approaches require more complex methods, such as deep learning, to map the associations and interdependencies between predictors compared to models solely using static predictors. Deep learning has previously been used in conjunction with EHRs to predict psychosis using a stacked denoising autoencoder on a test dataset of n = 704,857 patients with different disorders, achieving an AUROC of 0.853 in a test set of n = 76,214 patients [73]. However, this performance may be inflated due to previous diagnoses of psychosis and antipsychotic prescriptions were included as predictors [73]. Another example of deep learning in EHRs is Dynamic ElecTronic hEalth reCord deTection (DETECT), which leveraged recurrent neural networks to predict the risk of FEP 1 year prior to index date utilising demographics and dynamically collected medical events (e.g. diagnoses, prescriptions, procedures, encounters, admissions,

observations and laboratory test results) [74]. This study was based on EHR data from IBM Explorys, individual-level data collated from commercial healthcare providers in the United States that included primary and secondary health care [74]. The development dataset comprised of n = 51,015 FEP patients and n = 51,015 matched controls, with n = 21,845 FEP patients and n = 21,845 matched controls used as a validation dataset and the remaining n = 2287 FEP patients and n = 2483 matched controls used as an external validation subset [74]. DETECT showed adequate prognostic accuracy with an accuracy of 0.787 and an AUROC of 0.868 in the development dataset, an accuracy of 0.774 and AUROC of 0.856 in the validation dataset and a balanced accuracy of 0.724 and AUROC of 0.799 in the external validation subset [74]. Moreover, decision curve analysis in the validation dataset showed that detection informed by DETECT was associated with a positive net benefit for cost-benefit ratios below 1:3 when using a single-point risk assessment subset [74]. When this was repeated for continuous risk assessments over time, a positive net benefit was seen for cost-benefit ratios below 1:16 subset [74]. This study shows that it is feasible to utilise machine learning methods and EHR data to produce individualised, dynamic, real-time predictions of psychosis risk.

Conclusion

Current detection strategies for psychosis are idiosyncratic and inefficient. New approaches are needed to screen and identify individuals at risk for psychosis while preserving risk enrichment. EHRs provide detailed, individual-level data that is collected passively as part of clinical routine and ideally positioned for automated screening. A number of prognostic models have been developed and validated using data from primary and secondary care with both static and dynamically updating risk estimates. The feasibility of implementation in real-world clinical care has only been assessed in one model, a transdiagnostic risk calculator in secondary mental health care. Future work is needed to develop, refine and integrate different approaches to prognosticate psychosis onset, in addition to implementing and assessing their utility in clinical routine.

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Chapter 13
The Use of Artificial Intelligence to Identify Trajectories of Severe Mental Disorders

Francisco Diego Rabelo-da-Ponte, Taiane de Azevedo Cardoso, Flavio Kapczinski, and Ives Cavalcante Passos

Introduction

Recent decades have seen enormous progress in scientific literature of psychiatry through artificial intelligence techniques. Previously, the data were scarce containing few subjects and variables but that scenario has been changing nowadays [1]. The large amount of data produced by means of smartphones and genetic information, for instance, has built up complexity for the understanding of mental disorders. Sleep duration, step count, duration of time spent on social media, records of symptoms, and cognitive performance are some of the features that are collected in real time by smartphones. Clinically, the use of real-time information is highly relevant, since the clinician may monitor the patient's symptoms over time from a longitudinal view, rather than a cross-sectional perspective. Data associated with metabolomic and neuroimaging that use machine learning algorithms may provide a powerful tool to identify distinct trajectories of mental diseases [2].

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Machine learning, a branch of artificial intelligence (AI), is a method of data analysis based on the idea that a system can learn from data automatically, i.e., it reaches an optimal solution to a problem instead of being determined by a person [3]. The two most popular categories of machine learning in psychiatry are supervised and unsupervised learning. In supervised learning, the dataset is split into training and test sets. So, a mathematical model is built using the information presented in the training set and subsequently the model is tested in the test dataset to confirm whether the model "learned" accurately (Fig. 13.1). In other words, there are input and output variables (e.g., death—"yes" or "no") in the training dataset. The test dataset only shows the input variables and does not include the outcome. It is expected that the mathematical model built earlier will be able to predict who will or will not die using only the input variables [4]. In addition, the model identifies the probability that the event will happen for each subject. Supervised learning is applied to solve several problems such as spam classification and detection of diseases [4, 5].

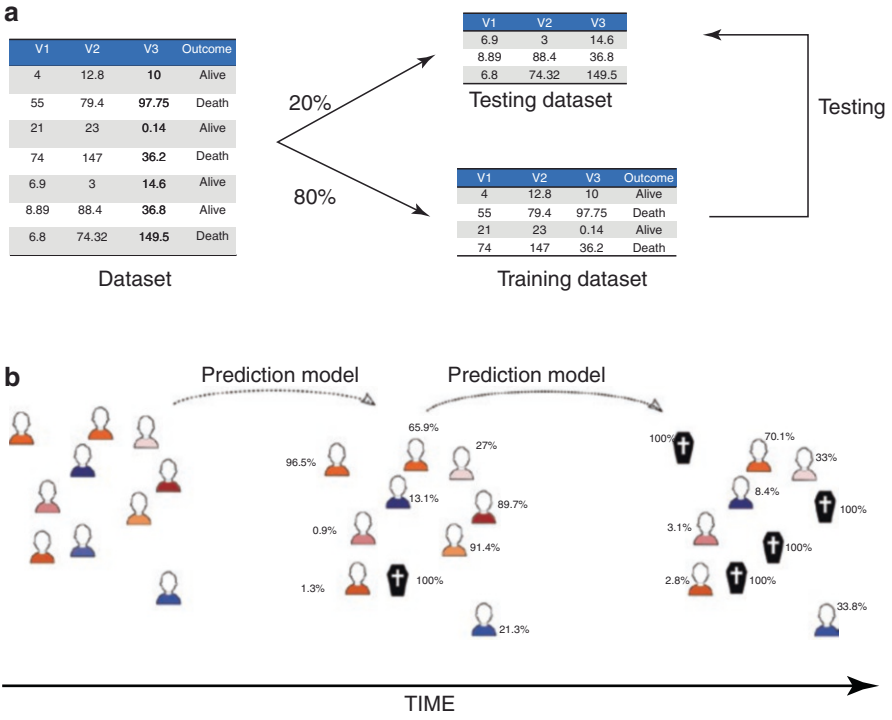

Fig. 13.1 Conceptual representation of the supervised machine learning approach. (**a**) The hold-out process is one type of strategy to validate a supervised machine model. Usually, the dataset is split into a training and a testing set and the testing set is used to assess how well the mathematical model performs on the "unseen" dataset. There are other strategies such as *k*-fold cross-validation, leave-one-out cross-validation, and nested cross-validation. (**b**) For each subject, the machine learning model estimates the probability of a specific outcome at the individual level

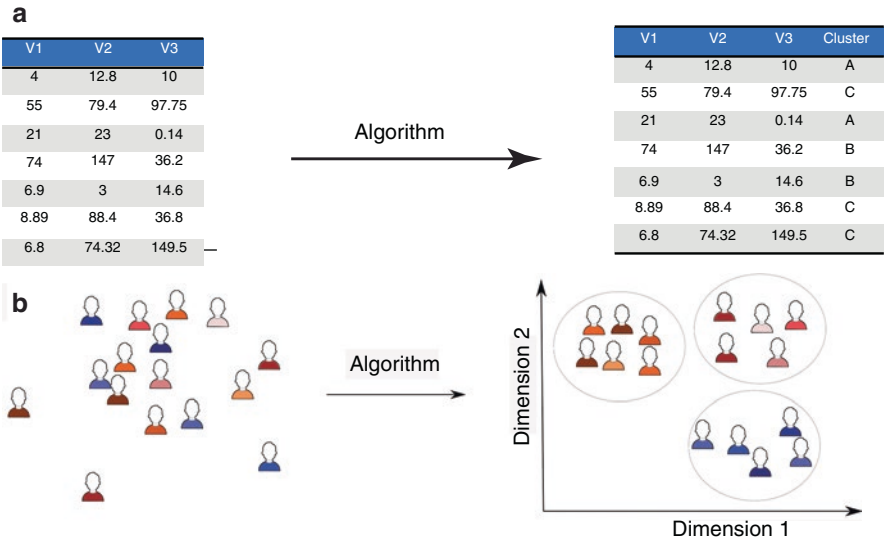

Fig. 13.2 Conceptual representation of the unsupervised machine learning approach. (**a**) The unsupervised machine learning algorithm identifies different subgroups according to their similarities and divides them based on their dissimilarities. (**b**) A clustering algorithm is applied to divide an unlabeled sample into groups labeled by color

Unsupervised learning, on the other hand, does not have an outcome to be learned. That is, it identifies unknown patterns in a database without an outcome (Fig. 13.2). The algorithm is able to group similar subjects and separate distinct individuals using the input variables. Unsupervised learning has been applied to identify different types of consumer behavior or to classify cognitive clusters among subjects with psychiatric disorders [6, 7].

Notably, machine learning methods can identify subgroups of subjects within a diagnosis and predict treatment response or future outcomes such as suicide attempts or psychotic episodes at the individual level. In relation to prognosis, traditional stepwise regression methods are not recommended because of the estimation bias that is critical in small sample size [8]. The estimation bias may lead to poor clinical prediction since the model is built in the same data [8]. Thus, machine learning methods move psychiatry beyond the evidence-based group level, into a more personalized precision psychiatry [9]. Clinicians can then apply these tailored interventions to change the disease trajectory of a subject before the illness onset or before a worse clinical outcome is in place. At this point, the patient will receive an accurate diagnosis and appropriate treatment, avoiding delays in diagnosis and the economic burden for multiple ineffective therapeutic interventions [10]. The purpose of this chapter is to provide a framework for understanding the role of artificial intelligence in predicting clinical trajectories of severe mental illnesses.

Bipolar Disorder

Bipolar disorder (BD) is a chronic and severe disease associated with high rates of morbidity and mortality, considered to be one of the main causes of disability worldwide. The functional impairment among patients is so severe that they have a shorter life expectancy with a decrease of approximately 10–20 years of life [11]. BD is defined by the presence of manic or hypomanic episodes and/or depressive episodes. The estimated global lifetime prevalence of BD-I is 0.6–1.0% and BD-II is 0.4–1.0% [12]. It is well known that more than 70% of subjects with BD show symptoms of the disease before the age of 25 years [13, 14]. However, the accurate identification of individuals with BD is still a clinical challenge, since there is a delay of 6 years between the first episode and the formal diagnosis [15]. This delay has a harmful effect on course of the disorder, because subjects with BD are 20–30 times more likely to die by suicide compared to the general population [16, 17]. Additionally, the lifetime prevalence of suicide attempts is 30–50% among adults with BD [16, 17]. It is known that suicide is a preventable outcome, and efforts have been made to identify the predictors of suicidality in individuals with mood disorders. For instance, a study including 144 individuals with mood disorders assessed the predictors of suicide attempts using machine learning techniques [18]. This study predicted suicide attempts with an area under the curve (AUC) of 0.77, and the main predictors of suicide attempts among individuals with mood disorders were: a high number of previous hospitalizations for depression, a history of psychosis, cocaine dependence, and post-traumatic stress disorder (PTSD) [18]. Hence, an accurate identification and the use of proper treatment such as lithium, a well-established medication with anti-suicidal effects, could decrease the risk of suicide among subjects with BD [11].

Moreover, some studies have been suggesting an association between the number of (hypo)manic episodes and cognitive or functional decline over time [19–21]. There is a model that proposes BD as a progressive disease but this is still a controversial topic, because some evidence does not support the neuroprogressive model [22]. However, some authors claim that BD is a highly heterogeneous disease, which may explain these divergences. For instance, around 60% of patients have some cognitive deficits and some patients had reduced gray matter volume in the right ventral prefrontal cortex, temporal cortex, and right fronto-insular cortex [19–21].

Recent machine learning techniques have shed light on the distinctions between subjects with BD through the use of cluster analysis. This approach allows for the identification of subgroups within groups of individuals that have the same diagnosis. Hence, a recent meta-analysis of 24 studies assessing cognitive clusters indicated the presence of three cognitive subgroups among subjects with BD: individuals presenting cognitive performance similar to unaffected individuals (32–48% of individuals with BD); participants with some impairments in specific neuropsychological domains (29–40% of individuals with BD); and subjects with multiple cognitive domains impaired (12–40% of individuals with BD) [23]. Among the

cognitive impairment clusters, deficits were found in neuropsychological functions such as verbal memory, executive function, and/or verbal fluency [24, 25]. Nevertheless, the degree of impairment is more important than the type of cognitive function affected, because the level of cognitive dysfunction may be a phenotype associated with different illness characteristics [26]. A recent cross-sectional study investigated the cognitive heterogeneity of subjects with BD and found three distinct clusters using the unsupervised technique [27]. Among these clusters, 35.3% of patients had cognitive performance similar to healthy controls, 34.7% had selective impairments, and 29.9% had severe impairments. Subsequently, the authors applied a supervised algorithm to identify clinical markers of severity among cognitive clusters and found that years of education, number of hospitalizations due to a severe mood episode, and age were the most relevant variables to separate the cognitive subgroups [27].

In light of this evidence, a 5-year longitudinal study found that a higher number of (hypo)manic episodes are related to poorer global cognitive functioning, working memory, and visual memory [28]. The authors suggest that the progressive course of BD may be common in a subset of individuals with BD. The association between mood episodes and cognitive impairment is still unclear, but a meta-analysis including 6859 patients with BD showed that individuals with BD have a higher risk of progression to dementia than controls [29]. Furthermore, the number of mood episodes was determined to be a predictor of dementia in BD [29]. The effects of mood episodes on the brain have been reported in several studies, which indicate a biological basis for clinical progression in BD. Alterations in hippocampal volume, frontolimbic system, cerebellum, and corpus callosum were associated with a higher number of mood episodes [30]. Machine learning approaches may be highly useful for identifying particular brain regions related to distinct stages of progression in BD. Additionally, a study using supervised machine learning algorithms found that late-stage BD patients had a lower cerebellar white matter density than healthy control individuals but, intriguingly, that difference was not found among early-stage BD compared to unaffected participants [31]. These findings suggest that the brain changes in BD vary depending on the stage of disease.

Similar results were found in peripheral biomarkers. Patients with late-stage BD presented high levels of inflammatory markers such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), as well as low concentrations of brain-derived neurotrophic factor (BDNF) compared to subjects at early stages [32, 33]. The differences between early and late stages indicate that multiple mood episodes trigger an elevated production of proinflammatory cytokines that exceed the capacity of biological systems to recover homeostasis and to repair the damage [33]. As BD is a heterogeneous illness, machine learning techniques hold promise for improving the prognosis and early detection of BD through the identification of a potential biomarker set. Recent studies using supervised models have compared BD, other mental disorders, and healthy control subjects to determine differential biomarker signatures. In summary, these reports pointed out eotaxin-1 (CCL11), glutathione S-transferase, BDNF, and TNF-α as the main peripheral biomarker signatures among individuals with BD [34–36]. Nevertheless, small sample sizes,

cross-sectional designs, and the lack of potential confounders such as smoking, medication use, or body mass index may be important limitations that hinder the clinical translation of these results.

Moreover, nonspecific symptoms appear before the full manifestation of BD [37]. Longitudinal studies with subjects at an ultra-high risk for BD found that those individuals manifested nonspecific childhood symptoms such as sleep problems, anxiety, attention-deficit hyperactivity disorder (ADHD), learning disabilities, and motor disabilities. Subsequently, the clinical manifestations shift to internalizing symptoms under stress, followed by depressive disorders, and finally the first manic episode [38]. Hence, the development of clinical risk calculators through machine learning is highly promising to detect those subthreshold manifestations before the transition to BD. A recent 22-year birth cohort study that assessed 3748 participants predicted BD 4 years before the formal diagnosis with good performance measures using a machine learning algorithm [39]. The most important variables to predict BD were suicide risk, generalized anxiety disorder (GAD), and parental physical abuse.

Major Depressive Disorder

Major depressive disorder (MDD) is a common mental disorder that affects about 4.7% of the population, worldwide [40]. A recent systematic review showed that the main sociodemographic factors associated with MDD were marital status (separated/divorced) and female sex [41]. This systematic review also showed that childhood trauma and comorbidity with physical and mental disorders were associated with MDD [41]. It is known that MDD is a highly disabling disorder. In this sense, a recent study showed that mood disorders were associated with elevated and early rates of disability services [42]. In addition, MDD is the third leading cause of disability according to the Global Burden of Diseases, Injuries, and Risk Factors Study 2017 [43].

Many sociodemographic and clinical characteristics have been associated with different clinical trajectories in MDD. However, these findings are based on group comparisons with unknown translational applicability. Machine learning techniques may help to identify characteristics associated with the clinical course of MDD at an individual level. For instance, a 5-year longitudinal study including 544 adolescents aged 14 years at baseline showed that the AUC to predict depression onset ranged between 0.70 and 0.72 in the training dataset, and between 0.68 and 0.72 in the independent validation sample [44]. The predictors of depression onset were baseline severity of depressive symptoms, female sex, neuroticism, stressful life events, and surface area of the supramarginal gyrus [44]. In addition, a prospective cohort study including 15,105 civil servants aged 35–74 years from Brazil found that 499 (3.58%) individuals presented with a new depressive episode at follow-up [45]. The machine learning model was trained to differentiate these incident cases from the non-depressed patients at follow-up [45]. The model had an AUC of 0.71

(0.66–0.77), and the predictors of incident depression were obsessive compulsive disorder (OCD), GAD, use of antidepressants, use of benzodiazepines, and sex [45]. Finally, a longitudinal study including 1538 elderly subjects found that activities of daily living, self-rated health, marital status, arthritis, and number of individuals cohabiting together were the most important predictors for depression, with an AUC = 0.629 [46]. Altogether, these data demonstrate that the predictors vary across studies. It is important to highlight that the aforementioned studies included individuals from different age ranges, which may explain some of the differences found.

In the context of mood disorders, an important challenge in the clinical setting is to differentiate unipolar depression from bipolar depression due to its similar clinical manifestations [47]. In this sense, recent studies aimed at distinguishing unipolar depression from bipolar depression using clinical and biological data coupled with machine learning techniques were conducted. A recent study including 81 currently depressed patients with BD, 127 currently depressed patients with MDD, and 32 healthy control individuals assessed whether immune-inflammatory biomarkers could help to differentiate unipolar depression from bipolar depression [36]. The study showed that the immune-inflammatory signatures differentiated the two disorders with a high accuracy (AUC = 97%). MDD diagnosis was predicted by high levels of markers related to both proinflammatory (i.e., IL-1β, IL-6, IL-7, IL-16) and regulatory responses (IL-2, IL-4, and IL-10), whereas BD was predicted by high levels of inflammatory markers (CCL3, CCL4, CCL5, CCL11, CCL25, CCL27, CXCL11, IL-9, and TNF-α) [36]. Similarly, another study showed that the comparison between bipolar depression and unipolar depression achieved an AUC of 0.69 using three selected biomarkers (interleukin-4, thiobarbituric acid reactive substances, and interleukin-10) [35]. Finally, another study differentiating BD (n = 126) from MDD (n = 187) found an AUC of 0.92, with the following clinical characteristics as the main predictors of BD: elevated mood, grandiosity, talkativeness, recklessness, and risky behavior [48]. The findings from this study are relevant to clinical practice, considering that the evaluation of these core clinical features can be easily administered by a digital self-report tool, thus contributing to a more accurate diagnosis.

Although the disease courses are heterogeneous, there is evidence for clinical progression in both MDD and BD [49]. This clinical progression is marked by an increased risk for recurrent episodes and an increased risk to develop dementia [49]. In this sense, recent studies used machine learning techniques to detect the potential predictors of this clinical progression, in order to design preventive strategies for the most vulnerable populations. One study which aimed to predict rehospitalization within 2 years of initial admission for a major depressive episode found that a multimodal panel containing structural imaging, blood biomarker, clinical, medication type, and sleep quality predictors achieved a test AUC of 67.74 [50]. In addition, a recent study used a machine learning model to estimate brain age from MRI data, which was compared to chronological age to determine the brain age gap [51]. This study assessed a midlife and an older cohort and found that the older adults with depression had significantly higher brain age gaps than the older adults without depression, while no differences were found in the midlife cohort [51]. Only in the

older cohort, an association between brain age gap and poorer cognitive performance was observed, showing that increased brain age gap is associated with greater disability [51]. These data demonstrate that unlike midlife depression, geriatric depression exhibits accelerated brain aging, which in turn is associated with cognitive and functional deficits [51].

There is also increasing interest in clinical predictive algorithms in psychiatry focusing on developing risk calculators to guide personalized diagnosis and treatment. A meta-analysis aimed at describing previous studies assessing the predictors of therapeutic outcomes in individuals with mood disorders using machine learning techniques found that the overall pooled estimate of classification accuracy for predictive models was 0.82 [52]. More specifically, they assessed four predictor variable categories, as follows: neuroimaging, phenomenological (e.g., psychometric, neurocognitive, anthropometric, sociodemographic, psychiatric history), genetic, or combined (e.g., neuroimaging and phenomenological; genetic and phenomenological) [52]. The classification accuracy was greatest among models with a combined predictor variable (0.93) when compared to neuroimaging predictors (0.85), phenomenological predictors (0.76), and genetic predictors (0.68) [52]. However, it is important to highlight that only two studies assessed combined predictors [52].

A recent meta-review showed that no single variable was found to consistently predict treatment response across multiple reviews [53]. In addition, this meta-review highlights that clinical prediction models were generally not validated in external populations, reinforcing the need for models with adequate external validation [53]. A more recent study assessed the predictors for treatment response and remission in individuals with MDD after up to 8 weeks of pharmacological treatment [54]. Treatment response was predicted with an optimal accuracy of 0.69 [54]. The predictors for treatment response were age of disease onset, overall duration of illness, severity of depressive symptoms at baseline, number of previous hospitalizations, functioning at baseline, suicidality, and other specific depressive symptoms [54]. Remission was predicted with maximal accuracy of 0.62, and the predictors for remission were recurrent episodes, the duration of the current episode and of the illness, emotional symptoms at baseline, symptoms of depersonalization and derealization, symptoms related to appetite, cardiac, gastrointestinal and other somatic conditions, as well as delusions, traits of neuroticism, extraversion, tolerance, and education level [54].

Schizophrenia

Schizophrenia is a severe mental disorder that affects 1% of the population, worldwide [55]. Despite the low prevalence, schizophrenia is one of the leading causes of disease burden in terms of mental disease [55]. Subjects with schizophrenia experience alterations of thought, hallucinations, delusions, apathy, and poor self-care, which can account for severe impairment in psychosocial functioning [56]. The psychosocial impairment in this population is a highly relevant factor for clinicians

since only 10–15% of individuals with schizophrenia are in paid jobs [57]. Antipsychotic medications are the main pharmacological treatment for schizophrenia but not all psychotic symptoms respond properly to these drugs [55]. Furthermore, only 1 in 7 individuals with schizophrenia achieve a full recovery [58]. Unfortunately, the suicide rate among subjects with schizophrenia is substantially high and thus, individuals with schizophrenia die approximately 15 years earlier than the general population [59, 60].

Individuals who develop schizophrenia tend to manifest subtle behavioral alterations during childhood and adolescence such as cognitive and social impairment, as well as anxiety and depressive symptoms [61]. These subtle changes in mental functions before the onset of a full-blown psychotic episode occur in about 20–35% of individuals aged 12–35 years [62]. Moreover, a recent meta-analysis pointed out that psychotic disorders may emerge in subjects who do not present a clinical high risk for psychosis (CHR-P) or subjects with CHR-P may develop other disorders such as BD or OCD [63]. There has been increasing effort to shift away from the CHR-P approach to a subject-level model using machine learning techniques to accurately identify those that will develop full psychosis [64]. Such an approach may improve the early detection, the understanding of illness trajectories, and the development of preventive therapeutic interventions for psychotic disorders. Hence, a recent longitudinal study assessed participants with CHR-P and recent-onset depression using clinical, cognitive, neuroimaging, and genetic data to detect psychosis through machine learning algorithms [65]. The report showed that the algorithm achieved good performance measures to predict psychosis (balanced accuracy: 85.5%; sensitivity: 84.6%; specificity: 86.4%) [65]. Another study developed a risk calculation model for prodromal psychosis 2 years before the first episode [66]. The probability of conversion to psychosis was 16% during the span of 2 years [66]. Some variables such as unusual thought content and suspiciousness, poor psychosocial functioning, as well as lower verbal learning and memory contributed to an increased risk of psychosis [66].

Moreover, another important point is the high prevalence of cognitive alterations in subjects with schizophrenia. Cognitive deficits and poor academic performance may be present at an early age, being considered as an important risk factor for developing schizophrenia [67]. These cognitive impairments might persist throughout one's lifespan in some cases, impacting quality of life, social functioning, and employability [7]. Thereby, some reports suggest that there is a wide cognitive heterogeneity in schizophrenia [7]. There are three cognitive clusters among schizophrenia subjects as pointed out by a systematic review: 25% of individuals with relatively intact cognitive function, 31% of individuals with intermediate cognitive impairment, and 44% of individuals with globally impaired cognitive function [7]. The first cluster shows a cognitive function similar to unaffected individuals but with subtle cognitive alterations, especially in verbal learning, processing speed, and executive function. The second cluster is composed of individuals with intermediate cognitive dysfunction in some neuropsychological domains. The cognitive domains affected may vary in each study, but the most important factor is the degree of impairment, not which neuropsychological functions are compromised [7, 19].

The last subgroup is characterized by global impairment in all the cognitive domains [7]. Among them, there are two distinctive trajectories in relation to premorbid cognitive performance: near-normal functioning and severe impairment. Nevertheless, it is still unclear which factors may explain these differences [7]. Intriguingly, a recent cluster analysis study identified three subgroups that exhibited higher academic performance during childhood, as well as during early and late adolescence, than the moderate and severe clusters [68]. These findings are consistent with previous studies including first-episode psychosis (FEP) patients, demonstrating that premorbid factors such as years of education and intellectual functioning (IQ) before the illness onset have an impact on the cognitive course [69].

In this regard, the FEP has been investigated enormously to better understand the impact of this phenomenon over time. The FEP shows a high variability in terms of symptomatology which is why patients with FEP should not be considered as a unique group [70]. Dimensional approaches in FEP have been proposed to develop more personalized clinical strategies. Thus, a study using unsupervised machine learning identified four different trajectories after 2 years of follow-up in patients with non-affective FEP: excellent prognosis, remitting course, clinical worsening, and chronic course [71]. Low doses of antipsychotic medications, depressive symptoms, and family history of mental disorders were risk factors that contributed to a worse clinical trajectory in patients with non-affective FEP, while higher cognitive reserve and better premorbid adjustment were protective factors for a remitting course [71].

The symptomatic heterogeneity seen in the clinical setting may have biological correlates that can explain it. A cohort study using structural magnetic resonance imaging (MRI) found two distinct neuroanatomical subtypes among subjects with SZ through machine learning techniques [72]. The first subgroup (subtype 1) showed widespread reduced gray matter and volumetric reductions in cortical and some subcortical areas, whereas the second one (subtype 2) had an increased volume of basal ganglia and internal capsule [72]. Subtype 1 showed lower educational attainment and the brain alterations were negatively associated with illness duration, suggesting that subtype 1 may exhibit a pernicious course [72]. However, subtype 2 achieved good academic performance and the gray matter volume was not related to illness duration, that is, these findings indicate differential etiologies in SZ [72].

Conclusion

In conclusion, this chapter demonstrates that artificial intelligence techniques have been used to predict the onset of severe mental disorders, poor outcomes, and treatment response in individuals with severe mental illness. Artificial intelligence techniques play an important role in this field, mainly because they move beyond group level comparison into individualized care. Personalized care is important in the context of severe mental illnesses, considering the high heterogeneity seen in this

population. Although several advances have been made in the field, these techniques are not implemented in clinical practice yet, mainly due to a lack of adequate external validation of the models proposed so far. In this sense, future studies are needed to translate these innovative findings to clinical practice.

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Chapter 14
The Use of Machine Learning Techniques to Solve Problems in Forensic Psychiatry

Devon Watts

Prevalence of Criminality Among Those with Mental Illness

Considering the importance of identifying the risk that forensic patients pose to themselves and broader society, there is a long-standing and well-established body of literature examining criminality among psychiatric patients. Among the pioneers in the field, Zitrin et al. [1] examined prospective criminal offenses in 876 inpatients discharged from a psychiatric facility. They found higher rates of subsequent arrest among psychiatric patients than those in the general population both in the same geographic region and among 4601 cities in the United States [1]. Similarly, Klassen and O'Connor [2] examined the relationship between arrests, hospitalization, and violence among 304 adult male inpatients at a community mental health centre, with 1 year of follow-up. They found higher rates of arrest and violent crimes among substance abusers, and notably larger violent readmission rates in patients with schizophrenia. Of note, they reported that a significant subset of patients in their sample showed a history of fluctuating between reimprisonment and rehospitalization in psychiatric facilities, highlighting the difficulty of appropriately managing such patients in legal and medical settings [2].

Following early work highlighting notable rates of criminality among those with serious mental illness, more recent efforts have largely focused on characterizing this from an epidemiological framework. For instance, in a systematic review of prevalence studies of serious mental illness among prisoners, comprising 33,588 individuals from 24 different countries, and 109 datasets, high rates of mental illness in prisoners were found in both high- and low-income countries over the timespan of four decades. Specifically, they reported a pooled prevalence of 3.6% (95% CI 3.1–4.2) in male prisoners with psychosis and 3.9% (95% CI 2.7–5.0) among female prisoners. With respect to major depression, the pooled prevalence was

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10.2% (95% CI 8.8–11.7) in male prisoners and 14.1% (95% CI 10.2–18.1) in female prisoners. Of note, they found that although rates of mental illness were high among prisoners, there is little evidence of an acceleration in prevalence over time [3].

Furthermore, in a study by Mullen et al. [4], 10 years of hospital records and lifetime criminal records were assessed in 6130 patients with schizophrenia, and 6130 controls matched for age, sex, and place of residence. Here, the patient group involved records from two cohorts, with 3719 patients from a 1975 sample and 2411 patients from a 1985 sample, respectively, to account for potential generational effects. In the 1975 sample, they found that those with schizophrenia showed a 3.5 relative risk of reoffending [95% CI 2.0–5.5], $p = 0.001$, for all categories of crimes, apart from sexual offenses. A similar finding was observed in the 1985 sample, where a 3.0 relative risk of reoffending was reported [95% CI 1.9–4.9, $p = 0.001$] [4].

Likewise, Simpson et al. [5] found that in a sample of 1498 homicides, 8.7% were conducted by those with a serious mental illness. Among them, 29% of those with a serious mental illness showed no history of hospitalization, and of those who were admitted, most were only hospitalized on one or two occasions over the last 5 years. This suggests that capital offenses such as murder are not isolated to a subset of the most severe cases who inevitably become repeat offenders. Rather, only 10% of the perpetrators were admitted to the hospital in the month prior to their offense [5]. Additionally, in a sample of 295 inpatients with serious mental illness, 49% of men and 39% of women were found to have committed a form of assault in the past 6 months. Further, rates of crime were found to be higher than the general population. This suggests that aggressive behaviour is a prevalent problem among patients with severe mental illness who require hospitalization [6]. Cumulatively, this work has helped elucidate the societal implications of criminality among a significant minority of patients with serious mental illness, and the importance of developing proactive and accurate ways to assess patient risk of subsequent crime.

Reoffending: Prevalence and Assessment Tools

Although the rates of reoffending in the forensic population remain relatively constant [7–9], available evidence suggests that one in eight men and one in sixteen women will subsequently commit a grave offense after release from a psychiatric facility [10]. It has also been shown in a large epidemiological study that the prevalence of arrest for those with psychiatric illness was approximately 32% [11].

Similarly, a recent study from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) involving 35,306 individuals showed that the presence of mental illness, irrespective of the specific disorder, was associated with a four to five times greater risk of criminal outcomes [12]. Of note, 28.5% of the participants with mental illness reported a history of criminal behaviour, while a substantial subset, 11.4%, reported a history of incarceration [12]. Additionally,

results from a large Swedish registry study comprising 98,082 individuals with a history of hospitalization suggest that those with severe mental illness commit one in every 20 violent crimes [13]. Given the high prevalence of criminal reoffending across cultures in individuals with severe mental illness, there has been a concerted effort to identify predictors of prospective criminal risk following release from psychiatric facilities.

Prior to the development of any standardized tools, clinical judgement was the gold standard measure to assess prospective patient risk [14]. However, this presented several clear limitations, including poor inter-rater reliability between clinicians, confirmation bias, and the propensity for human error [15]. Importantly, clinical judgement alone has not provided a more valid metric by which to identify individuals with mental illness who will prospectively commit serious crime [15].

In response to this, actuarial assessments became increasingly widespread, which concentrated on statistical models, while largely disavowing clinical judgement [16]. This involved using explicit statistical algorithms to identify prospective patient risk, usually at the group level [17]. Moreover, the accuracy of these risk assessment tools varies as a function of the clinical population they are administered to. For example, in a study assessing the predictive validity of the VRAG, the H-10 scale of the HCR-20 and the Psychopathy Checklist Revised (PCL-R) among 169 inpatients with schizophrenia, all risk assessment scales showed poor predictive capabilities in identifying those who would subsequently commit violent crime. Of note, the performance of these instruments in identifying recidivism was similar to simply identifying patients with greater symptom severity and chronicity [18].

Considering the clear limitations of current strategies in detecting which patients will subsequently commit violent crime, there is a major unmet need for accurate and individualized predictions to triage inpatient care and rehabilitation strategies. In the absence of this, given the high false positive and false negative rate of gold standard actuarial tools, a substantial number of patients will be mischaracterized as either high or low risk for committing violent crime if released from psychiatric care. As such, this precipitates unnecessarily denying civil liberties of patients who will not subsequently reoffend on the one hand and endangering the lives of those in the community when they do, on the other hand.

Differences Between Actuarial and Machine Learning Approaches

To understand the differences between actuarial and machine learning approaches to making predictions, it is important to briefly discuss where they diverge philosophically and statistically. While both attempts to capture relationships between dependent variables to model an underlying phenomenon and use information from past occurrences to predict future outcomes, there are noteworthy differences in how this is achieved.

Namely, actuarial science is concerned with the probability of certain events occurring, using a group-average aggregate of risk predictors [19]. As such, the primary consideration is risk management, and identifying relevant factors that precipitate higher risk among individuals. This involves a large degree of statistical approaches, including Bayesian inference and generalized linear modelling. While these approaches can also be used in a machine learning context, actuarial science uses domain knowledge to select relevant variables and is oriented towards understanding the underlying phenomenon of interest. As such, actuarial methods statistically analyse patterns of data in stochastic and deterministic scenarios to explain an outcome, placing less of a focus on making precise predictions [20].

Supervised machine learning models, on the other hand, are more concerned with predicting a phenomenon of interest with the highest possible accuracy [21]. Indeed, model optimization represents an entire subfield within machine learning [22]. However, in machine learning, interpretability can become a difficult problem [23], especially when using more sophisticated algorithms. Despite this trade-off, machine learning methods provide the benefits of an exploratory approach to selecting relevant variables in classification and regression problems, based on a data-driven, rather than a hypothesis-driven framework [24]. As such, this provides a greater degree of flexibility in feature selection [25], which is an integral component of model development. This is especially important if there are latent or unexamined variables within a given dataset that are useful risk factors but have not yet been identified in previous literature.

Similarly, this approach is often more conducive to novel discoveries, which may be better suited to capturing the idiosyncrasies of a specific population. For instance, a common problem highlighted among actuarial risk assessment tools is the difference in performance accuracy in predicting sexual recidivism between subpopulations of sexual offenders [26]. This suggests that the relationship between risk factors may not be linear across these populations. By disregarding the assumption that each risk factor is related in a linear fashion, machine learning methods can more easily examine the complex interactions between variables to make individualized predictions.

Predictive Models of Criminal and Violence-Related Outcomes in Psychiatry

While machine learning techniques present with a great deal of promise in forensics to predict patient outcomes at an individual level, the field currently remains in its infancy. Of the available studies in the context of psychiatry, Delfin and colleagues conducted a 10-year follow-up of 44 individuals who underwent a single-photon emission CT scan. This data, alongside eight evidence-based clinical risk factors, was used in a random forest model to predict criminal recidivism, resulting in an accuracy of 82%, and an AUC of 0.81. Of note, when only clinical risk factors were used, model performance degraded, resulting in an accuracy of 64% and AUC of

0.69, emphasizing the importance of combining clinical and biological features to predict criminal recidivism. The top features reflecting neuronal activity in predicting recidivism included the right and left parietal lobe, left temporal lobe, and right cerebellum. Watts et al. distinguished sexual offences from violent and nonviolent offences in a large transdiagnostic sample of psychiatric patients with an accuracy of 71.58% [27]. Furthermore, Kirchebner and colleagues used a series of known stressors to predict violent offending in 370 patients with schizophrenia. The overarching goal was to determine whether accumulated stressors precipitated violent outcomes in patients. Using boosted classification trees, they reported an accuracy of 76.4% [28].

Predictive Models of Criminal and Violence-Related Outcomes in Non-psychiatric Individuals

Apart from this, there are a few interesting machine learning models of forensic-related outcomes in non-psychiatric individuals that may serve as a useful reference point for prospective work. For instance, Cope and colleagues used structural magnetic resonance imaging (MRI) and clinical variables to distinguish between 20 incarcerated youth who committed homicide, and 135 incarcerated offenders who did not commit suicide. Additional control groups were used, corresponding to 20 incarcerated offenders who did not commit suicide matched on important demographic and psychometric variables, and 21 healthy aged-matched youth from the community. Following feature selection, six a priori regions of interest (ROIs) and three clinical assessment variables were identified. This model classified 75.00% of homicide offenders and 82.22% of non-homicide offenders, with an overall accuracy of 81.29%. The model achieved similar performance when brain volume was included, with 81.29% overall accuracy, 80.00% specificity, and 81.48% sensitivity [29].

Additionally, Haarsma and colleagues developed an innovative assessment tool to predict criminal re-offense in 730 probationers, using a self-administered mobile neurocognitive risk assessment (NCRA). The NCRA measured key criminogenic factors (attentiveness, aggression, risk seeking, empathy, future planning, emotional processing, and impulsivity), that have been linked to reoffending based on prior literature. Raw scores from each test, in conjunction with demographic variables, including age, gender, and current offense category, were used as a feature set in the model. The best performance was found in an elastic net model, with an AUC of 0.70 [30].

Furthermore, Vilares and colleagues assessed whether it was possible to predict whether an individual was in a reckless or knowing mental state using fMRI data alone. This involved asking 40 healthy controls, during an fMRI, to decide whether to carry a hypothetical suitcase, which could have contraband in it, through a checkpoint. The probability that the suitcase could have contraband in it varied, so the participants could be in a knowing situation (if they knew the suitcase had

contraband) or a reckless situation (they were not sure but were aware of a varying level of risk). Voxels with a positive survival rate were considered as predictive of a reckless situation, and voxels with a negative survival rate were considered as predictive of a knowing situation. Using a regularized linear model, the authors reported an AUC of 0.789, in distinguishing knowing and reckless mental states in the search-first group, and a correct classification rate of 71% after internal validation [31].

Predictive Models of Malingering

Another long-standing problem in forensic psychiatry is that of malingering, or feigning a serious mental illness following arrest to avoid a prison sentence [32]. This issue is also commonly encountered in emergency settings, particularly among a subset of individuals presenting with depression or suicidality [33]. To address this long-standing issue, a handful of studies thus far have used machine learning techniques to predict malingering. Monaro and colleagues developed a new tool to detect malingering by tracking motor response using a computer mouse while participants answered questions about depressive symptoms. Features were derived from calculating the average value of responses to questions, as well as the velocity and acceleration of mouse movements. Feature selection was performed by selecting variables with the maximum correlation with the outcome, and minimum correlation across variables, using a greedy stepwise search method, resulting in an accuracy of 94.4% [34].

Additionally, Mazza and colleagues assessed the performance of a computerized task to detect malingering, relative to traditional psychometric techniques. Sixty-eight participants were randomly assigned to one of four research groups, defined by a combination of two instructions (honest vs underperforming intentionally), and time pressure (timed vs. untimed). Separate models were developed to classify participants with and without time pressure. In the time pressure models, performance in the testing set was reported to be 95%, whereas accuracy in the untimed models ranged from 75% to 95% [35]. Finally, Pace and colleagues developed a classifier using a simple psychometric test (b Test), to detect malingering. The sample consisted of three groups: 21 individuals with mixed neurological aetiology, 21 healthy aged-matched individuals completing the test in the absence of specific instructions, and 21 healthy aged-matched individuals instructed to respond to the test as if they were cognitively impaired. The authors reported an AUC of 0.88–0.91 and an accuracy of 88.09–92.9%, depending on the classifier [36].

Methodological Recommendations

While there have been a number of interesting studies using machine learning techniques to predict forensic outcomes, further refinement in the field is warranted. For instance, future work may benefit from including larger sample sizes, using various data modalities, such as clinical, biological, and physiological features, and

validating models with independent and cross-cultural cohorts. Apart from making individualized predictions, various machine learning techniques and experimental designs can be leveraged to address long-standing problems within the field. This section aims to provide a broad view for moving the field from advancements in risk prediction towards precision forensics.

Integrating Evidence-Based and Novel Biological and Physiological Features

Within machine learning models, one of the most important considerations is the features, or variables, used to derive predictions [37]. It has been argued that theory-driven approaches are important to leverage domain knowledge and prior evidence within a field. Conversely, it has also been claimed that a purely exploratory data-driven approach is useful to facilitate novel discoveries [38]. Considering the veracity of both sets of claims, a realistic trade-off may be to include both evidence-based and novel variables to improve our understanding of forensic conditions, patient outcomes, and improve clinical care for these marginalized individuals. However, it is important to ensure that exploratory variables are of high quality, and that future work includes novel biological and physiological features to inform potential mechanisms. Moreover, it is argued that future work may benefit from moving away from using immutable characteristics such as ethnicity, gender, or prior criminal history when making prospective predictions. Rather, it may be useful to build separate models along these bases, such as determining whether model accuracy and top predictors vary as a function of socioeconomic status, gender, or age. However, basing our predictions on immutable characteristics may carry several biases and inadvertently stigmatize those we are attempting to treat.

Predicting Treatment Response to Routine Clinical Care

Furthermore, it is known that individuals with severe mental illness that end up in the forensic mental health system often present with multiple comorbidities [39]. As such, determining the appropriate course of treatment for each patient remains a fine balance between science and art. To the best of the author's knowledge, there are currently no studies using machine learning techniques to predict treatment response to routine clinical care in forensic contexts. This represents an important avenue for prospective work, to move towards more individualized and personalized treatment plans. While there are several punitive experimental designs that may be useful to facilitate this, a realistic starting point may be recording routinely collected clinical data in large cohorts. Outcome measures would depend largely on the diagnostic composition of patients, but would ideally involve validated psychometric scales, such as the Positive and Negative Syndrome Scale (PANSS) for Schizophrenia [40], as well as the Young Mania Rating Scale (YMRS) [41] and Montgomery-Asberg

Depression Rating *Scale* (MADRS) [42]. Therefore, it may be useful to build predictive models using baseline data when new patients enter forensic care and predict subsequent treatment response to routine care. If validated in independent samples, and across cultures, such hypothetical models may prove to be useful assistants to forensic psychiatrists when selecting a course of treatment for patients.

Apart from predicting treatment response, an equally important consideration is treatment non-response. For instance, it is known that approximately 30% of patients with schizophrenia fail to respond to two (or more) trials of dopaminergic antipsychotics [43]. A similar experimental design as aforementioned may be useful to predict non-response in patients at baseline, and stratify these patients into clinical trials, or start with underutilized medications such as clozapine [44]. Furthermore, once predictive models are developed that have sufficient accuracy, an important consideration will be to improve model accuracy by incorporating other types of data. While there are several options for this, it is argued that cost-effective markers will be needed if the goal is to incorporate this into routine clinical care. Physiological markers such as heart rate variability, electroencephalography, and biological markers that can be measured en masse within peripheral samples may prove to be useful in such contexts.

Predicting the Timing of Short-Term Inpatient Outcomes

Apart from treatment considerations, machine learning techniques may be useful to predict several other short-term outcomes, which can be operationalized as outcomes while patients remain in inpatient care. For instance, while there are a small number of studies predicting violent outcomes in psychiatric inpatients, there is a lack of longitudinal studies to predict the timing of such events, and triage care to at-risk patients before such events occur. This is an important consideration from the perspective of the safety of hospital staff, and the interests of patients, and their families. Furthermore, machine learning models to predict length of stay using baseline variables in conjunction with feature importance methods may identify currently concealed modifiable factors, thereby identifying new ways to reduce inpatient stay while retaining high quality care. Moreover, such models may have utility from a hospital administration standpoint, as they hold potential to improve resource allocation, and provide insight into how long a given bed may be in use.

Data-Driven Phenotyping of Forensic Patients

Apart from supervised machine learning, where we are attempting to optimize the prediction of a prespecified outcome, unsupervised clustering techniques represent a promising, yet underutilized method in forensic psychiatry. In brief, unsupervised learning involves organizing unlabelled data into similar groups called clusters. In this context, a cluster involves a collection of patients that are “similar” between

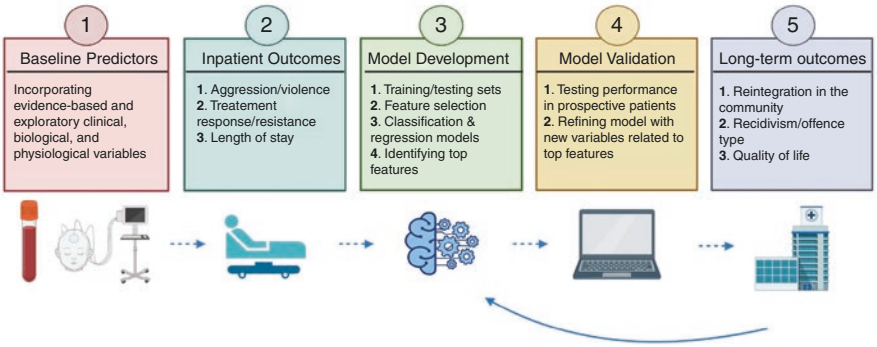
them, and "dissimilar" to other patients [45]. As described elsewhere, data-driven phenotyping may be useful to identify latent phenotypes of patients within and across diagnostic categories [46]. However, this same approach may also be useful to identify phenotypes of patient outcomes, namely aggressive tendencies, offences committed, and response to treatment. There are various forms of unsupervised clustering methods, with each making several statistical assumptions of the underlying data [47].

While unsupervised clustering can be useful to identify clinical phenotypes, it is argued that this may be particularly useful when combining clinical, physiological, and biological data. That is because while patients may exhibit the same underlying clinical characteristics, differing biological and physiological phenomena may give rise to similar symptom profiles [46]. However, it is known that there are several limitations to unsupervised clustering. Namely, since our outcome is unlabelled, meaning that we are not specifying what we are trying to predict, we cannot guarantee that the clusters we are observing are due to the phenomena of interest. To highlight an example, if we are attempting to derive meaningful clusters of schizophrenia, we cannot guarantee that these clusters are not due to some other immutable characteristic.

Recently, new local explanation methods have been developed, including SHapley Additive exPlanations (SHAP), to explain variable contributions at the individual level [48]. SHAP can be used within supervised machine learning tasks, so it circumvents the challenge of not specifying our outcome. Adaptations of this, such as TreeExplainer, leverage the internal structure of tree-based models to efficiently compute local explanations using Shapley values. As such, cluster characteristics can be identified by examining the top features that have a positive and negative impact on each predicted label [49].

Methodological Pipeline for Prospective Machine Learning Cohorts in Forensic Psychiatry

Given that the field of machine learning techniques in forensic psychiatry remains preliminary, it is argued that prospective machine learning-based cohorts are needed to advance the field. As such, this section details a methodological pipeline to conduct such cohort studies.



1. *Baseline predictors*: Patients who consent to be included within a given cohort study will first be provided with a battery of clinical, biological, and physiological measures. Given that few machine learning studies in forensic psychiatry have included biological or physiological measures, initially such work will be exploratory in nature. However, it is important that future models incorporate predictors identified within the literature, to evaluate their replicability. At the outset, various forms of data may be useful, such as electroencephalography, functional magnetic resonance imaging, various blood, urine, and saliva markers, as well as wearable devices such as actigraphy and heart rate monitors. Furthermore, standardized clinical batteries that incorporate both self-report and clinician administered assessments may be useful to expand the range of potential outcomes that can be investigated in any given cohort. Multiple assessments during inpatient stay may be useful, depending on the size of the cohort, and number of available resources.
2. *Inpatient outcomes*: There are several short-term inpatient outcomes that may be relevant to investigate, including (1) aggressive incidents, (2) acts of violence against oneself, staff, or other patients, and (3) parameters related to care such as length of stay. When recording these outcomes, it is important that reliability and validity are carefully considered.
3. *Model development*: While initial studies may be preliminary in nature, and as such, lack sufficient sample sizes for training and testing sets, it is nonetheless important to emphasize that without this crucial step, model accuracy tends to be inflated. Furthermore, given that multimodal data is encouraged in such cohort studies, feature selection will be an important step to substantially reduce the number of potential predictors. This, in turn, reduces the chance of overfitting. Moreover, depending on the outcome of interest, it may be more appropriate to select a classification (e.g., response vs. resistance), or regression (e.g., PANSS scores) task, depending on the outcome. From here, various feature importance measures can be used, to identify important predictors in the models.
4. *Model validation*: Following model development, a necessary subsequent step is to test the model in prospective patients. Ideally, this would be performed both with subsequent patients enrolled in the same cohort study, and in independent cohorts conducted elsewhere. Furthermore, after identifying top features in predicting relevant outcomes, it would be useful to incorporate other features of a similar nature. For instance, assuming that impulse control parameters are important for predicting inpatient aggression in the model development stage, the inclusion of other variables related to this, such as measures of autonomic arousal, may improve model accuracy. Other clinical, biological, and physiological variables that were initially collected as baseline predictors which were not found to be relevant in predicting outcomes may be discarded prospectively to decrease associated collection costs and derive simpler models.
5. *Long-term outcomes*: Apart from inpatient outcomes that can be assessed short term, long-term outcomes that occur after an individual is released into the community are also important to investigate. This step may involve linking prospec-

tive hospital and criminal records, with patient permission. While there are several outcomes that may be relevant, aspects such as reintegration into the community, employment, recidivism, and quality of life may prove to be useful to improve prospective patient care.

Conclusion

Currently machine learning techniques applied to forensic psychiatry mostly involve the use of routinely collected data to predict criminal and violence-related outcomes. Since more work has been done in non-psychiatric individuals, such studies may elucidate potential markers that could prove useful to investigate in prospective models. Moreover, a small number of studies have investigated predictive models of malingering, which although remain preliminary may prove to be useful in several contexts. It is argued that future studies would benefit from integrating evidence-based novel biological and physiological features, predict treatment response to routine clinical care, and the timing of inpatient outcomes. Moreover, prospective machine learning cohorts may help to advance the field, from risk assessment towards precision forensics.

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Chapter 15
Gaming Disorder and Problematic Use of Social Media

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Gaming Disorder

Introduction

Gaming has become a widespread form of entertainment and the gaming industry is on the rise. Reports from 2018 described that the gaming business was worth 4.85 billion dollars, which represented a larger amount than the music and video industries combined [1]. Nowadays, this number is likely to be bigger, considering the growth of the sector during the COVID-19 pandemic, with people being restricted to indoor activities for long periods [2]. Estimates from 2021 report that only in the USA, approximately 227 million people play digital games regularly; in addition, new generations are ranking gaming as their favorite leisure activity [3, 4].

Since the creation of the first video games in the 1950s [5], the technology applied by the gaming industry has improved significantly. These technological upgrades allowed for the generation of more immersive experiences for gamers, which is generally considered to be a highly pleasurable experience, and the popularization of this form of entertainment, now widely accessible in most regions of the world [6, 7]. Nonetheless, despite these technological advancements, people started reporting problems related to excessive and problematic gaming [7].

Considering this context, gaming disorder is an emergent condition that has increased in relevance in the past decade. It was included in the *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* (DSM-5) as a condition for further study [8], and in the *International Classification of Diseases—11th Revision* (ICD-11) as a distinct diagnosis [9]. According to the ICD-11, gaming disorder is defined as a specific pattern of digital gaming behavior (which can be either online or offline), recurrent or persistent, which leads to significant distress or functional impairment (in areas such as education, social, occupational, etc.) that lasts for at least 12 months, with this period being shortened in case of severe symptomatology. In addition, gaming disorder is defined by three specific criteria: "(1) impaired control over gaming (e.g., onset, frequency, intensity, duration, termination, context); (2) increasing priority given to gaming to the extent that gaming takes precedence over other life interests and daily activities; and (3) continuation or escalation of gaming despite the occurrence of negative consequences" [9]. The ICD-11 also describes another diagnostic category called *hazardous gaming*. In general terms, *hazardous gaming* is a less severe pattern of gaming, and is associated with less negative consequences in comparison with gaming disorder; nevertheless, there is still the need for a better definition of this concept [9].

The prevalence of gaming disorder is heterogeneous and presents a considerable variety depending on the study. According to a recent systematic review [10] that included 53 studies from 17 countries, representing a total of 226,247 participants, the global prevalence of gaming disorder is 3.05%. The prevalence rate decreased to approximately 2% when the inclusion of studies was restricted to those presenting more robust and representative sampling criteria. The same study highlighted another finding commonly reported in empirical studies concerning differences

across genders. Gaming disorder is more common in males, with the male to female ratio being around 2.5 [10].

Gaming disorder has been associated with several negative health-related outcomes. These negative consequences may present in the form of social, academic, work, and functional impairment; excessive time spent on gaming-related activities with the neglect of other areas in life; mental health symptoms such as depression, anxiety, irritability and aggression, sleep problems (including sleep deprivation and reversal of day–night cycle); general health problems associated with lack of self-care, poor diet and hygiene, sedentary lifestyle; family-related problems and impoverished social relationships, interpersonal conflicts, among other problems [7, 11, 12]. Even some deaths have been connected with extremely intensive and prolonged gaming sessions [13].

Given the public health impact of gaming disorder, the condition has called the attention of world leaders. For instance, the Chinese government restricts access to online games for children and adolescents, who are not allowed to play on school days, but only for 1 h each day during weekends and holidays [14]. The Chinese government justifies this restriction on minors by saying that the addiction to online games was a significant threat to young people in China [14].

Etiology and Explanatory Models

The causes of gaming disorder are yet to be unfolded, with some researchers suggesting that the neurobiology of problematic gaming is similar to that of gambling. This argument is based on the hypothesis that gaming is a highly rewarding and addictive behavior due to the increased levels of dopamine in the brain and activation of the reward system, which is somewhat related, in the case of specific game genres such as massively multiplayer online role-playing games (MMORPG), to the generation of specific rewards after the completion of each game-related cycle by the players, thus keeping them playing for prolonged periods of time and leading to a compulsive behavior [15]. Furthermore, some neuroimaging studies described findings commonly associated with other addictive disorders, including activation of neural areas associated with dopamine and reward; decreased activity in brain regions related to impulse control such as the prefrontal cortex; and diminished functional connectivity in brain circuits associated with executive function, cognitive control, processing of reward, and motivation [16].

Gaming disorder has been associated with several psychiatric conditions, including depression, anxiety, attention deficit hyperactivity disorder (ADHD), social anxiety, and obsessive–compulsive symptoms [17, 18]. These conditions could represent potential risk factors for gaming disorder. In addition, there is some evidence of the comorbidity of gaming disorder with other addictions, including problematic use of social media, gambling disorder, internet addiction, as well as disorders related to the use of alcohol, nicotine, cannabis, and caffeine [19]. These findings suggest the potential role of maladaptive coping strategies and decreased emotional regulation [19, 20].

Specific personality traits such as neuroticism and impulsivity have also been associated with gaming disorder [21]. Other potential risk factors suggested in previous studies are social withdrawal, stressful life events, aggressive behavior, peer victimization, conflicting family environment, rumination, short-term thinking, all-or-none thinking, avatar attachment, flow experience, achievement, and rule-breaking behavior [22]. In addition, some gaming associated factors have also been suggested as potential risk factors: preference for specific game genres (such as MMORPG, first-person shooters, real-time strategy games), longer gaming sessions, more time in years playing digital games, higher frequency of gaming behavior, and preference of online gaming sessions [21].

Considering all the risk factors associated with gaming disorder, it is important to combine these variables into reasonable and unified explanatory models. For instance, a theoretical model for the development of behavioral addictions, known as the Interaction of Person-Affect-Cognition-Execution (I-PACE) model, may help in the understanding of the pathophysiology of gaming disorder [23]. This model is shown in Fig. 15.1.

Previous literature has also outlined factors that may protect against the development of gaming disorder. For instance, higher self-esteem, social integration with

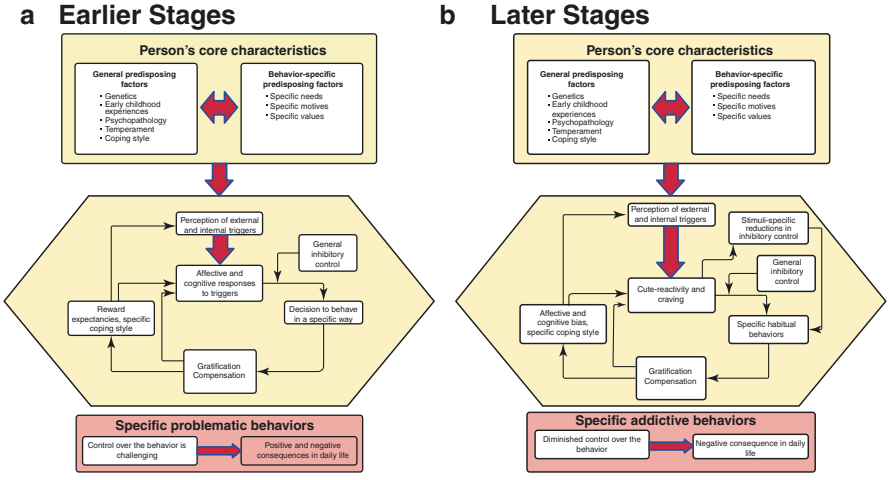

Fig. 15.1 Adapted from [23]—The Interaction of Person-Affect-Cognition-Execution (I-PACE) model is a theoretical model that may explain the development of behavioral addictions, ranging from gaming and gambling disorders to compulsive sexual behaviors and problematic use of pornography. This model attempts to explain that behavioral addictions develop due to the complex interplay between several variables, including predisposing factors, cognitive and affective response patterns, and executive functioning concerning decision-making and inhibitory control. Habitual behaviors develop due to the interaction between cravings/cue-reactivity and reduced inhibitory control. Part "(**a**)" refers to the early stages in the development of addictive behaviors, whereas part "(**b**)" conceptualizes later stages, also describing factors associated with the persistence of the maladaptive behavior. Stronger connections between variables are depicted in larger arrows

peers, good school-related well-being, perceived behavioral control, personality traits such as extraversion and agreeableness were all regarded as potentially protective factors [21]. Life satisfaction, self-efficacy, resilience, social skills, good emotional regulation, family cohesion, positive father–child relationship, good school climate and school engagement, and social support were other protective factors described in the literature [22, 24].

It is also relevant to understand why gaming disorder is significantly more prevalent in males. One reason for this difference has been attributed to the strategy of the gaming industry, in which games are in its majority produced by men aiming at a male audience, with the design of games being planned to impact this audience [25]. Male gamers also seem to be more driven by the achievement element in games, in comparison with female gamers [25]. Nevertheless, there is evidence concerning the rising in female participation in gaming-related activities, with several reports of problematic gaming in this population [26]. In addition, the research in the field of gaming disorder is biased towards the male gender, with an overrepresentation of this population in empirical studies, with the need for more research targeting female gamers [26].

Assessment of Gaming Disorder

The clinical assessment of patients with gaming disorder is a challenging and complex process; nevertheless, it also represents an initial step in the treatment process due to the need to motivate and build a therapeutic alliance with the patient [27]. The clinician should not only investigate the gaming behavior (frequency, type of game genres played, lifestyle and the social context surrounding gaming, beliefs about gaming) and the associated harms (education, work, family climate, relationships, mental and physical health conditions) but also should help the patient to understand the negative consequences of this maladaptive behavior, always paying attention to avoid over-pathologizing the activity of gaming. It is essential to interview other relatives in order to have a more accurate description of the clinical presentation and to engage family or other caregivers in the treatment process. The assessment of psychiatric comorbidities is also an essential aspect of the clinical investigation of these patients, as these conditions will have to be treated as well [27].

Over the years, several instruments have been proposed for measuring and diagnosing gaming disorder and related conditions. A recent systematic review [28] evaluated 32 of these measurement tools from 320 empirical studies, corresponding to 462,249 participants. According to their results, 2.5 measurement tools for gaming disorder have been published annually since 2013; nevertheless, these instruments present inconsistent coverage of diagnostic criteria from ICD-11 or DSM-V [28]. Even though specific scales present better evidence support, according to this systematic review no instrument can be classified as an optimal option for the measuring of gaming disorder [28].

Currently, there is a project led by the World Health Organization, with the contribution of several experts in the field, who are working towards the development of gold standard instruments for the screening and diagnosis of gaming disorder and hazardous gaming. The aim of this working group is to provide psychometrically robust instruments, which may be used not only in research settings but also in clinical practice, and which can be used across nations and cultures [29].

Treatment Strategies

Several different strategies and modalities of treatment have been explored in patients with gaming disorder. The majority of studies focused on cognitive behavioral therapy (CBT) approaches, ranging from standard CBT, gaming-specific CBT, mindfulness-based strategies, craving-specific CBT, and CBT plus parental psychoeducation [30]. Even though most of these treatment strategies presented significant results in the treatment of gaming disorder-related outcomes, and CBT presents the largest evidence base in comparison with other potential treatments of the condition, the current quality level of the literature is poor with significant limitations preventing the reliable recommendation of these approaches [30, 31].

Only a few pharmacological options have been tested, with all the clinical trials being done in South Korea [30]. Medications for the treatment of ADHD, such as methylphenidate and atomoxetine, as well as antidepressants, especially bupropion and escitalopram, have been tested with significant results on gaming disorder symptoms and other gaming-related outcomes [30]. Nonetheless, very few randomized controlled trials have been conducted so far, and most studies presented significant limitations, including small sample sizes [30]. In addition, clinical experience suggests the use of pharmacological options in the treatment of psychiatric comorbidities rather than for the treatment of gaming disorder itself.

Other interventions have also been investigated. Family therapy, motivational interviewing, and treatment camps all presented promising results in terms of treatment of gaming disorder [30]. Repetitive transcranial magnetic stimulation (rTMS) has been explored as a potential treatment strategy for a case of gaming disorder, with marked improvement in the addictive behavior [32]. Even virtual reality-based treatments have been investigated, with a preliminary study ($n = 24$) showing a significant reduction in gaming disorder symptoms after a 4-week treatment trial (2 weekly sessions of virtual reality therapy which were composed of three subsequent stages: relaxation, simulation of high-risk situations, and cognitive reconstruction), with this reduction not being significantly different from the one produced by a CBT comparison arm [33].

Nonetheless, it is essential to consider that gaming disorder is a complex condition, which may require the use of different treatment modalities simultaneously. In this sense, the combination of the above-mentioned interventions, including pharmacotherapy, psychological treatments, physical activity, treatment of family members, social skills training, among others, may be a better strategy than applying

only one option alone [12]. Furthermore, there is still debate about the aim of the treatment, with clinicians suggesting gaming abstinence as a necessary step for improvement, mainly among adult patients [12]. Other strategies commonly used for the treatment of addictions may be used for gaming disorder. An example of a transdiagnostic model for the treatment of substance and behavioral addictions, based on specific underlying mechanisms that may be common to both types of conditions, was proposed recently [34]. This model, seen in detail in Fig. 15.2, can be applied to the treatment of patients with gaming disorder and other technology-related problematic behaviors as well.

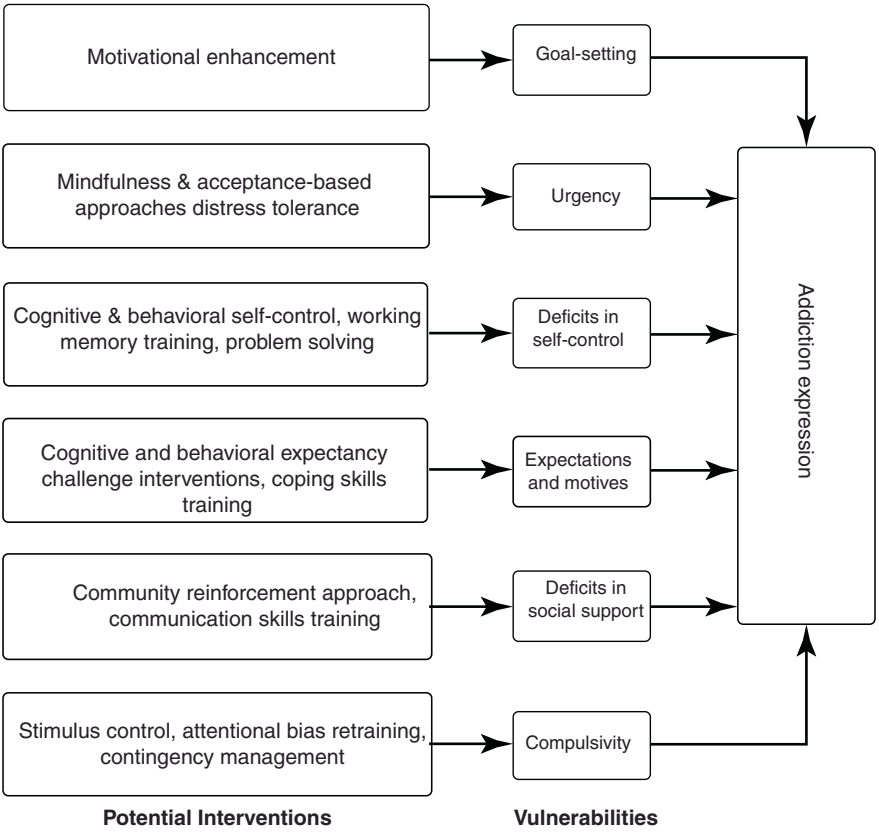

Fig. 15.2 Adapted from [34]—According to this transdiagnostic model that can be applied to either substance or behavioral addictions (including gaming disorder), each individual patient presents specific vulnerabilities (i.e., lack of self-control and motivation, poor social support, urgency), which may be connected with the expression and persistence of a given addiction. Each of these vulnerabilities, in spite of being enduring, may be modifiable and can be treated with the use of specific interventions. The treatment of each patient can use different combinations of interventions, based on the vulnerabilities identified. Furthermore, as the treatment progresses, different vulnerabilities may be addressed

Hikikomori

Hikikomori is a psychiatric syndrome reported initially in Japan in the 1990s, which corresponds to a state of severe and prolonged social withdrawal usually not attributable to psychosis and other severe forms of psychopathology [35]. The typical vignette of a Hikikomori patient is a young male in his twenties or thirties, who still lives with his parents, does not work or study, lacks meaningful personal connections with friends or romantic partners, and who is physically isolated in his own room or house [35, 36]. Previously considered to be a Japanese cultural syndrome, hikikomori has been reported in several countries, including Brazil, and is considered to be a public health problem in parts of Asia, with some prevalence estimates in community samples reaching approximately 2% [36, 37].

In 2020, a group of researchers published a proposal of updated criteria for the diagnosis of hikikomori [35]. In order to be diagnosed as presenting hikikomori, an individual must meet all the three following criteria: "(a) marked social isolation in one's home; (b) duration of continuous social isolation of at least 6 months; (c) significant functional impairment or distress associated with the social isolation." Individuals presenting this behavioral pattern for a period between 3 and 6 months are considered to be pre-hikikomori. In addition, if the person leaves his house/apartment four or more days/week, that person does not meet the definition of social isolation characteristic of the syndrome. In severe cases of hikikomori, the person hardly ever leaves his own room [35].

Major depression, social anxiety, and other psychiatric conditions have been reported in hikikomori patients, with this condition also being associated with an increased risk of suicide [36, 38, 39]. Furthermore, problematic internet use, gaming disorder, and other technology-related behaviors have been connected with hikikomori [38, 39]. Even though it is not possible to make inferences about causality, there are reports of hikikomori patients who used to spend at least 14 h/day in gaming-related activities, presenting remission of hikikomori after a marked improvement in their excessive gaming behavior [36].

The evidence base of treatment interventions for hikikomori cases is weak due to the lack of studies in the area. Preliminary reports suggest the potential benefits of applying multimodal treatment strategies, including pharmacological treatment of comorbidities, family and psychosocial interventions, individual psychotherapy, online treatment, physical activity, and training of social skills for these patients [36, 39]. Nonetheless, clinical experience suggests that it is difficult to engage patients with hikikomori in their own treatment. In severe cases, patients may spend decades socially withdrawn, with some of them not having any contact with people outside their household. After the passing of their parents or a caregiver, these patients may experience a significant worsening of self-neglect because they are incapable of taking care of themselves, with some dramatic reports describing hikikomori cases who have died of malnutrition being found only several days after the death [40].

Problematic Use of Social Media

It was estimated that, in 2016, 2.34 billion people regularly made use of social media around the world [41]. Its use has substantially increased in recent years among adults and adolescents, and the impact of social media on mental health has received a lot of attention [42]. Social media use is associated with addiction-like symptoms, such as craving, tolerance, and withdrawal [43], and problematic social media use (PSMU) can be described as an addictive pattern of social media use, associated with negative outcomes in well-being and in functional aspects of daily life, including decreased life satisfaction and impaired productivity [44].

Over the years, social media platforms have developed several strategies for maximizing the time users spend on it [45]. Design elements, such as "infinite scrolls," which disturb the notion of time spent online [43], notification push, which competes with the attention of the users [46], likes, which bring gratification through social acceptance [41], and "closed portals," which allow the user to consume the content from other websites while remaining on the same social media platform (i.e., clicking a link in Facebook and viewing a news article that load within the same application) [47], are some of the design factors associated with addictive behaviors. In addition, mechanisms such as screening the users' preferences via algorithms and producing specific content for them induce a more immersive state during one's use of social media platforms, which ultimately can contribute to this addictive pattern of use [45].

Nevertheless, PSMU can affect individuals at different levels, based on features associated with the pattern of use of these platforms, such as frequency and type of content consumed [44]. For instance, self-injurious thoughts and behaviors, cyberbullying, and social exclusion may be more associated with the content consumed on the platform itself, opposed to the time spent on it [42], while the impaired quality of sleep and symptoms of ADHD are positively associated with high-frequency digital media use [48, 49]. Moreover, the relationship between psychiatric conditions and PSMU is described by some as bidirectional, with some patients being more vulnerable to the effects of social media [namely, patients with ADHD, autism spectrum disorders (ASD), anxiety disorders, and mood disorders], and these platforms bearing the potential of worsening mental health symptoms, as the social media strategies have a differential effect on individuals with these disorders. For instance, time regulation difficulties, unhealthy comparisons leading to negative self-esteem, and perpetuation of *learned helplessness* (defined as a "sense of feeling powerless in a situation due to previous persistent failures") are detrimental aspects that may be accentuated in the context of social media use by individuals with psychiatric disorders [47].

In addition, different age groups report different vulnerabilities to the negative effects of social media networks [47, 50]. As it is generally known, adolescents are a vulnerable group for engaging in risky behaviors, also being at a developmental stage in which socialization with peers is given more importance in comparison with other sources of social support; thus it is expected they spend more time in social media platforms in comparison with other age groups [50].

Fear of Missing Out

The fear of missing out, commonly referred to as FoMO, is defined as "pervasive apprehension that others might be having rewarding experiences from which one is absent" [51] or even as "the uneasy and sometimes all-consuming feeling that you're missing out—that your peers are doing, in the know about, or in possession of more or something better than you" [52]. Although the term is not exclusively related to an online context, it has become frequently associated with social media use, due to its components that result in easier and highly efficient continual connection with one's inner social circle and overall happenings in the world—possibly increasing the chances of people subjectively missing out on events and communications [53]. As a result, it causes frequent or even excessive use of social networking sites and other messaging services. It appears to be a somewhat universal phenomenon, with studies reporting and supporting FoMO as a construct deriving from numerous countries and languages [54].

As a relatively new concept, empirical evidence is rather scarce. Research findings show that higher levels of FoMO are associated with lower levels of life satisfaction and general mood [51], as well as increases in feelings of loneliness and boredom, which in turn are also linked to the use of social media [55, 56]. Furthermore, FoMO is associated with higher levels of problematic social media use, disrupted daily life activities due to smartphone notifications, rumination, and negative affect and mood, with inverse correlations shown with life satisfaction and emotional well-being [54]. Importantly, FoMO has also been associated with distracted pedestrian behavior due to smartphone use [57] and distracted driving in young adults [51].

Dating Apps

The idea of using technology as a way to improve dating is not new. The first record of a computer-date-matched party dates back to 1959 when two Stanford undergraduate students developed the "Happy Families Planning Service"—an IBM model 650 computer-based program that paired up 98 men and women based on their similarity of answers [58]. But it was only in 1995, with the official launch of Match.com, that online dating in a similar fashion as we know today came to be. Since then, the online dating industry has grown immensely, with reports showing a generated revenue of $2.23 billion in 2019 and an estimated number of 8000 dating websites worldwide, with about 219.7 million online dating sites or app users around the world [59].

Nevertheless, online dating has not remained a stable phenomenon over time. Paradigm shifts occurred with the development of new technologies. The more drastic one appears to be the shift from computer-only access sites to smartphone access, resulting in a user behavioral change, with more messages being sent, more

matches achieved, and an increased number of visits to other's profiles [60]. Concomitantly, this shift resulted in a new model of online dating, the so-called swipe-based dating applications (SBDAs), with new characteristics including the concept of image-dominated profiles and the incorporation of geolocation, promoting matches based on geographical proximity, as well as a design change that reproduces the swiping, scrolling, and typing of other social media apps [61].

Due to the expanding popularity of these new tools, numerous studies aimed to understand the sociodemographic characteristics and personality correlates of online dating users. Although the findings in many of these studies are contradictory, specific results are convergent across studies, including the greater likelihood of men, young adults, and sexual minorities members being dating apps users [62–64]. Concerning personality characteristics, studies using the five-factor model (also known as the Big Five) [65] found higher scores on open-mindedness and extraversion and lower conscientiousness in this population [66], as well as high sensation-seeking and sexual permissiveness [67, 68].

To this date, specific negative outcomes have been associated with the regular use of dating apps. These include sexual harassment; the potential of meeting untrustworthy people and behaving impulsively in terms of risky sexual choices; as well as the objectification of the potential date (i.e., the use of marketplace and economic metaphor applied to the culture of dating) which, in turn, may increase self-objectification, presenting serious mental health consequences, such as clinical symptoms of depression and eating disorders [69, 70]. Furthermore, there has been described an association between SBDA use and higher levels of psychological distress, along with symptoms of anxiety and depression. Although causality cannot be inferred due to the cross-sectional design of the study, it reflects that these users may be an at-risk population [61].

Healthy Use of Social Media

The ubiquity of social media in the present day is undisputed. Yet, the negative aspect of their usage is arguably overstated across media reports, government guidelines [71], and mental health practices [72], overlooking the evidence suggesting that only a minority of users are at risk [73], while its benefits are potentially underestimated [74]. Concerning the positive effects of social media, focusing mainly on mental health topics, research suggests the potential to reduce isolation, improve social skills, provide a platform for continued communication, contribute to maintaining long-distance friendships, as well as providing a mechanism to relieve stress and prevent mental illness [75]. Moreover, social media might also contribute to self-branding among individuals of specific stigmatized groups (i.e., patients with ADHD), promoting ways to ward off said stigma, while building and sustaining identities [76], also contributing to the development of a more well-defined sense of self [77].

Fake News and Hate Speech

Another timely discussion whenever debating the problematic use of social media is the spread of fake news, as well as hate speech and supremacist propaganda with the use of social media platforms. The presence of fake news is so pervasive in social media, that it is presenting an impact on public health outcomes due to the widespread misinformation of scientific concepts, mainly during the COVID-19 pandemic [78, 79]. Empirical evidence suggests the connection between online extremist content and real-life dramatic events, with serious adverse political, social, and humanitarian consequences, also suggesting that social media platforms have the ability to amplify the outreach of hate speech [80].

For instance, reports connect the genocide of the Rohingya minority group, who are predominantly Muslims, in Myanmar, to the spread of fake news and hate speech, including false allegations about Islam threatening the existence of Buddhism, and about criminal behaviors of Muslims against Buddhists. These posts were done on Facebook by military personnel from the country as part of an ethnic cleansing campaign that lasted several years. They used fake accounts, including celebrity and news pages with more than a million followers, where they posted inflammatory comments and fake news about Muslims and the Rohingya. This propaganda against the Rohingya significantly contributed to rapes, physical aggression, murders, and other forms of violence against this minority, ultimately leading to the forced mass migration of the affected populations, mostly to Bangladesh [81].

Another example of how Facebook can be used to promote hate speech and call for violence, with dreadful consequences, is taking place in Ethiopia. Ethiopia is facing a civil war since the end of 2020, and several leaders with thousands of followers have been stimulating people to engage in violent actions, mostly against an ethnic minority, the Tigray, which corresponds to 7% of the population in the country and is currently suffering a genocide. Several of these posts and accounts spreading hate speech have connections with the government of Ethiopia, militias, and other armed groups, with some being made by the Prime Minister himself. Other ethnic groups are also the target of hate content online, with consequences manifesting in a number of episodes of murders and violent attacks [82, 83].

Online Subcultures

The internet and social media platforms allow for the meeting and grouping of individuals with all sorts of interests, beliefs, and values, who would otherwise never be in contact due to geographic and cultural limitations. The forming of such online spaces creates a strong sense of community, which has given birth to several online subcultures, with some being mixed with specific ideologies, as well as political and extremist agendas, bearing the potential to generate violent actions which are justified and stimulated by other members of the same group [84].

The world of the Incels

The term "Incel" stands for "involuntary celibate," which is a self-proclaimed expression used to define those, mostly young men between the ages of 18 and 30, who have had difficulties in their sexual life to the point of, in most cases, not presenting any past sexual experience [84]. Incels usually communicate in online forums, where they discuss, with the use of their own and very specific jargon, the struggle of the transition into adulthood with the focus on romantic relationships, with such forums working as support groups and platforms of validation of their beliefs [84, 85]. In these online forums, the self-proclaimed incels usually spread conspiracy theories and misogynistic ideas that they call anti-feminist, justifying the hate speech with a biased view that most males are being oppressed by current cultural values [84–86].

These online forums are anonymous spaces where this type of idea tends to radicalize and be normalized. Some incels defend the idea that "women are naturally evil" and debate about how to deal with their problematic "celibacy" by engaging in violent actions, with reports of a few incels taking part in mass murders in the past [84–86]. Some men, considered to be biologically more fit to reproduction and sexual interactions than incels according to their own view, are also targets of hate speech and violent actions, which is generally related to the resentment incels have of them [84]. Nevertheless, even though incels usually express their condition of sexually frustrated men as hopeless and helpless, only a small minority of them engage in violent actions, with others being at an increased risk of suicide [84, 85].

Another feature of the incel community which is worth discussing is its very unique vocabulary, composed of several neologisms that people outside their community have trouble understanding. The incel lexicon is vast, being intimately connected with their worldview and misogynistic opinions [87]. Examples of specific terms are "Chad," which refers to an idealized and attractive male who, according to the incel's view, has plenty of sexual opportunities; "Stacy," which represents the female equivalent to the Chads, and who supposedly date only this idealized version of men; "Normie" who refers to average people who are not part of the incel community; "bluepill," referring to those who, in their view, "swallowed the bluepill" and remain ignorant of the discrimination that males suffer in today's society; and "blackpill" which is a nihilistic view that the potential of dating is predetermined by someone's genetic predisposition and associated physical attractiveness, leading those incels who "swallow" this pill to be hopeless and desperate, with some of them engaging in violent acts [88]. A rich glossary of Incel terms can be found in manuals, such as the one produced by Moonshot, an organization working against online extremism [88].

Conclusion

Technology has offered several advantages and improvements in modern life, including novel forms of communication and entertainment, such as digital games and social media platforms. Nonetheless, along with the benefits, these modern

tools have been associated with negative consequences that range from physical and mental health problems to political movements and humanitarian crises. Therefore, it is essential that health professionals be aware of these emerging mental health conditions, with some already being considered in diagnostic manuals. Even though the field presents several limitations concerning the level of the scientific evidence, significant advancements were made recently in the quality of published studies.

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