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Digital Interventions for Mental Disorders: Key Features, Efficacy, and Potential for Artificial Intelligence Applications

David Daniel Ebert, Mathias Harrer, Jennifer Apolinário-Hagen and Harald Baumeister

Abstract

Mental disorders are highly prevalent and often remain untreated. Many limitations of conventional face-to-face psychological interventions could potentially be overcome through Internet-based and mobile-based interventions (IMIs). This chapter introduces core features of IMIs, describes areas of application, presents evidence on the efficacy of IMIs as well as potential effect mechanisms, and delineates how Artificial Intelligence combined with IMIs may improve current practices in the prevention and treatment of mental disorders in adults. Meta-analyses of randomized controlled trials clearly show that therapist-guided IMIs can be highly effective for a broad range of mental health problems. Whether the effects of unguided IMIs are also clinically relevant, particularly under routine care conditions, is less clear. First studies on IMIs for the prevention of mental disorders have shown promising results.

D. D. Ebert (✉)
Department of Clinical Psychology, Vrije Universiteit Amsterdam,
Van der Boechorststraat 1, 1881 BT Amsterdam, The Netherlands
e-mail: d.d.ebert@vu.nl

M. Harrer
Clinical Psychology and Psychotherapy, Friedrich-Alexander-University
Erlangen-Nuremberg, Erlangen, Germany
e-mail: mathias.harrer@fau.de

J. Apolinário-Hagen
Faculty of Psychology, Department of Health Psychology,
FernUniversität in Hagen, Hagen, Germany
e-mail: jennifer.apolinario-hagen@fernuni-hagen.de

H. Baumeister
Clinical Psychology and Psychotherapy,
University of Ulm, Ulm, Germany
e-mail: harald.baumeister@uni-ulm.de

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Despite limitations and challenges, IMIs are increasingly implemented into routine care worldwide. IMIs are also well suited for applications of Artificial Intelligence and Machine Learning, which provides ample opportunities to improve the identification and treatment of mental disorders. Together with methodological innovations, these approaches may also deepen our understanding of how psychological interventions work, and why. Ethical and professional restraints as well as potential contraindications of IMIs, however, should also be considered. In sum, IMIs have a high potential for improving the prevention and treatment of mental health disorders across various indications, settings, and populations. Therefore, implementing IMIs into routine care as both adjunct and alternative to face-to-face treatment is highly desirable. Technological advancements may further enhance the variability and flexibility of IMIs, and thus even further increase their impact in people's lives in the future.

Keywords
Internet interventions · eHealth · Mental disorders · Psychotherapy · Prevention · Artificial intelligence · Machine learning

Introduction

Mental disorders are highly prevalent, with lifetime and 12-month prevalence rates estimated to range between 18–36% and 10–19%, respectively [1, 2]. Worldwide, mental disorders are one of the leading causes of disability [3]. They are associated with an enormous disease burden, including poorer quality of life [4], worse educational attainment and social role functioning [4–8], increased risk of developing chronic somatic conditions and related mortality [10], as well as suicidality [11, 12]. The World Health Organization (WHO) estimates that by 2030, depression alone will be the largest contributor to the total burden of disease worldwide [13].

It is well established that psychological interventions are an effective procedure for the treatment of various mental disorders, including depression [14–16], anxiety disorders [17–19], posttraumatic stress disorder [20, 21], personality disorders [22, 23], psychosomatic disorders [24–26], or sexual dysfunction disorders [27], to name only a few indications. However, research also documents a large treatment gap, as the majority of individuals suffering from a mental disorder remain untreated. In developed countries alone, treatment coverage of mental disorders only ranges from 23 to 46% [28–30]. Structural shortfalls, such as a lack of therapists within proximity, or long waiting times, do not appear to be the sole reason for such low treatment rates. Research suggests that psychological barriers to treatment may also play an important role. Despite the availability of effective treatment, many individuals prefer to deal with mental health issues on their own or are afraid of stigmatization [31, 32]. Furthermore, even in successfully treated patients, relapse remains frequent [33, 34], and cost-effective measures for after-care are needed.

Technological advancements in the last decades have enabled the development and provision of Internet and Mobile-based psychological Interventions (IMIs [35]). Many limitations of traditional psychotherapeutic interventions could potentially be overcome with such interventions. IMIs are free from the restraints of location and time, and allow for reaching participants who would not make use of mental health treatments otherwise. They may therefore be a viable means to optimize current practices in mental health treatment. Nevertheless, the implementation of IMIs also raises new questions concerning effectiveness, safety, as well as patient and professional preferences.

In this chapter, we will provide an overview on the status and future development of IMIs. We aim to define the core elements of IMIs and review available evidence for their efficacy and mechanisms of change in treating and preventing mental disorders. We will also describe the important ethical and professional considerations associated with IMIs. Lastly, we illustrate current advances and future directions of the field, such as the application of data-driven methods and Machine Learning, and discuss their implications.

Key Features of Internet- and Mobile-Based Interventions

A basic feature of all IMIs is the transference of therapeutic processes to a digital environment. Like face-to-face psychotherapy, IMIs aim to modify individuals' emotions, cognitions, and behaviors, and promote their generalization to the daily life of users through established psychotherapeutic techniques. There is, however, a wide range of possibilities for using IMIs for the prevention and treatment of mental disorders, including mobile applications, stand-alone self-help interventions, or IMIs integrated into conventional on-site psychotherapy (i.e., blended concepts). IMIs can be categorized according to the technology they use, the extent of human support, the theoretical basis, and with respect to their areas of application. In Fig. 1, key aspects of IMIs are presented.

Theory Base

It is of utmost importance to resort to evidence-based psychotherapeutic models and techniques when developing and implementing IMIs. Among all psychotherapeutic approaches, most empirical evidence currently supports the efficacy of cognitive behavioral (CBT) techniques for common mental disorders [36, 37]. Furthermore, most CBT manuals are highly structured, standardized, and focus on specific strategies and concrete behavior. This is probably why most evaluated IMIs have used CBT principles as their treatment rationale [38]. Such approaches are often referred to as *iCBT* (Internet-based cognitive behavioral therapy [39]) or *cCBT* (computerized cognitive behavioral therapy). Nevertheless, IMIs are not

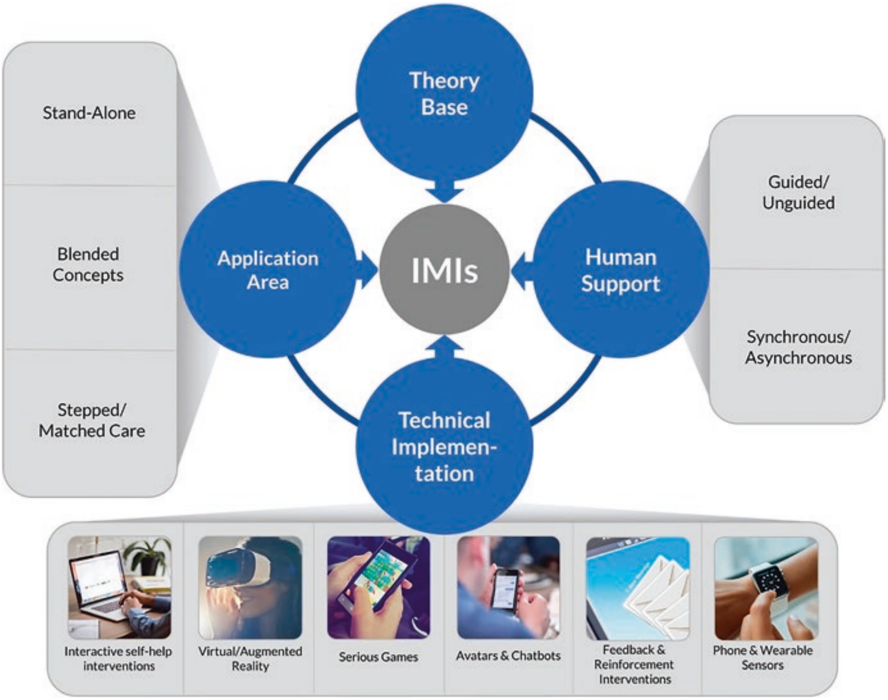

Fig. 1 Key aspects of Internet- and mobile-based interventions

restricted to any type of specific therapy approach. In recent years, other psychotherapeutic theories have also been used as the basis of IMIs, such as psychodynamic or mindfulness-based approaches [40–45].

Technical Implementation

For the implementation of IMIs, developers rely on a diverse and rapidly growing technical repertoire. Such modes of delivery include:

1. Interactive self-help interventions providing evidence-based psychological strategies through web-based platforms and/or mobile apps.
2. Virtual or augmented reality interventions for exposure to feared stimuli [46–48].
3. Serious games, training psychological strategies in a video game format [49].
4. Avatar-led therapy sessions [50] or chatbot-mediated interventions [51].
5. Automated memory, feedback, and reinforcement interventions delivered through apps, e-mails, text messages, or short prompts, which support the participant in incorporating intervention content into everyday life [52].

6. Phone and wearable sensors, as well as apps to monitor symptoms or motivate health behavior, such as homework completion or healthy behaviors to support the therapeutic process [53].

Videoconferencing [54] and other telehealth services, which primarily assist communication between therapist and patient may also be classified as IMIs. However, such services share greater similarities with conventional on-site psychotherapy and will therefore not be discussed here.

Human Support

IMIs can integrate varying degrees of human support. A commonly used method is guided self-help approaches. Such interventions provide multimedia-based self-help material, so that most tasks and techniques can be performed independently. A clinical psychologist, health professional or trained lay health worker then provides feedback or guidance in a regular interval. A major aim of human support in stand-alone IMIs is to foster adherence to intervention contents [55–57]. To reach this, communication can happen either synchronously (per chat or video) or asynchronously (e.g., via e-mail). Asynchronous communication formats are more commonly used and usually take from a few minutes to a few hours per participant and intervention. For users, the processing of self-help material, execution of exercises, and correspondence with a therapist can be very intense. IMI users may thus invest much greater time than the supporting therapist. Nevertheless, asynchronous contact and time-independent communication allow for increased flexibility and autonomy for both participants and therapists.

Area of Application

Possible applications of IMIs in the mental health field are manifold. IMIs can be used, among other things, for mental health promotion, prevention and treatment of mental disorders, prevention of relapse or recurrence of mental disorders, or chronic illness management. From a public health perspective, IMIs can be considered a promising approach to increase the accessibility of evidence-based psychotherapeutic techniques in the general population due to their low threshold for accessibility, location and time independence, and anonymous usability [58]. IMIs can be applied as stand-alones, within a stepped-care approach, or as blended treatment approaches, in which IMI and conventional face-to-face psychotherapy components are combined.

Stand-alone IMIs. A large asset of stand-alone IMIs is their independence from space and time. Stand-alone IMIs can be accessed through the Internet or a smartphone app at any time, and everywhere, thus facilitating the access to evidence-based interventions for individuals with limited mobility or people living in underserved areas. Such approaches could also overcome common psychological barriers by helping people with difficulties expressing themselves or individuals not appreciating social or human contact [59]. People who are not inclined to use conventional face-to-face psychotherapy due to reasons such as fear of stigma could access IMIs as an alternative. Despite the increasing social acceptance of psychotherapy, having mental health problems still causes a feeling of shame in many individuals, resulting in help-seeking barriers [60]. Using distant technologies such as IMIs may be a suitable way to address such issues. Stand-alone IMIs can also be disseminated as massive open online interventions (MOOIs) to offer free behavioral health services worldwide at minimal costs [61]. They could therefore be an innovative instrument to increase access to evidence-based interventions in countries with defunct or insufficient health care services around the globe [62].

Blended Care. In blended concepts, face-to-face psychotherapies are combined with IMIs [63]. The extent to which treatment is provided through online-based components can vary in such concepts. In some blended concepts, face-to-face treatment remains the primary delivery mode, and only some treatment elements are supported through digital components. For example, traditional psychotherapy can be supported with mobile-based exercises to facilitate adherence to homework assignments. Conversely, IMIs can also serve as the major part of the treatment, and face-to-face meetings are scheduled as a support element. In blended care concepts, IMIs may either replace parts of psychological treatment, especially parts of the treatment which do not require mediation by a psychotherapist. This enables that time during therapy sessions can be used more efficiently, providing more time for face-to-face process work. However, conventional treatment could also be augmented through application of IMIs to improve its effectiveness. IMIs can be used in such contexts to provide exercises for the participant to work on between sessions, or to support the integration of behavior changes into daily life. Instruments to achieve this are mobile-based diaries, ultrashort prompts aimed at training previously learned strategies, or mobile coaches leading patients through difficult situations. This allows expanding the “therapeutic arm” into patients’ everyday experiences and behaviors. Another promising application of blended concepts might be the delivery of psychological IMIs in chronic somatic care [64–68].

Stepped and Matched Care. Stepped-care approaches adapt the degree of therapeutic support based on previous intervention effects, while matched care matches patients based on baseline characteristics such symptom severity or comorbidity indicators to specific treatment formats such as self-help-guided self-help or blended care. For depression, for example, self-help IMIs can be offered in a stepped-care approach as a first step to individuals showing prodromal symptoms of the disease to prevent the onset of a major depressive episode [69, 70]. Intensive therapeutic support is provided in case patients do not respond to IMIs. As step-down interventions, IMIs can be used for relapse prevention and chronic care in remitted patients to stabilize treatment effects [71–76].

Efficacy

Internet Interventions Compared to Control Groups

The substantial potential of IMIs to prevent and treat mental and behavioral disorders is documented by countless randomized controlled trials (RCTs) which have been conducted within the last 20 years. The efficacy of guided self-help interventions is particularly well established. Common mental disorders, such as depression and anxiety disorders, have been studied frequently in IMI research. In such studies, IMIs have been found to be highly efficacious when compared to untreated controls (e.g., [77–82]). A recent meta-analysis, comprising ten studies, found a statistically significant pooled effect of Hedges' $g = 0.90$ (95% CI 0.73-1.07, $p < 0.001$) favoring IMIs compared to waitlist controls in the treatment of major depression [83]. Compared to waitlist controls, a recent Cochrane review on Internet-based therapist-assisted self-help for anxiety disorders found a large effect of $g = 1.06$ (95%CI: 0.92–1.29, $p < 0.001$; 28 studies) favoring IMIs [82].

Table 1 Efficacy of IMIs based on selected meta-analytic reviews

Target population	Study authors	SMD	[95% CI]	*k*	*N*	I^2
Adults						
Major depression	Königbauer et al. (2017)	0.90	[0.73; 1.07]	10	727	0
Panic disorder	Olthuis et al. (2015)	1.52	[0.48; 2.56]	6	323	93
Social phobia	Olthuis et al. (2015)	0.92	[0.74; 1.09]	8	661	48
Generalized anxiety disorder	Olthuis et al. (2015)	0.80	[0.42; 1.19]	6	394	69
Posttraumatic stress disorder	Kuester et al. (2016)	0.95	[0.56; 1.43]	8	936	91
Insomnia	Zachariae et al. (2015)	1.09	[0.74; 1.45]	8	1071	83
Eating disorders	Melioli et al. (2016)	0.31[a]	[0.21; 0.42]	16	1643	0
Hazardous alcohol use	Riper et al. (2014)	0.20	[0.13; 0.27]	16	5612	27
Obsessive-compulsive disorder	Own calculations[b]	0.90	[0.61; 1.19]	3	122	0
Chronic pain	Buhrmann et al. (2016)	0.42	[0.28; 0.55]	15	2213	54
Irritable bowel syndrome	Own calculations[c]	0.74	[0.37; 1.11]	4	353	58
Children and Adolescents						
Depression	Ebert et al. 2015	0.76	[0.41,1.12]	4	796	61
Anxiety	Ebert et al. 2015	0.68	[0.45,0.92]	7	796	0

[a]Purging

[b]Own calculations (Hedges' g using Comprehensive Meta-Analyses 2.0) based on primary study results of Andersson et al. (2012), Herbst et al. (2014), and Lenhard et al. (2017)

[c]Own calculation of between-group effect sizes, based on studies reported in Hedman et al., 2012. SMD = standardized mean difference (Cohen's d/Hedges' g); CI = confidence interval; k = number of primary randomized trials; N = number of participants in primary studies included in the meta-analysis

Meta-analytic evidence also supports the effectiveness of IMIs for a plethora of other indications, including posttraumatic stress disorder (PTSD), sleep disorders, eating disorders, chronic pain, or substance abuse [84–88]. Table 1 presents current meta-analytical evidence on the effects of IMIs for different disorders compared to untreated controls.

Individual RCTs also provide promising evidence for the efficacy of IMIs for a range of other disorders, such as obsessive-compulsive [89–92], dissociative [93, 94], body dysmorphic [95], and bipolar disorders [96], as well as for sexual dysfunction [97–101], tinnitus [102–111], complicated grief [112–114], pathological gambling [115, 116], fatigue [117, 118], as well as suicidal thoughts and behaviors [119].

However, for some indications, the substantial heterogeneity of effects between studies should be considered. Not all IMIs result in similar effects, and more research is warranted to disentangle which intervention works for whom, and in which context. Many of the studies mentioned above used waitlist control designs to determine the effectiveness of IMIs, which is a rather weak control group design. Treatment expectancies have been discussed as an artifact in such trials, because participants with delayed access to treatment might be less motivated to initiate behavior changes [120]. This may cause such studies to overestimate the effects of IMIs compared to what can be expected in routine care.

Internet Interventions Compared to Face-to-Face Treatments

The potential of IMIs is also illustrated by their efficacy compared to face-to-face therapy. In 2014, Andersson and colleagues synthesized evidence from 13 RCTs focusing on various disorders (including depression, phobias, tinnitus, anxiety disorders, and sexual dysfunction disorders), and found no differences in effect size for direct comparisons between guided IMIs and face-to-face psychotherapy ($g = 0.01$; 95% CI 0.13–0.12; [111]). These results were further corroborated by a Cochrane review for IMIs targeting anxiety disorders in adults ($g = 0.06$; 95% CI 0.37–0.25; in the direction of favoring face-to-face; [82]), a meta-analysis by Andersson and colleagues for the treatment of depression ($g = 0.12$, 95% CI 0.06–0.30; in the direction of favoring guided IMIs [121]), and an update of the initial meta-analysis in 2018 by Carlbring, Andersson, and colleagues [122]. Even though the number of RCTs evaluating IMIs in direct comparison to face-to-face psychotherapy is still limited, all current meta-analyses indicate that IMIs and conventional psychotherapy are equivalent in their effects. However, these results do only count for individuals who are willing to participate in Internet-based or onsite treatment. IMIs, which usually have a strong self-help focus, are not an option for some patients [123–126], while face-to-face treatment is not an attractive intervention format for all either [31]. A recent survey among 641 patients with depressive symptoms in primary care, for example, revealed that younger individuals with higher levels of education could be more likely to prefer IMI-based treatments than other patient groups [127].

There is a small, but steadily increasing number of studies suggesting that blended concepts can also serve as an effective approach to increase the effects of current state-of-the-art treatments [63]. Sethi and colleagues [128] found, for example, that blended face-to-face and iCBT was superior to both face-to-face therapy and iCBT alone in the treatment of depression and anxiety in youth. A meta-analysis by Lindhiem and colleagues [129] supports that increasing the effectiveness of psychological interventions through blended concepts might be possible. Synthesizing 10 RCTs, they found that psychological interventions were considerably more effective for various indications when on-site sessions were supplemented by mobile-based treatment components (SMD = 0.27, $p < 0.05$). Preliminary evidence also suggests that blended concepts can reduce the time clinicians have to invest for each client without compromising treatment efficacy [130, 131]. However, Kenter and colleagues [132], comparing blended CBT in routine care to routine face-to-face data in a naturalistic study, in which therapist was not asked to follow a specific standardized concept, found that, while outcomes were equivalent, blended concepts were associated with a higher number of sessions and more time invested by the therapist. This was the case because Internet-based contents were only provided in addition to face-to-face therapy. Such findings underline the importance of developing a stringent implementation model aimed at allowing therapists to delegate tasks to digitalized tools. More valuable insight on the potential of blended concepts can be expected from a number of large international studies investigating the topic [133–136] which have currently been finalized, or are still ongoing.

Prevention of Mental Disorders

Ebert, Cuijpers, Muñoz, and Baumeister [137] identified 10 RCTs focusing on the effect of IMIs on the incidence of mental disorders in asymptomatic or subclinical populations. Six of these studies reported positive results, with the number needed to treat (NNT) to avoid one additional disorder onset ranging from 9.3 to 41.2. Since then, Buntrock, Ebert, and colleagues found a guided IMI to be effective in reducing the risk of developing depression by 41% within 1 year [70, 138, 139]. They also found the intervention to show an acceptable cost-benefit ratio [140]. Findings on the prevention of relapse in patients with fully or partially remitted depression using IMIs are mixed. While Holländare and colleagues [141] found that guided iCBT led to significantly reduced relapse rates during a 2-year follow-up compared to controls, Klein and colleagues [142] did not find such effects when evaluating an IMI providing less human support to patients, despite favorable short-term results.

In sum, current evidence indicates that, potentially, prevention of mental disorders using IMIs is possible. Furthermore, there is a large body of evidence supporting the effectiveness of IMIs in promoting health behavior, such as the reduction of problematic alcohol consumption [143, 144], improving sleep [85, 145, 146], and reducing work-related or academic stress [147–152], all of which might contribute to preventing mental disorders from a broader perspective as well.

Nonetheless, the research on preventive IMIs is still in its infancy, making it impossible to draw definite conclusions. For both the prevention of depression and anxiety, observed effects of psychological preventive interventions in general tend to be lower in studies with follow-up periods longer than 1 year, indicating that current available psychological interventions might potentially only delay, and not prevent the onset of the disorder [153, 154]. As by now, whether IMIs actually have the potential to prevent mental disorders can thus not be ultimately decided.

Cost-Effectiveness

Mental disorders result in enormous societal costs [155–157], both directly (e.g., through general practitioner visits, medication, social services, stationary treatment) and indirectly (e.g., through sickness leave, worse job functioning, or mortality). In European countries alone, the total costs of depression are estimated to sum up to as much as 118 billion Euro (app. 137 billion US-Dollars [157]). As health care resources are limited, and thus have to be used economically, health economic analyses of IMIs allow to analyze if intervention costs stand in proportion to their effectiveness [158]. There are two recent systematic reviews supporting the cost-effectiveness of guided IMIs [159, 160]. Paganini and colleagues found a net benefit of 3,088–22,609 Euro (3,581–26,288 US-Dollars) per participant for guided depression prevention IMIs. These findings support the implementation of IMIs from a health economic perspective. However, current evidence does not allow to come to ultimate conclusions if IMIs are the most economical of all available treatment approaches for mental disorders [159].

Routine Care

Accumulating evidence suggests that IMI-based treatment can also result in clinically relevant improvements for many disorders when implemented into routine care [161–168]. In a recent paper, Titov and colleagues [169] describe that in Sweden, Denmark, Norway, Canada, and Australia, online clinics providing guided IMIs have already been successfully implemented, and have shown to be effective in treating patients under routine conditions. Whether unguided IMIs also have this potential is much less clear. Meta-analyses have shown that unguided IMIs can be effective, for example, in addressing anxiety disorders [82], or depression [170]. It should be considered, however, that such evidence is based on RCTs, in which researchers indirectly provide a high level of structure and positive regard to subjects as part of the study procedures. These factors are unlikely to be found in routine clinical care. Human support functions as an adherence-promoting element in IMIs. It is therefore likely that the effect sizes of IMIs which do not provide any human contact are overestimated in RCTs when compared to their potential in routine care [171]. Lin and colleagues [172], for example, found that adherence to an unguided IMI for chronic pain was remarkably low when the intervention was not provided in a clinical trial context, with virtually none of the patients completing the intervention. In a pragmatic study, Littlewood and colleagues [173] found no additional benefit of an unguided IMI compared to standard treatment. However, when the same intervention was delivered with additional telephone support in addition to general practitioner care, it was found to be superior to the pure unguided intervention [174]. Based on current evidence, preference in routine care should thus be given to guided interventions. Nevertheless, unguided interventions do also offer some advantages, including their low costs. Research by Muñoz and colleagues [61] suggests that unguided IMIs can be used as MOOIs to facilitate the provision of evidence-based mental health interventions worldwide. Such interventions could be combined within digital apothecaries [175] to promote behavioral health and address mental disorders through prevention and treatment, especially in countries with limited access to free health care. Overall, more research is warranted into how digital health care services can be optimally integrated into routine care [176]. *ImpleMentAll*, a current large project investigating the implementation of IMIs into routine care in 11 European countries, may provide more insight into this matter in the future.

Acceptance-Facilitating Interventions

Despite the increasing implementation of IMIs into routine care, uptake is still often low, with rates ranging from 3 to 25% [177–181]. Psychological factors are a common barrier toward seeking treatment [31], and thus may also apply to IMIs. Research also documents that many individuals in the general population have little knowledge about IMIs [125, 126]. Many misperceive IMIs as being less effective than conventional therapies [126], including therapists [182, 183], although previously presented evidence clearly shows that this is not the case. In a survey of the German general population ($N = 646$), Apolinário-Hagen and colleagues [126] found that awareness of Internet-based treatment is associated with higher preference for IMIs. This finding points to the importance of developing measures to increase awareness of and knowledge about the efficacy of IMIs in the public to raise their acceptance. Recent developments, such as acceptance-facilitating interventions (AFIs) using brief, highly scalable educational videos have been shown to be a valid strategy to enhance the acceptability of Internet interventions in clinical practice [124, 184–187]. AFIs can be easily disseminated through official health care information channels. Therefore, they might be a promising approach to increase the public acceptance of IMIs and their utilization.

Limitations and Possible Negative Effects

Although IMIs may have immense benefits for individual patients and the health care system, risks and potential negative effects must also be properly considered. As by now, however, no reliable information is available on potential contraindications for IMIs, warranting further research. An individual patient data meta-analysis by Ebert and colleagues [188] found that guided IMIs significantly reduce the risk for symptom deterioration compared to controls. In this analysis, no patient subgroup with increased risk for deterioration was detected. However, it was found that education level moderated effects on deterioration, meaning that participants with a low level of education should be more closely monitored, as they might show a greater risk for deterioration. In the context of stand-alone methods with no human support, it has often been argued that emergencies, such as acute suicidality, cannot be addressed appropriately in IMIs. Suicidality is therefore often considered as an exclusion criterion for stand-alone IMIs. Studies show, however, that IMIs can be used effectively in treating suicidal patients, and can decrease suicidal thoughts and behaviors [189, 190]. Further research should therefore explore in which contexts IMIs can be used safely in patients showing suicidal ideation. Overall, although initial studies address the subject of negative effects of IMIs [188, 191–193], little more can be said about this topic right now. In addition, there is currently no consensus about the reporting of adverse events in clinical trials of IMIs. Other negative effects of IMIs, including imprecise diagnoses, lowered health-related self-efficacy or negative attitudes toward psychological interventions in patients who do not profit from IMIs, excessive demands on IMI users, increased dependence on technology, or the delivery of potentially harmful techniques may be possible, but further research is needed to shed more light on this topic.

Mechanisms of Change

In the past, IMI research has primarily focused on the question if such formats can be effective at all. Current research is increasingly concerned with establishing mechanisms of change in IMIs. However, such research questions are still in their beginnings, and it cannot be fully answered what makes IMIs work. As most IMIs integrate evidence-based psychotherapeutic techniques into their rationale, one can assume that the mechanisms of change underlying those techniques are an active component in IMIs. Yet, confirming specific effects of an active component is notoriously difficult in psychotherapy research (cf. [194] p. 241ff.). A recent systemic review by Domhardt et al. [195] on IMIs for anxiety suggests, seemingly, that the different psychotherapeutic techniques are not active ingredients of IMIs (neither CBT vs. other techniques, nor disorder-specific vs. transdiagnostic techniques). Furthermore, cognitive factors (e.g., negative automatic thoughts, rumination, or dysfunctional attitudes), emotion regulation, expectancy, attributional style, coping strategies, perfectionism, therapeutic alliance, and treatment credibility have been examined as mechanisms of change [108, 196–205]. It seems plausible to assume that nonspecific factors equal to those of face-to-face psychotherapy also contribute to the efficacy of IMIs. Nevertheless, when focusing on mechanisms of change in IMIs, features which are special to such interventions should also be properly considered. Here, we will describe three mechanisms through which IMIs may contribute to individuals' mental health and well-being: self-empowerment, reinforcement mechanisms, and human guidance.

Self-empowerment

Previously, we described that IMIs do not have to be inferior to on-site psychological interventions in section "Internet Interventions Compared to Face-to-Face Treatments". One explanation for this finding could be that IMIs, while providing less human contact, put a stronger emphasis on self-empowerment. Empowering patients through IMIs may therefore foster users' self-management skills, with then translate to treatment benefits. Alpay and colleagues [206] delineate specific components of empowerment which IMIs may use to foster self-management, such as increasing health or disorder literacy, promoting coping self-efficacy, and specific problem-solving skills, as well as providing heuristics for decision-making. There is evidence showing that IMIs can contribute to the empowerment of patients with mental disorders [207] or chronic diseases [208, 209]. However, whether amelioration of self-management is indeed a mechanism of change contributing to the efficacy of IMIs is still largely unclear. Further process studies are needed to gain a better understanding of the mechanisms underlying patient empowerment in IMIs.

Reinforcement Mechanisms

In contrast to traditional psychotherapy, IMIs allow for sending automatized reminders, feedback, and reinforcements (so-called *prompts*) to increase the application of previously learned strategies and techniques into daily life. One way to implement this is through ultra-brief exercises sent to users' mobile phones via SMS. Another important way is reminders to support the usage of IMIs, which can increase treatment adherence. At the same time, such applications are very economical and easily programmed. A meta-analysis by Cowpertwait and Clarke [210] supports the relevance of prompts in driving IMI effectiveness. In subgroup analyses, they found that IMIs for depression in which reminders were integrated showed larger effect sizes ($g = 0.49$) than interventions without reminders ($g = 0.24$).

Human Support

Technology-mediated human support (guidance) can be considered a more well-studied mechanism of effective IMIs. Meta-analytic research suggests that guided IMIs show greater effects than IMIs with no human support element [80, 147, 152, 210, 211]. In these analyses, guided IMIs also show lower attrition rates and higher numbers of completed modules ($g = 0.52$). For the treatment of depression, guidance seems to be particularly influential. Richards and Richardson (2012) found a small effect of unguided IMIs for depression ($g = 0.36$), but high effects ($g = 0.78$) for guided interventions. A more recent meta-analysis [83] could not corroborate this finding, but this might have been due to limited power. No significant differences in effects between unguided and guided IMIs could be found in the treatment of anxiety in one meta-analysis [82], while a more recent analysis suggests that guided IMIs are superior over unguided IMIs [195]. This suggests that the effect of guidance might be more complex than the simple generic superiority hypothesis suggests.

Evidence from systematic reviews indicated that the efficacy of IMIs increases with the degree of human guidance provided. Yet, Andersson and colleagues [212, 213] estimated that exceeding 100 min of support per participant in a 10-week IMI does not translate to higher treatment effects anymore. It is still unclear, however, which dosage of guidance is optimal at which stage of treatment. Further research is needed to discern which characteristics of human support are most important: is it the quantity, or the quality (viz., coach qualification) of human support that matters? Which communication medium (e-mail, face-to-face, video chat, phone) and communication mode (asynchronous or synchronous) should be used, and does this vary for different disorders and patient subgroups?

Despite this lack of in-depth knowledge concerning the intricate details of human support in IMIs, there is evidence showing that therapeutic alliances of high quality can be achieved with such interventions. Although IMIs provide less therapeutic contact, and social and nonverbal cues are often completely absent, the quality of therapeutic relationships in IMIs is often comparable to face-to-face treatment [214–219].

Some models have been proposed to conceptualize and optimize human support in IMIs, such as the supportive accountability [220] and efficiency model [56]. According to the supportive accountability model, human support can be used to increase adherence to an intervention by providing accountability through a coach who is perceived as caring, trustworthy, and competent. The model states that patient motivation plays a crucial role in determining the importance of guidance. While patients who are intrinsically motivated to use an IMI do not require as much feedback and guidance to adhere to the intervention, patients for which this is not the case need more human support to uphold extrinsic motivation to stay engaged. The efficiency model of support, on the other hand, might be a valuable framework to guide researchers in developing optimally tailored, efficient support systems for IMIs.

Ethical and Professional Considerations

As a novel approach to the prevention and treatment of mental disorders, new risks and opportunities arise from the implementation of IMIs. Since mental and physical health plays an important role in many individuals' lives, there is a large demand for freely available technological instruments to promote one's own well-being. Thus, many start-ups and corporations have started to capitalize on this interest by providing an ever-growing number of commercial Internet portals, mobile health apps, or online life coaching services. For costumers, however, it is often hard to see which services are based on sound empirical evidence, and which ones are not. Recent studies have shown that less than 4% of all commercial apps for symptoms of depression [221] and anxiety [222] have been subject to rigorous clinical examination like the studies we presented in 3.1–3.5 [223]. To protect costumers from dubious products and to provide assistance in finding evidence-based, effective services, consolidated quality standards for commercially available IMIs are needed [224]. Such standards have been recently established in countries such as the Netherlands, the United Kingdom, and Germany [224].

On the other hand, the enormous potential of strictly evidence-based IMIs also suggests that withholding such interventions as a complementary treatment option for patients is also ethically questionable. As we have shown before, IMIs can lead to comparable outcomes as state-of-the-art services and have the potential to reach individuals who may not want to use conventional treatment approaches. Therefore, one should differentiate if IMIs are used as a supplement to, or a replacement of current treatments. Using IMIs to improve existing health care infrastructure might be beneficial to both patients and the health care system. Aiming to replace conventional treatments with IMIs because they are more economic, of course, is much more critical from an ethical perspective.

Future Advances: Machine Learning and Data-Driven Applications

Most IMIs developed today still resemble conventional face-to-face psychological interventions in many ways. Typical IMIs contain bundles of various psychological techniques and modules (e.g., psychoeducation, behavioral activation, cognitive restructuring, progressive muscle relaxation) adapted from evidence-based face-to-face interventions. Such modules are then assembled into a "treatment package" and delivered on a digital platform. Although the evidence we presented before clearly documents the effectiveness of such approaches, recent advances in the field of statistical learning may allow to make IMIs even more pervasive and impactful in the lives of their users in the future.

The last decades have seen the advent and proliferation of "Artificial Intelligence", especially in terms of the development of Machine Learning methods [225]. Machine Learning algorithms automatically determine ("learn") parameters from data to optimally fulfill a certain task. They also have a tight focus on predicting outcomes in unseen data and are thus often referred to as *predictive modeling* methods [226, 227]. Applications of predictive modeling have been facilitated by the increased volume, variety, and velocity (the *Three V's* [228]) of data collected, stored, and processed. In this respect, IMIs have an enormous advantage compared to traditional face-to-face psychotherapy, as they easily allow for the collection of unprecedented amounts of fine-grained patient and process data [229]. IMIs are therefore a key field in which Machine Learning and

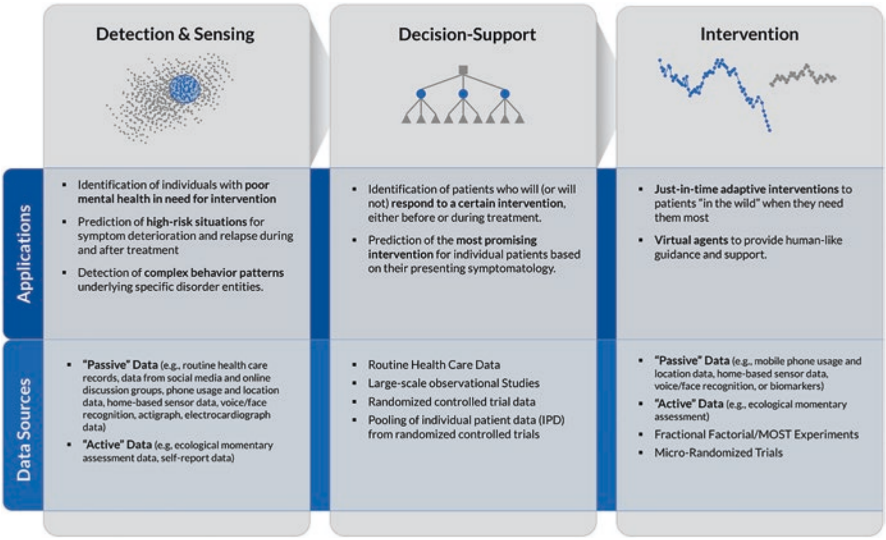

Fig. 2 Overview of artificial intelligence applications in psychological intervention research

data-driven approaches can be applied to advance the prevention and therapy of mental disorders as a whole.

In the following, we will provide a brief overview of recent advances in data mining and Machine Learning to (i) detect mental disorders, (ii) generate data-driven decision-support systems, and (iii) optimize intervention approaches, focusing on Internet- and mobile-based measures. Presented findings were gathered by searching two large bibliographical databases (*PubMed* and *PsycInfo*) on August 26th, 2018, and screening previous review articles on overlapping topics. Nevertheless, our overview is not meant to be exhaustive (Fig. 2).

Detection and Sensing

Although there is no dearth of evidence-based, effective measures to treat mental disorders, research still documents a large treatment gap in the general population, with 54–77% of all mental disorders remaining undiagnosed and untreated [28–30]. As mental disorders have a long-standing negative impact on individuals' physical health, mortality, and social functioning [4–10], early detection of mental disorder symptoms is of paramount importance. Due to their capability to accrue meaningful information from large and complex data sets, Machine Learning approaches could therefore be successfully applied to overcome current limitations in the:

- Identification of individuals with poor mental health in need for intervention.
- Prediction of high-risk situations for symptom deterioration and relapse during and after treatment.

- Detection of complex behavior patterns underlying specific disorder entities.

Predictive models for the identification and prediction of poor mental health can be derived from two types of data sources: *passive data* (such as routine health care records, data from social media and online discussion groups, phone usage and location data, home-based sensor data, voice/face recognition, actigraph, and electrocardiograph data), and *active data* (such as ecological momentary assessment (EMA) data, self-report data).

Identification of individuals with poor mental health. Although the field is still in its infancy, a rising number of studies suggests that Machine Learning applications may play a pivotal role in detecting mental health issues in the general population in the future [230]. Social media in particular provides an unprecedented opportunity to crawl real-life mental health-related data, extract and select relevant features, and train valid models to detect untreated individuals facing mental health issues on the Internet using Machine Learning algorithms. Already, social media data have been used to determine symptoms of depression [231–240], stress and well-being [241–244], PTSD [245, 246], eating disorders [247, 248], or suicidality [249–254], to name a few indications. Burnap and colleagues [253], for example, developed a machine classifier to distinguish factual reporting of suicide on Twitter from content reflective of suicidal ideation in users. Employing face detection, color and metadata analysis, Reece and Danforth [240] extracted statistical features from more than 40.000 photos posted by 166 individuals on Instagram. With this data, they could train a model predicting the prevalence of depression with higher accuracy than general practitioners. The model also outperformed clinicians when only photos posted by individuals before they were diagnosed with depression were used. Kornfield and colleagues [255], using a bag-of-words-based Machine Learning approach, were able to identify struggling alcohol abuse patients in an online discussion forum with an excellent accuracy of AUC = 0.92.

Routine health care data sets, on the other hand, can also be used to better detect mental health issues [256–261], and improve their diagnosis [262, 263]. Chekroud and colleagues [259], for example, obtained large data sets from US National Health Surveys. Using various Machine Learning techniques, they developed a prediction model to identify individuals with depression who do not receive needed treatment. The learned model reached a prediction accuracy of 72% in detecting untreated patients. This approach may be particularly promising, as patients identified with such models could be offered IMI-based services to overcome structural or psychological barriers to treatment on a population level. Jiménez-Serrano and colleagues [264], for example, developed a classification model for mothers at high risk for postpartum depression the first week after childbirth, along with a tailored mobile-based app to more easily provide interventions to identified cases.

Prediction of high-risk situations for symptom deterioration and relapse. As technological advances have expanded the ability to collect and process real-time behavioral and biological data, predictive modeling is also a promising approach to forecast high-risk situations for mood decrements, symptom deterioration, or relapses. Such approaches may be used either during treatment, or for relapse prevention in remitted patients. Portable sensors play an important role in this development. *Wearables*, such as Smart Watches or Fitness Trackers, can serve as accelerometers, pedometers, actigraphs, GPS trackers, or electrocardiographs, thus producing enormous amounts of diverse personal data to predict mood states and behavior [265, 266]. Smartphones, a ubiquitous companion for most people, can also be turned into mobile sensors using applications developed for this purpose in recent years (e.g., *Purple Robot* [267] or *Beiwe* [268]). By aggregating such information, general or personalized predictive models [229, 269] can be learned to extrapolate mood states [269], refine mental disorder diagnoses [270, 271], or predict relapse [272, 273], to name only a few applications. Predictive modeling has already been applied to detect symptoms of depression [274–277], stress [278–280], and autism [281], to predict sleep quality [282] or relapse risk in patients with substance addictions [270] and psychosis [283]. Pratap and colleagues [275], for example, collected passive phone usage data from 241 patients with depression. Results of this study show that personalized Machine Learning models can reach promising results in predicting mood changes in depressive patients. Depp and colleagues [284], using daily self-report data from 86 individuals with bipolar disorder, were able to reach an excellent AUC (area under the curve; defining the quality of a screening assessment to predict the presence of the respective condition) of 0.91 in predicting heightened suicidality in patients, thus doubling the predictive accuracy compared to only using baseline symptomatology data.

Detection of complex behavior patterns underlying specific disorder entities. Predictive modeling approaches may not only provide ample opportunity to improve the detection of mental health issues as well as the timely prediction of high-risk states, but may also have a paradigm-shifting impact on the way mental disorders are conceptualized. Hofmann and colleagues [285] propose that in the future, mental disorders may be seen less as latent disease entities, but as complex networks of symptoms and behaviors, which can change abruptly once a critical threshold is reached (i.e., through the onset of a disorder or relapses). Fine-grained time series data is needed to predict such complex network transitions. Hofmann and colleagues therefore stimulate that personalized predictive models based on experience sampling may be used to achieve this, and may thus help to better understand and predict the complex underpinnings of mental disorders (for applications, see [286, 287]).

Decision Support

Despite an abundance of evidence showing that psychological interventions can be effective in treating mental disorders, there is still little evidence of differential effects between various treatment types [288]. On a patient level, the benefits of psychological interventions are highly heterogeneous, with 18–62% of all patients not responding to the evidence-based treatment they receive [289, 290].

Among depressive patients, only 30% of all patients achieve remission through the first treatment they receive, but roughly 70% after several courses of treatment [291]. Thus, many patients either have to try out multiple treatments until they find the one approach that works for them, or become demoralized by many failed treatment attempts and drop out without any substantial improvements [292]. Knowledge of which intervention strategy works best for which individual thus has an enormous potential to improve the real-life impact of current psychological treatments. Machine Learning approaches have the potential to support clinical decisions on which intervention might be best suited for which patient. Such approaches may be used for the:

- Identification of patients who will (or will not) respond to a certain intervention, either before or during treatment.
- Prediction of the most promising intervention for individual patients based on their presenting symptomatology.

Data to derive such decision-support algorithms can either stem from *clinical trials* (such as RCTs and individual patient data sets containing data from many similar clinical trials [293]) or large-scale observational studies.

Identification of intervention (non)responders. Currently, Machine Learning has already been used to derive risk stratification tools through which patients at risk for nonresponse [294–299], chronic mental illness trajectories [300], or grave emergencies, such as suicide [301] can be identified. Lenhard and colleagues [296], for example, used RCT baseline data of 61 adolescents to establish a Machine Learning algorithm predicting response to an IMI for obsessive-compulsive disorder (OCD). While conventional logistic regression approaches could not detect any predictors, Machine Learning algorithms identified responders with 75–83% accuracy. Månsson and colleagues [297] could predict long-term responders of an IMI for social anxiety disorder using Support Vector Machines and fMRI data, reaching an accuracy of 92%. However, this finding could not be replicated in a similar study by Sundermann and colleagues [299] when aiming to predict response to CBT for panic disorder. In another application, Perlis [302], drawing data from the STAR*D cohort, developed a risk stratification tool predicting treatment-resistant depression cases.

However, risk stratification based on Machine Learning may also be used in patients who already receive treatment. IMIs are well suited for this purpose, as virtually all communication with patients is stored digitally on the Internet and thus usable for prediction. Hoogendoorn and colleagues [295], for example, analyzed the writings of patients undergoing guided IMI treatment for social anxiety disorder and were able to predict the treatment outcome with 78% precision halfway through therapy. Mikus and colleagues [303], using EMA data of depressive patients from the *E-COMPARED* project, were able to predict mood fallbacks in treated patients with similar accuracy.

Prediction of the most promising intervention for individual patients. Predictive modeling may also be used to derive concrete decision-support systems to determine which treatment may best fit which patient based on baseline data. For example, Chekroud and colleagues [304], using a large database of depression patients ($N = 4041$), used elastic net regression and gradient boosting machines to derive a parsimonious model predicting response to antidepressive medication, thereby requiring only 25 questionnaire items as input. The model was found to accurately generalize to new samples and showed high specificity. Along with further research [305], the model has since been implemented into a web-based decision-support service for primary care [306]. In another recent study, Bremer and colleagues [307] used data of 350 patients in an RCT comparing treatment-as-usual to blended care for depression (see, in section "Area of Application"). They derived a personalized treatment recommendation model through which patients can be allocated to the most suitable treatment type based on baseline data. Results show that such recommendations can be used to decrease treatment costs (5.42%) without having to sacrifice treatment effects to a substantial degree (1.98%).

Kessler [292] recently delineated future pathways to establish reliable decision-support systems for the treatment of depression using Machine Learning. While current approaches have mostly been based on RCT data comprising no more than 200–800 participants, much larger data sets are needed to establish valid allocation systems based on predictive modeling. He therefore stimulates that large pragmatic trials and observational studies should be conducted. On this basis, prediction models could be established to determine which patient subsets might be suited for inexpensive first-line monotherapies, such as exercise or minimally guided IMIs, and which patients will likely need more intensive care. Another possibility may be to compound large databases using individual patient data (IPD) from previous RCTs [293]. However, this requires studies to provide a shared set of baseline and outcome variables to be used for modeling. Recently, Ebert and Cuijpers [308] thus proposed that researchers should include broad assessments of variables which may predict differential treatment outcomes when conducting clinical trials in the future.

Intervention

Irrespective of being digital or face-to-face, current psychological treatments are still largely incapable of providing real-time support for patients between sessions, especially in situations in which individuals may be most at risk. Previously, we described the enormous potential of Machine Learning methods in the prediction of mood and behavior, and in deciding which interventions might be most promising throughout varying contexts. These capabilities may therefore be combined in data-driven psychological interventions to:

- Deliver just-in-time adaptive interventions to patients "in the wild" when they need them most.
- Develop virtual agents to provide human-like guidance and support.

Data needed for such applications may again be categorized as either passive (e.g., mobile phone usage and location data, home-based sensor data, voice/face recognition, or biomarkers) or active (e.g., self-report data). In addition, data can be obtained from innovative research designs such as micro-randomized trials [309] or multiphase optimization strategy (MOST) designs [310], which allow for a data-driven understanding of which intervention components are effective, and when.

Just-In-Time Adaptive Interventions. To prevent symptom fallbacks from occurring, and to provide help in real time to patients “in the wild”, *Just-In-Time Adaptive Interventions* (JITAIs [311–317]) have gained increasing attention in recent years. JITAIs aim to predict changes in an individual’s status to deliver personalized support when a person needs it most, or is most likely to be receptive [312]. Previously, we described the potential of Artificial Intelligence in predicting mood and behavior (see, in section “Detection and Sensing”), as well as for guiding treatment decisions (see, in section “Decision Support”). In JITAIs, these components are combined to create a personalized digital intervention framework. Nahum-Shani and colleagues [312] named four core components of JITAIs: *decision points*, *interventions*, *tailoring variables*, and *decision rules* (for a model, see Fig. 3). Juarascio and colleagues [317] recently delineated ways in which JITAIs could be integrated to optimize existing psychological treatments in the future. As JITAIs are not aimed at providing in-depth therapeutic content, they could primarily be implemented to bridge the time between longer intervention sessions, thereby picking up previously learned techniques. JITAIs could thus be used in conjunction with standard IMI or face-to-face treatment, either during the first weeks of treatment to promote skill-building and uphold adherence, or after termination of treatment to prevent relapse. On the other hand, JITAIs may also be used as low-intensity entry points to treatment and could be enhanced with full-blown

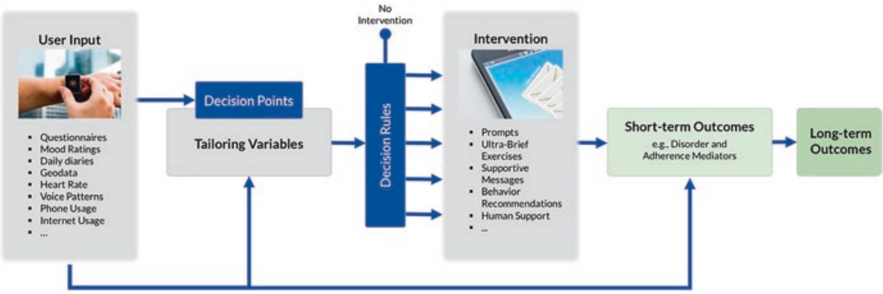

Fig. 3 Generic model of a just-in-time adaptive-intervention (adapted from Nahum-Shani et al. [339]). Description: *Decision points* are either prespecified time intervals and dates or triggered by user input, such as sensor data (e.g., reaching a critical skin conductance threshold). *Interventions* may range from quick alerts and nudges to tailored advice, coping strategies, or eCoach referral, and can be delivered through the Internet. *Tailoring variables* can be personalized progressively by various types of user input. They build the basis for *decision rules*, demarcating which intervention should be provided for which patient, and when

IMIs or psychotherapy in case more help is needed. There is first evidence showing that JITAIs can be successfully applied to mental and behavioral health promotion [318–323]. For example, Wahle and colleagues [318] evaluated a just-in-time intervention app for depression in $N = 126$ individuals. They used GPS, activity, and passive phone usage data to establish predictive models, and delivered CBT-based intervention components (e.g., behavioral activation, breathing exercises) at real time to individuals predicted to be at risk for depression. Participants in this feasibility study who kept using the intervention showed significant decreases in depressive symptoms at posttest. Gustafson and colleagues [321] conducted an RCT evaluating *A-CHESS*, a just-in-time intervention for patients after alcohol use disorder treatment. The intervention tracked geolocation data to trigger alerts when patients neared a high-risk location for relapse. The intervention was shown to have significant benefits on alcohol use compared to treatment-as-usual at post-test and 4-month follow-up.

Virtual Agents. Previously, we described that human support plays an important role in IMIs in section "Human Support" and may be one reason why unguided IMIs are often less effective than guided interventions (see section "Routine Care"). However, even guided IMIs aim to provide human support in a very efficient manner, and mostly resort to highly standardized and adherence-focused communication. Potentially, such communication patterns could also be emulated by Artificial Intelligence to provide patients with a feeling of accountability and assistance, and thus promote adherence. If feasible, this would greatly enhance the value of unguided treatment and free the dissemination of effective IMIs even more from restraints of time and money. First tentative steps have been undertaken in recent years to study the potential of such automated *virtual agents* in mental health research [51, 324–329]. Fitzpatrick and colleagues [51], for example, evaluated *Woebot*, a digital chatbot providing CBT principles through brief daily conversations. The agent uses decision trees and natural language processing to tailor response to patients, and to provide accountability through empathic responses to user input. In an RCT among 70 young adults, *Woebot* was found to significantly reduce symptoms of depression compared to an active control group receiving psychoeducation.

Limitations and Ethical Considerations

Although the evidence presented before points at the enormous potential of Machine Learning, methodological and ethical issues should also be properly considered. As described, Machine Learning approaches require large observational data sets to enable valid personalized predictions. However, even large data are fraught with biases [330, 331], especially when taken from routine care [293], and can lead to a multiplication of spurious correlations and ecological fallacies. This is further aggravated by the fact that currently, many predictive modeling studies in medicine are of suboptimal quality, either in their methodological approach [332], reporting [333], or by using weak comparators to assess prediction fidelity [334]. It should also be noted, as Pearl and MacKenzie [335] recently emphasized, that Machine Learning techniques are purely correlational. Thus, they cannot establish causal relationships [229], which is the core aim of most psychological research. Machine Learning should thus not be seen as a panacea for all limitations in current mental health research. Chen and Asch [336] recently suggested that Machine Learning may have reached its "peak of inflated expectations" in medicine. This, however, should be seen in a positive light, as it allows a soberer look at where Machine Learning can be applied in a meaningful way, and where limitations and risks prevail.

Ethical aspects should play an important role in such considerations. Data security, for example, is an important issue in social media, as has only recently been illustrated by the data breaches involving Facebook [337]. Another risk is that Machine Learning approaches may further fortify social inequality in mental health care. Even today, some minorities and people with a low socioeconomic background are missing or underrepresented in health care data, which may lead to imprecise or false predictions for such individuals, for example within decision-support systems [338].

Overall, Khoury and Ioannidis [330] emphasize that the implementation of Machine Learning and Personalized Medicine approaches, despite their enormous capacities, cannot substitute rigorously conducted clinical research. From an ethical viewpoint, the recent advances in mental health and invention research should also be accompanied by a societal discourse to ensure that Artificial Intelligence can promote mental health for all.

Conclusions

IMIs are flexible, technically diverse methods which lend themselves to a variety of application areas as well as indications of varying degrees of severity. As empirical findings on the impact of human support show, IMIs are seen less as a substitute for conventional psychotherapeutic interventions, and should rather be understood more as a useful addition to the current treatment spectrum. IMIs have an ability to reach target groups in a way not yet achieved by classical on-site activities, and on the other hand, can excellently accompany conventional psychotherapy and thereby reduce cost or increase effectiveness. Findings suggest that stand-alone IMIs can be effective in routine conditions, although further research is needed. As IMIs make it easier to collect and process fine-grained patient data in real time, they are well suited as instruments in innovative Machine Learning applications. Despite important limitations and ethical considerations, Artificial Intelligence-enhanced IMIs thus have an enormous potential to advance mental health care in the next decades.

References

1. Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, Ustün TB, Wang PS. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. Epidemiol Psichiatr Soc NIH Public Access; 2009;18(1):23–33 PMID:19378696.
2. Steel Z, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V, Silove D. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980–2013. Int J Epidemiol. 2014;43(2):476–93 PMID:24648481.
3. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJ, Vos T. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet. 2013;382(9904):1575–86. https://doi.org/10.1016/S0140-6736(13)61611-6.
4. Saarni SI, Suvisaari J, Sintonen H, Pirkola S, Koskinen S, Aromaa A, Lönnqvist J. Impact of psychiatric disorders on health-related quality of life: general population survey. Br J Psychiatry. 2007;190:326–32.
5. Hysenbegasi A, Hass SL, Rowland CR. The impact of depression on the academic productivity of university students. J Ment Health Policy Econ. 2005;8(3):145.
6. Eisenberg D, Golberstein E, Hunt JB. Mental health and academic success in college. B E J Econom Anal Policy. 2009;9(1). https://doi.org/10.2202/1935-1682.2191.
7. Ishii T, Tachikawa H, Shiratori Y, Hori T, Aiba M, Kuga K, Arai T. What kinds of factors affect the academic outcomes of university students with mental disorders? A retrospective study based on medical records. Asian J Psychiatr. 2018;32:67–72. https://doi.org/10.1016/j.ajp.2017.11.017.
8. Kessler RC, Foster CL, Saunders WB, Stang PE. Social consequences of psychiatric disorders, I: educational attainment. Am J Psychiatry Am Psychiatr Assoc. 1995;152(7):1026.
9. Fergusson DM, Woodward LJ. Mental health, educational, and social role outcomes of adolescents with depression. Arch Gen Psychiatry Am Med Assoc. 2002;59(3):225–31.
10. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. J Affect Disord. 2002;72(3):227–36 PMID:12450639.
11. Nock MK, Hwang I, Sampson N, Kessler RC, Angermeyer M, Beautrais A, Borges G, Bromet E, Bruffaerts R, De Girolamo G. Cross-national analysis of the associations among mental disorders and suicidal behavior: findings from the WHO World Mental Health Surveys. PLoS Med Public Libr Sci. 2009;6(8):e1000123.
12. Nock MK, Hwang I, Sampson NA, Kessler RC. Mental disorders, comorbidity and suicidal behavior: results from the national comorbidity survey replication. Mol Psychiatry. 2009;15:868. http://dx.doi.org/10.1038/mp.2009.29 Macmillan Publishers Limited.
13. World Health Organization. The Global Burden of Disease: 2004 update. 2008 PMID:15572474.
14. Barth J, Munder T, Gerger H, Nüesch E, Trelle S, Znoj H, Jüni P, Cuijpers P. Comparative efficacy of seven psychotherapeutic interventions for patients with depression: a network meta-analysis. Focus (Madison) Am Psychiatric Assoc. 2016;14(2):229–43.
15. Cuijpers P, van Straten A, Andersson G, van Oppen P. Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. J Consult Clin Psychol. 2008;76(6):909–22 PMID:19045960.
16. Cuijpers P, Smit F, Bohlmeijer E, Hollon SD, Andersson G. Efficacy of cognitive–behavioural therapy and other psychological treatments for adult depression: meta-analytic study of publication bias. Br J Psychiatry RCP. 2010;196(3):173–78.
17. Hofmann SG, Smits JAJ. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. J Clin Psychiatry. 2008;69(4):621–32 PMID:18363421.

18. Cuijpers P, Sijbrandij M, Koole S, Huibers M, Berking M, Andersson G. Psychological treatment of generalized anxiety disorder: a meta-analysis. Clin Psychol Rev. 2014;34(2):130–40 Elsevier.
19. Mayo-Wilson E, Dias S, Mavranezouli I, Kew K, Clark DM, Ades AE, Pilling S. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2014;1(5):368–76 PMID:26361000.
20. Bisson JI, Ehlers A, Matthews R, Pilling S, Richards D, Turner S. Psychological treatments for chronic post-traumatic stress disorder: systematic review and meta-analysis. Br J Psychiatry Camb Univ Press. 2007;190(2):97–104.
21. Powers MB, Halpern JM, Ferenschak MP, Gillihan SJ, Foa EB. A meta-analytic review of prolonged exposure for posttraumatic stress disorder. Clin Psychol Rev. 2010;30(6):635–41 Elsevier.
22. Leichsenring F, Leibing E. The effectiveness of psychodynamic therapy and cognitive behavior therapy in the treatment of personality disorders: a meta-analysis. Focus (Madison) Am Psychiatric Assoc. 2005;160(3):1223–1428.
23. Cristea IA, Gentili C, Cotet CD, Palomba D, Barbui C, Cuijpers P. Efficacy of psychotherapies for borderline personality disorder: a systematic review and meta-analysis. Jama Psychiatry Am Med Assoc. 2017;74(4):319–28.
24. Kleinstäuber M, Witthöft M, Hiller W. Efficacy of short-term psychotherapy for multiple medically unexplained physical symptoms: a meta-analysis. Clin Psychol Rev. 2011;31(1):146–60 Elsevier.
25. Olatunji BO, Kauffman BY, Meltzer S, Davis ML, Smits JAJ, Powers MB. Cognitive-behavioral therapy for hypochondriasis/health anxiety: a meta-analysis of treatment outcome and moderators. Behav Res Ther. 2014;58:65–74 Elsevier.
26. Glombiewski JA, Sawyer AT, Gutermann J, Koenig K, Rief W, Hofmann SG. Psychological treatments for fibromyalgia: a meta-analysis. PAIN®. 2010;151(2):280–95 Elsevier.
27. Frühauf S, Gerger H, Schmidt HM, Munder T, Barth J. Efficacy of psychological interventions for sexual dysfunction: a systematic review and meta-analysis. Arch Sex Behav Springer; 2013;42(6):915–33.
28. Auerbach RP, Alonso J, Axinn WG, Cuijpers P, Ebert DD, Green JG, Hwang I, Kessler RC, Liu H, Mortier P, Nock MK, Pinder-Amaker S, Sampson NA, Aguilar-Gaxiola S, Al-Hamzawi A, Andrade LH, Benjet C, Caldas-de-Almeida JM, Demyttenaere K, Florescu S, de Girolamo G, Gureje O, Haro JM, Karam EG, Kiejna A, Kovess-Masfety V, Lee S, McGrath JJ, O'Neill S, Pennell B-E, Scott K, Ten Have M, Torres Y, Zaslavsky AM, Zarkov Z, Bruffaerts R. Mental disorders among college students in the World Health Organization world mental health surveys. Psychol Med. 2016 Oct 3 [cited 2017 Mar 20];46(14):1–16 PMID:27484622.
29. Kessler RC, Berglund PA, Bruce ML, Koch RJ, Laska EM, Leaf PJ, Manderscheid RW, Rosenheck RA, Walters EE, Wang PS. The prevalence and correlates of untreated serious mental illness. Health Serv Res. 2001;36(6):987–1007.
30. Bijl RV, de Graaf R, Hiripi E, Kessler RC, Kohn R, Offord DR, Ustun TB, Vicente B, Vollebergh WAM, Walters EE. The prevalence of treated and untreated mental disorders in five countries. Health Aff Project HOPE-The People-to-People Health Foundation, Inc.; 2003;22(3):122–33.
31. Andrade LH, Alonso J, Mneimneh Z, Wells JE, Al-Hamzawi A, Borges G, Bromet E, Bruffaerts R, de Girolamo G, de Graaf R, Florescu S, Gureje O, Hinkov HR, Hu C, Huang Y, Hwang I, Jin R, Karam EG, Kovess-Masfety V, Levinson D, Matschinger H, O'Neill S, Posada-Villa J, Sagar R, Sampson NA, Sasu C, Stein DJ, Takeshima T, Viana MC, Xavier M, Kessler RC. Barriers to mental health treatment: results from the WHO World Mental Health surveys. Psychol Med. 2014;44(6):1303–17 PMID:23931656, Cambridge University Press.

32. Clement S, Schauman O, Graham T, Maggioni F, Evans-Lacko S, Bezborodovs N, Morgan C, Rüsch N, Brown JSL, Thornicroft G. What is the impact of mental health-related stigma on help-seeking? A systematic review of quantitative and qualitative studies. Psychol Med. 2015 [cited 2017 May 10];45(1):11–27 PMID:24569086.
33. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry. 2005;62(6):593–602 PMID:18188442.
34. Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet. 2012;379(9820):1045–55 Elsevier.
35. Ebert DD, Van Daele T, Nordgreen T, Karekla M, Compare AT, Zarbo C, Brugnera A, Oeverland S, Trebbi G, Jensen K, Kaehlke F, Baumeister H. Internet- and mobile-based psychological interventions: applications, efficacy, and potential for improving mental health. Eur Psychol 2018. https://doi.org/10.1027/1016-9040/a000318.
36. Craske MG, Stein MB. No psychotherapy monoculture for anxiety disorders; Authors' reply. Lancet. 2017;389(10082):1883. https://doi.org/10.1016/s0140-6736(17)31208-4 Elsevier.
37. Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJH. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. World Psychiatry. 2016;15(3):245–58 Wiley Online Library.
38. Berking M, Rief W, editors. Klinische Psychologie und Psychotherapie. Epidemiology. Berlin Heidelberg: Springer;2012. ISBN:9783642130175 PMID:15003161.
39. Andersson G, Carlbring P, Lindefors N. History and current status of ICBT. In: Lindefors N, Andersson G, editors. Guid internet-based treat psychiatry. Cham: Springer International Publishing; 2016. p. 1–16. https://doi.org/10.1007/978-3-319-06083-5_1.
40. Andersson G, Paxling B, Roch-Norlund P, Ostman G, Norgren A, Almlöv J, Georén L, Breitholtz E, Dahlin M, Cuijpers P, Carlbring P, Silverberg F. Internet-based psychodynamic versus cognitive behavioral guided self-help for generalized anxiety disorder: a randomized controlled trial. Psychother Psychosom. 2012;81(6):344–55 PMID:22964540.
41. Johansson R, Hesser H, Ljótsson B, Frederick RJ, Andersson G. Transdiagnostic, affect-focused, psychodynamic, guided self-help for depression and anxiety through the internet: study protocol for a randomised controlled trial. BMJ Open. 2012;2(6):1–6 PMID:23257775.
42. Donker T, Batterham PJ, Warmerdam L, Bennett K, Bennett A, Cuijpers P, Griffiths KM, Christensen H. Predictors and moderators of response to internet-delivered Interpersonal Psychotherapy and Cognitive Behavior Therapy for depression. J Affect Disord. 2013;151(1):343–51.
43. Mak WWS, Chan ATY, Cheung EYL, Lin CLY, Ngai KCS. Enhancing Web-based mindfulness training for mental health promotion with the health action process approach: randomized controlled trial. J Med Internet Res. 2015;17(1):e8 PMID:25599904.
44. Lin J, Lüking M, Ebert DD, Buhrman M, Andersson G, Baumeister H. Effectiveness and cost-effectiveness of a guided and unguided internet-based acceptance and commitment therapy for chronic pain: study protocol for a three-armed randomised controlled trial. Internet Interv 2015;2(1). https://doi.org/10.1016/j.invent.2014.11.005.
45. Johansson R, Björklund M, Hornborg C, Karlsson S, Hesser H, Ljótsson B, Rousseau A, Frederick RJ, Andersson G. Affect-focused psychodynamic psychotherapy for depression and anxiety through the Internet: a randomized controlled trial. PeerJ. 2013;1(Suppl 2):e102- PMID:23862104.
46. Garcia-Palacios A, Hoffman H, Carlin A, Furness TA, Botella C. Virtual reality in the treatment of spider phobia: a controlled study. Behav Res Ther. 2002;40(9):983–93 PMID:12296495.
47. Freeman D, Haselton P, Freeman J, Spanlang B, Kishore S, Albery E, Denne M, Brown P, Slater M, Nickless A. Automated psychological therapy using immersive virtual reality

for treatment of fear of heights: a single-blind, parallel-group, randomised controlled trial. Lancet Psychiatry. 2018;5(8):625–32 Elsevier.

48. Pot-Kolder RMCA, Geraets CNW, Veling W, van Beilen M, Staring ABP, Gijsman HJ, Delespaul PAEG, van der Gaag M. Virtual-reality-based cognitive behavioural therapy versus waiting list control for paranoid ideation and social avoidance in patients with psychotic disorders: a single-blind randomised controlled trial. Lancet Psychiatry. 2018;5(3):217–26 Elsevier.
49. Fleming T, Dixon R, Frampton C, Merry S. A pragmatic randomized controlled trial of computerized CBT (SPARX) for symptoms of depression among adolescents excluded from mainstream education. Behav Cogn Psychother. 2012;40(5):529–41. https://doi.org/10.1017/s1352465811000695 12/06. Fleming, Theresa, University of Auckland, Department of Psychological Medicine, Private Bag 92019, Auckland, New Zealand, 1142.
50. An LC, Demers MRS, Kirch MA, Considine-Dunn S, Nair V, Dasgupta K, Narisetty N, Resnicow K, Ahluwalia J. A randomized trial of an avatar-hosted multiple behavior change intervention for young adult smokers. J Natl Cancer Inst Monogr. 2013;2013(47):209–15 PMID:24395994, Oxford University Press.
51. Fitzpatrick KK, Darcy A, Vierhile M. Delivering cognitive behavior therapy to young adults with symptoms of depression and anxiety using a fully automated conversational agent (Woebot): a randomized controlled trial. JMIR Ment Heal. 2017;4(2) JMIR Publications Inc.
52. Schlicker S, Ebert DD, Middendorf T, Titzler I, Berking M. Evaluation of a text-message-based maintenance intervention for Major Depressive Disorder after inpatient cognitive behavioral therapy. J Affect Disord. 2017;227:305–12 Elsevier.
53. Lin J, Ebert DD, Lehr D, Berking M, Baumeister H. Internetbasierte Gesundheitsinterventionen: State of the Art und Einsatzmöglichkeiten in der Rehabilitation. Rehabilitation. 2013;52(03):155–63. https://doi.org/10.1055/s-0033-1343491.
54. Backhaus A, Agha Z, Maglione ML, Repp A, Ross B, Zuest D, Rice-Thorp NM, Lohr J, Thorp SR. Videoconferencing psychotherapy: a systematic review. Psychol Serv. 2012;9(2):111–31 PMID:22662727.
55. Ebert DD, Lehr D, Smit F, Zarski A-C, Riper H, Heber E, Cuijpers P, Berking M. Efficacy and cost-effectiveness of minimal guided and unguided internet-based mobile supported stress-management in employees with occupational stress: a three-armed randomised controlled trial. BMC Public Health. 2014;14(1):807. https://doi.org/10.1186/1471-2458-14-807.
56. Schueller SM, Tomasino KN, Mohr DC. Integrating human support into behavioral intervention technologies: the efficiency model of support. Clin Psychol Sci Pract. 2016;24(1):27–45. https://doi.org/10.1111/cpsp.12173.
57. Zarski A-C, Lehr D, Berking M, Riper H, Cuijpers P, Ebert DD. Adherence to internet-based mobile-supported stress management: a pooled analysis of individual participant data from three randomized controlled trials. J Med Internet Res. 2016;18(6):e146. https://doi.org/10.2196/jmir.4493.
58. Buntrock C, Ebert DD, Lehr D, Cuijpers P, Riper H, Smit F, Berking M. Evaluating the efficacy and cost-effectiveness of web-based indicated prevention of major depression: design of a randomised controlled trial. BMC Psychiatry BioMed Cent. 2014;14:25. https://doi.org/10.1186/1471-244x-14-25.
59. Lal S, Adair CE. E-mental health: a rapid review of the literature. Psychiatr Serv Am Psychiatric Assoc. 2014;65(1):24–32.
60. Henderson C, Evans-Lacko S, Thornicroft G. Mental illness stigma, help seeking, and public health programs. Am J Public Health 2013 [cited 2017 May 10];103(5):777–80 PMID:23488489.
61. Muñoz RF, Bunge EL, Chen K, Schueller SM, Bravin JI, Shaughnessy EA, Pérez-Stable EJ. Massive open online interventions: a novel model for delivering behavioral-health services

worldwide. Clin Psychol Sci. 2016;4(2):194–205 Los Angeles, CA: Sage Publications Sage CA.
62. Fairburn CG, Patel V. The impact of digital technology on psychological treatments and their dissemination. Behav Res Ther. 2017;88:19–25 Elsevier.
63. Erbe D, Eichert H-C, Riper H, Ebert DD. Blending face-to-face and internet-based interventions for the treatment of mental disorders in adults: systematic review. J Med Internet Res. 2017;19(9):e306 PMID:28916506.
64. Ebert DD, Nobis S, Lehr D, Baumeister H, Riper HM, Auerbach RP, Snoek F, Cuijpers P, Berking M. The 6-month effectiveness of Internet-based guided self-help for depression in adults with Type 1 and 2 diabetes mellitus. Diabet Med. 2016; https://doi.org/10.1111/dme.13173.
65. Nobis S, Lehr D, Ebert DD, Baumeister H, Snoek F, Riper H, Berking M. Efficacy of a web-based intervention with mobile phone support in treating depressive symptoms in adults with type 1 and type 2 diabetes: a randomized controlled trial. Diabetes Care. 2015 PMID:25710923.
66. Sander L, Paganini S, Lin J, Schlicker S, Ebert DD, Buntrock C, Baumeister H. Effectiveness and cost-effectiveness of a guided Internet- and mobile-based intervention for the indicated prevention of major depression in patients with chronic back pain-study protocol of the PROD-BP multicenter pragmatic RCT. BMC Psychiatry. 2017;17(1). https://doi.org/10.1186/s12888-017-1193-6.
67. van Bastelaar KMP, Pouwer F, Cuijpers P, Riper H, Snoek FJ. Web-based depression treatment for type 1 and type 2 diabetic patients: a randomized, controlled trial. Diabetes Care. 2011;34(2):320–5 PMID:21216855.
68. van Bastelaar KMP, Pouwer F, Cuijpers P, Riper H, Twisk JWR, Snoek FJ. Is a severe clinical profile an effect modifier in a Web-based depression treatment for adults with type 1 or type 2 diabetes? Secondary analyses from a randomized controlled trial. J Med Internet Res. 2012;14(1):e2 PMID:22262728.
69. Buntrock C, Ebert DD, Lehr D, Smit F, Riper H, Berking M, Cuijpers P. Effect of a web-based guided self-help intervention for prevention of major depression in adults with subthreshold depression a randomized clinical trial. JAMA J Am Med Assoc. 2016;315(17). https://doi.org/10.1001/jama.2016.4326.
70. Ebert DD, Buntrock C, Cuijpers P, K van Z, P C, C B, C B, H B. Online intervention for prevention of major depression—reply. JAMA. 2016;316(8):881. https://doi.org/10.1001/jama.2016.9586 American Medical Association.
71. Bockting CLH, Kok GD, van der Kamp L, Smit F, van Valen E, Schoevers R, van Marwijk H, Cuijpers P, Riper H, Dekker J, Beck AT. Disrupting the rhythm of depression using Mobile Cognitive Therapy for recurrent depression: randomized controlled trial design and protocol. BMC Psychiatry. 2011;11:12 PMID:21235774.
72. Ebert DD, Gollwitzer M, Riper H, Cuijpers P, Baumeister H, Berking M. For whom does it work? moderators of outcome on the effect of a transdiagnostic internet-based maintenance treatment after inpatient psychotherapy: randomized controlled trial. J Med Internet Res. 2013;15(10):e191 PMID:24113764.
73. Ebert DD, Tarnowski T, Gollwitzer M, Sieland B, Berking M. A transdiagnostic internet-based maintenance treatment enhances the stability of outcome after inpatient cognitive behavioral therapy: a randomized controlled trial. Psychother Psychosom. 2013;82(4):246–56 PMID:23736751.
74. Golkaramnay V, Bauer S, Haug S, Wolf M, Kordy H. The exploration of the effectiveness of group therapy through an Internet chat as aftercare: a controlled naturalistic study. Psychother Psychosom. 2007;76(4):219–25 PMID:17570960.
75. Kok G, Bockting C, Burger H, Smit F, Riper H. Mobile cognitive therapy: adherence and acceptability of an online intervention in remitted recurrently depressed patients. Internet Interv. 2014;1(2):65–73. https://doi.org/10.1016/j.invent.2014.05.002.

76. Holländare F, Johnsson S, Randestad M, Tillfors M, Carlbring P, Andersson G, Engström I. Randomized trial of Internet-based relapse prevention for partially remitted depression. Acta Psychiatr Scand. 2011;124(4):285–94 Wiley Online Library.
77. Andrews G, Cuijpers P, Craske MG, McEvoy P, Titov N. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. PLoS One. 2010;5(10):e13196 PMID:20967242.
78. Ebert DD, Zarski A-C, Christensen H, Stikkelbroek Y, Cuijpers P, Berking M, Riper H. Internet and computer-based cognitive behavioral therapy for anxiety and depression in youth: a meta-analysis of randomized controlled outcome trials. PLoS One 2015;10(3). https://doi.org/10.1371/journal.pone.0119895.
79. Mayo-Wilson E, Montgomery P. Media-delivered cognitive behavioural therapy and behavioural therapy (self-help) for anxiety disorders in adults. Cochrane database Syst Rev. 2013;9:CD005330 PMID:24018460.
80. Richards D, Richardson T. Computer-based psychological treatments for depression: a systematic review and meta-analysis. Clin Psychol Rev. 2012;32(4):329–42 PMID:22466510 Elsevier Ltd.
81. Richards D, Richardson T, Timulak L, McElvaney J. The efficacy of internet-delivered treatment for generalized anxiety disorder: a systematic review and meta-analysis. Internet Interv. 2015;2(3):272–82. https://doi.org/10.1016/j.invent.2015.07.003 Elsevier B.V.
82. Olthuis JV, Watt MC, Bailey K, Hayden JA, Stewart SH. Therapist-supported Internet cognitive behavioural therapy for anxiety disorders in adults. Cochrane database Syst Rev. 2015;3:CD011565 PMID:25742186.
83. Josephine K, Josefine L, Philipp D, David E, Harald B. Internet- and mobile-based depression interventions for people with diagnosed depression: a systematic review and meta-analysis. J Affect Disord. 2017;223:28–40 PMID:28715726 Elsevier.
84. Kuester A, Niemeyer H, Knaevelsrud C. Internet-based interventions for posttraumatic stress: a meta-analysis of randomized controlled trials. Clin Psychol Rev. 2016; 1–16 PMID:26655959 Elsevier Ltd.
85. Zachariae R, Lyby MS, Ritterband L, O'Toole MS. Efficacy of Internet-delivered cognitive-behavioral therapy for insomnia–a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev. 2015;30:1–10 PMID:26615572.
86. Melioli T, Bauer S, Franko DL, Moessner M, Ozer F, Chabrol H, Rodgers RF. Reducing eating disorder symptoms and risk factors using the internet: a meta-analytic review. Int J Eat Disord. 2016;49(1):19–31. https://doi.org/10.1002/eat.22477.
87. Buhrman M, Gordh T, Andersson G. Internet interventions for chronic pain including headache: a systematic review. Internet Interv. 2016;4:17–34. https://doi.org/10.1016/j.invent.2015.12.001.
88. Riper H, Blankers M, Hadiwijaya H, Cunningham J, Clarke S, Wiers R, Ebert D, Cuijpers P. Effectiveness of guided and unguided low-intensity internet interventions for adult alcohol misuse: a meta-analysis. PLoS One. 2014;9(6). https://doi.org/10.1371/journal.pone.0099912.
89. Andersson E, Enander J, Andrén P, Hedman E, Ljótsson B, Hursti T, Bergström J, Kaldo V, Lindefors N, Andersson G, Rück C. Internet-based cognitive behaviour therapy for obsessive–compulsive disorder: a randomized controlled trial. Psychol Med. 2012;42(10):2193–203 PMID:22348650.
90. Herbst N, Voderholzer U, Thiel N, Schaub R, Knaevelsrud C, Stracke S, Hertenstein E, Nissen C, Külz AK. No talking, just writing! Efficacy of an Internet-based cognitive behavioral therapy with exposure and response prevention in obsessive compulsive disorder. Psychother Psychosom. 2014;83(3):165–75 PMID:24732962.
91. Lenhard F, Andersson E, Mataix-Cols D, Rück C, Vigerland S, Högström J, Hillborg M, Brander G, Ljungström M, Ljótsson B, Serlachius E. Therapist-guided, internet-delivered cognitive-behavioral therapy for adolescents with obsessive-compulsive disorder:

a randomized controlled trial. J Am Acad Child Adolesc Psychiatry. 2017;56(1):10–19.e2. https://doi.org/10.1016/j.jaac.2016.09.515.
92. Storch EA, Caporino NE, Morgan JR, Lewin AB, Rojas A, Brauer L, Larson MJ, Murphy TK. Preliminary investigation of web-camera delivered cognitive-behavioral therapy for youth with obsessive-compulsive disorder. Psychiatry Res. 2011;189(3):407–12 PMID:21684018.
93. Gottlieb JD et al. Web-based cognitive-behavioral therapy for auditory hallucinations in persons with psychosis: a pilot study. Schizophr Res. 2013;145(1–3):82–7 PMID:23410709 Elsevier.
94. Harper KM. An Investigation of an Internet-based cognitive behavioral Therapy Program fpr auditory hallucinations. University of North Carolina at Chapel Hill; 2013.
95. Enander J, Andersson E, Mataix-Cols D, Lichtenstein L, Alstroem K, Andersson G, Ljotsson B, Rueck C. Therapist guided internet based cognitive behavioural therapy for body dysmorphic disorder: single blind randomised controlled trial. BMJ-BRITISH Med J. 2016;352. https://doi.org/10.1136/bmj.i241.
96. Hidalgo-Mazzei D, Mateu A, Reinares M, Matic A, Vieta E, Colom F. Internet-based psychological interventions for bipolar disorder: review of the present and insights into the future. J Affect Disord. 2015;188:1–13 PMID:26342885.
97. Andersson E, Walén C, Hallberg J, Paxling B, Dahlin M, Almlöv J, Källström R, Wijma K, Carlbring P, Andersson G. A randomized controlled trial of guided Internet-delivered cognitive behavioral therapy for erectile dysfunction. J Sex Med. 2011;8(10):2800–9 PMID:21797983.
98. Jones LM, Mccabe MP. The effectiveness of an internet-based psychological treatment program for female sexual dysfunction. J Sex Med. 2011;8(10):2781–92 PMID:21771279.
99. Schover LR, Canada AL, Yuan Y, Sui D, Neese L, Jenkins R, Rhodes MM. A randomized trial of internet-based versus traditional sexual counseling for couples after localized prostate cancer treatment. Cancer. 2012;118(2):500–9 PMID:21953578.
100. van Lankveld JJ, Leusink P, van Diest S, Gijs L, Slob AK. Internet-based brief sextherapy for heterosexual men with sexual dysfunctions: a randomized controlled pilot trial. J Sex Med. 2009;6(8):2224–36.
101. Zarski A-C, Berking M, Fackiner C, Rosenau C, Ebert DD. Internet-based guided self-help for vaginal penetration difficulties: results of a randomized controlled pilot trial. J Sex Med. 2017;14(2). https://doi.org/10.1016/j.jsxm.2016.12.232.
102. Abbott J-AM, Kaldo V, Klein B, Austin D, Hamilton C, Piterman L, Williams B, Andersson G. A Cluster Randomised Trial of an Internet-Based Intervention Program for Tinnitus Distress in an Industrial Setting. Cogn Behav Ther 2009;38(3):162–73 PMID:19675959.
103. Nyenhuis N, Zastrutzki S, Weise C, Jäger B, Kröner-Herwig B. The efficacy of minimal contact interventions for acute tinnitus: a randomised controlled study. Cogn Behav Ther. 2013;42(2):127–38 PMID:22413736.
104. Andersson G, Strömgren T, Ström L, Lyttkens L. Randomized controlled trial of internet-based cognitive behavior therapy for distress associated with tinnitus. Psychosom Med. 64(5):810–6 PMID:12271112.
105. Weise C, Kleinstäuber M, Andersson G. Internet-delivered cognitive-behavior therapy for tinnitus. Psychosom Med. 2016;78(4):501–10 PMID:26867083.
106. Kaldo V, Levin S, Widarsson J, Buhrman M, Larsen H-C, Andersson G. Internet versus group cognitive-behavioral treatment of distress associated with tinnitus: a randomized controlled trial. Behav Ther. 2008;39(4):348–59 PMID:19027431.
107. Nyenhuis N, Zastrutzki S, Jäger B, Kröner-Herwig B. An internet-based cognitive-behavioural training for acute tinnitus: secondary analysis of acceptance in terms of satisfaction, trial attrition and non-usage attrition. Cogn Behav Ther. 2013;42(2):139–45 PMID:23205617.
108. Hesser H, Westin VZ, Andersson G. Acceptance as a mediator in internet-delivered acceptance and commitment therapy and cognitive behavior therapy for tinnitus. J Behav Med. 2014;37(4):756–67 PMID:23881309.

109. Hesser H, Gustafsson T, Lundén C, Henrikson O, Fattahi K, Johnsson E, Westin VZ, Carlbring P, Mäki-Torkko E, Kaldo V, Andersson G. A randomized controlled trial of internet-delivered cognitive behavior therapy and acceptance and commitment therapy in the treatment of tinnitus. J Consult Clin Psychol. 2012;80(4):649–61 PMID:22250855.
110. Jasper K, Weise C, Conrad I, Andersson G, Hiller W, Kleinstäuber M. Internet-based guided self-help versus group cognitive behavioral therapy for chronic tinnitus: a randomized controlled trial. Psychother Psychosom. 2014;83(4):234–46 PMID:24970708.
111. Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman E. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. World Psychiatry. 2014;13(3):288–95 PMID:25273302.
112. Wagner B, Knaevelsrud C, Maercker A. Internet-based cognitive-behavioral therapy for complicated grief: a randomized controlled trial. Death Stud. 2006;30(5):429–53 PMID:16610157.
113. Wagner B, Maercker A. A 1.5-year follow-up of an internet-based intervention for complicated grief. J Trauma Stress. 2007;20(4):625–29. https://doi.org/10.1002/jts.20230 Wiley Subscription Services, Inc., A Wiley Company.
114. Eisma MC, Boelen PA, van den Bout J, Stroebe W, Schut HAW, Lancee J, Stroebe MS. Internet-based exposure and behavioral activation for complicated grief and rumination: a randomized controlled trial. Behav Ther. 2015;46(6):729–48 Elsevier.
115. Luquiens A, Tanguy M-L, Lagadec M, Benyamina A, Aubin H-J, Reynaud M. The efficacy of three modalities of internet-based psychotherapy for non-treatment-seeking online problem gamblers: a randomized controlled trial. J Med Internet Res. 2016;18(2):e36 PMID:26878894.
116. Carlbring P, Smit F. Randomized trial of internet-delivered self-help with telephone support for pathological gamblers. J Consult Clin Psychol. 2008;76(6):1090–4 PMID:19045977.
117. Nijhof SL, Priesterbach LP, Uiterwaal C, Bleijenberg G, Kimpen JLL, Putte EM. Internet-based therapy for adolescents with chronic fatigue syndrome: long-term follow-up. Pediatrics; 2013. p. e1788–95. https://doi.org/10.1542/peds.2012-2007.
118. Nijhof SL, et al. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. Lancet (London, England). 2012;379(9824):1412–8 PMID:22385683 Elsevier.
119. Franklin JC, Fox KR, Franklin CR, Kleiman EM, Ribeiro JD, Jaroszewski AC, Hooley JM, Nock MK. A brief mobile app reduces nonsuicidal and suicidal self-injury: evidence from three randomized controlled trials. J Consult Clin Psychol. 2016;84(6):544–57 PMID:27018530.
120. Mohr DC, Ho J, Hart TL, Baron KG, Berendsen M, Beckner V, Cai X, Cuijpers P, Spring B, Kinsinger SW, Schroder KE, Duffecy J. Control condition design and implementation features in controlled trials: a meta-analysis of trials evaluating psychotherapy for depression. Transl Behav Med. 2014 [cited 2017 May 10];4(4):407–23 PMID:25584090 Springer.
121. Andersson G, Topooco N, Havik O, Nordgreen T. Internet-supported versus face-to-face cognitive behavior therapy for depression. Expert Rev Neurother. 2016;16(1):55–60 PMID:26610160.
122. Carlbring P, Andersson G, Cuijpers P, Riper H, Hedman-Lagerlöf E. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. Cogn Behav Ther. 2018;47(1):1–18 PMID:29215315.
123. Ebert DD, Berking M, Cuijpers P, Lehr D, P?rtner M, Baumeister H. Increasing the acceptance of internet-based mental health interventions in primary care patients with depressive symptoms. A randomized controlled trial. J Affect Disord. 2015;176. https://doi.org/10.1016/j.jad.2015.01.056.
124. Baumeister H, Nowoczin L, Lin J, Seifferth H, Seufert J, Laubner K, Ebert DD. Impact of an acceptance facilitating intervention on diabetes patients' acceptance of Internet-based interventions for depression: a randomized controlled trial. Diabetes Res Clin Pract. 2014;105(1):30–9. https://doi.org/10.1016/j.diabres.2014.04.031.

125. Apolinário-Hagen J, Vehreschild V, Alkoudmani RM. Current views and perspectives on e-mental health: an exploratory survey study for understanding public attitudes toward internet-based psychotherapy in Germany. JMIR Ment Heal. 2017;4(1):e8 PMID:28232298.
126. Apolinário-Hagen J, Harrer M, Kählke F, Fritsche L, Salewski C, Ebert DD. Public attitudes toward guided internet-based therapies: web-based survey study. JMIR Ment Health. 2018;5(2):e10735 PMID:29764797, JMIR Publications Inc.
127. Dorow M, Löbner M, Pabst A, Stein J, Riedel-Heller SG. Preferences for depression treatment including internet-based interventions: results from a large sample of primary care patients. Front Psychiatry. 2018;9 Frontiers Media SA.
128. Sethi S, Campbell AJ, Ellis LA. The use of computerized self-help packages to treat adolescent depression and anxiety. J Technol Hum Serv. 2010, 31;28(3):144–60. https://doi.org/10.1080/15228835.2010.508317 Routledge.
129. Lindhiem O, Bennett CB, Rosen D, Silk J. Mobile technology boosts the effectiveness of psychotherapy and behavioral interventions: a meta-analysis. Behav Modif. 2015;39(6):785–804 PMID:26187164.
130. Kenwright M, Liness S, Marks I. Reducing demands on clinicians by offering computer-aided self-help for phobia/panic. Feasibility study. Br J Psychiatry. 2001;179:456–9 PMID:11689405.
131. Marks IM, Kenwright M, McDonough M, Whittaker M, Mataix-Cols D. Saving clinicians' time by delegating routine aspects of therapy to a computer: a randomized controlled trial in phobia/panic disorder. Psychol Med. 2004 PMID:14971623, Cambridge University Press.
132. Kenter RMF, van de Ven PM, Cuijpers P, Koole G, Niamat S, Gerrits RS, Willems M, van Straten A. Costs and effects of Internet cognitive behavioral treatment blended with face-to-face treatment: results from a naturalistic study. Internet Interv. 2015;2(1):77–83. https://doi.org/10.1016/j.invent.2015.01.001.
133. Kleiboer A, Smit J, Bosmans J, Ruwaard J, Andersson G, Topooco N, Berger T, Krieger T, Botella C, Ba?os R, Chevreul K, Araya R, Cerga-Pashoja A, Cie?lak R, Rogala A, Vis C, Draisma S, Schaik A, Kemmeren L, Ebert D, Berking M, Funk B, Cuijpers P, Riper H. European COMPARative Effectiveness research on blended Depression treatment versus treatment-as-usual (E-COMPARED): study protocol for a randomized controlled, non-inferiority trial in eight European countries. Trials 2016;17(1). https://doi.org/10.1186/s13063-016-1511-1.
134. Kooistra LC, Wiersma JE, Ruwaard J, van Oppen P, Smit F, Lokkerbol J, Cuijpers P, Riper H. Blended vs. face-to-face cognitive behavioural treatment for major depression in specialized mental health care: study protocol of a randomized controlled cost-effectiveness trial. BMC Psychiatry 2014;14(1):290 PMID:25326035.
135. Romijn G, Riper H, Kok R, Donker T, Goorden M, Roijen LH Van, Kooistra L, Balkom A Van, Koning J. Cost-effectiveness of blended vs. face-to- face cognitive behavioural therapy for severe anxiety disorders : study protocol of a randomized controlled trial. BMC Psychiatry BMC Psychiatry; 2015;1–10. https://doi.org/10.1186/s12888-015-0697-1.
136. Vara D, Herrero R, Etchemendy E, Espinoza M, Baños R, García-Palacios A, Lera G, Folch B, Palop-Larrea V, Vázquez P. Efficacy and cost-effectiveness of a blended cognitive behavioral therapy for depression in Spanish primary health care: study protocol for a randomised non-inferiority trial. BMC Psychiatry BioMed Central. 2018;18(1):74.
137. Ebert DD, Cuijpers P, Muñoz RF, Baumeister H. Prevention of mental health disorders using internet and mobile-based interventions: a narrative review and recommendations for future research. Front Psychiatry Front. 2017;8:116. https://doi.org/10.3389/fpsyt.2017.00116.
138. Buntrock C, Ebert DD, Lehr D, Smit F, Riper H, Berking M, Cuijpers P. Effect of a web-based guided self-help intervention for prevention of major depression in adults with subthreshold depression. JAMA. 2016;315(17):1854. https://doi.org/10.1001/jama.2016.4326 American Medical Association.
139. Buntrock C, Ebert D, Lehr D, Riper H, Smit F, Cuijpers P, Berking M. Effectiveness of a web-based cognitive behavioural intervention for subthreshold depression:

pragmatic randomised controlled trial. Psychother Psychosom. 2015;84(6). https://doi.org/10.1159/000438673.

140. Buntrock C, Berking M, Smit F, Lehr D, Nobis S, Riper H, Cuijpers P, Ebert D. Preventing depression in adults with subthreshold depression: health-economic evaluation alongside a pragmatic randomized controlled trial of a web-based intervention. J Med Internet Res. 2017;19(1):e5. https://doi.org/10.2196/jmir.6587.
141. Holländare F, Anthony SA, Randestad M, Tillfors M, Carlbring P, Andersson G, Engström I. Two-year outcome of internet-based relapse prevention for partially remitted depression. Behav Res Ther. 2013. https://doi.org/10.1016/j.brat.2013.08.002.
142. Klein NS, Kok GD, Burger H, van Valen E, Riper H, Cuijpers P, Dekker J, Smit F, van der Heiden C, Bockting CLH. No sustainable effects of an internet-based relapse prevention program over 24 months in recurrent depression: primary outcomes of a randomized controlled trial. Psychother Psychosom. 2018;87(1):55–57 Karger Publishers.
143. Riper H, Blankers M, Hadiwijaya H, Cunningham J, Clarke S, Wiers R, Ebert DD, Cuijpers P. Effectiveness of guided and unguided low-intensity internet interventions for adult alcohol misuse: a meta-analysis. PLoS One. 2014;9(6):e99912 PMID:24937483, Stewart R, editor, Public Library of Science.
144. Boß L, Lehr D, Schaub MP, Paz Castro R, Riper H, Berking M, Ebert DD. Efficacy of a web-based intervention with and without guidance for employees with risky drinking: results of a three-arm randomized controlled trial. Addiction Wiley Online Library; 2017.
145. Ebert DD, Berking M, Thiart H, Riper H, Laferton J, Lehr D. Restoring depleted resources: efficacy and mechanisms of change of an Internet-based unguided recovery training for better sleep and psychological detachment from work. Heal Psychol. 2015;Suppl(1). https://doi.org/10.1037/hea0000277.
146. Thiart H, Lehr D, Ebert DD, Berking M, Riper H. Log in and breathe out: internet-based recovery training for sleepless employees with work-related strain–results of a randomized controlled trial. Scand J Work Environ Health. 2015; https://doi.org/10.5271/sjweh.3478 Online Fir.
147. Lehr D, Heber E, Sieland B, Hillert A, Funk B, Ebert DD. Occupational eMental Health and teachers' health: a meta-analytic review on the efficacy of internet-based intervention for promoting mental health in teachers | "Occupational eMental Health" in der Lehrergesundheit: Ein metaanalytisches Review zur Wirksa. Pravention und Gesundheitsforderung 2016; https://doi.org/10.1007/s11553-016-0541-6.
148. Heber E, Lehr D, Ebert DD, Berking M, Riper H. Web-based and mobile stress management intervention for employees: results of a randomised controlled trial. J Med Internet Res. 2016;18(1):e21. https://doi.org/10.2196/jmir.5112.
149. Ebert DD, Heber E, Berking M, Riper H, Cuijpers P, Funk B, Lehr D. Self-guided internet-based and mobile-based stress management for employees: results of a randomised controlled trial. Occup Environ Med. 2016;73(5). https://doi.org/10.1136/oemed-2015-103269.
150. Ebert DD, Lehr D, Heber E, Riper H, Cuijpers P, Berking M. Internet- and mobile-based stress management for employees with adherence-focused guidance: efficacy and mechanism of change. Scand J Work Environ Health. 2016 Sept 1 [cited 2017 May 2];42(5):382–94 PMID:27249161.
151. Harrer M, Adam SH, Fleischmann RJ, Baumeister H, Auerbach RP, Bruffaerts R, Cuijpers P, Kessler RC, Berking M, Lehr D, Ebert DD. Effectiveness of an internet- and app-based intervention for college students with elevated stress: results of a randomized controlled trial (in press). J Med Internet Res. 2018.
152. Heber E, Ebert DD, Lehr D, Cuijpers P, Berking M, Nobis S, Riper H. The benefit of web- and computer-based interventions for stress: a systematic review and meta-analysis. J Med Internet Res. 2017;19(2):e32 PMID:28213341.
153. van Zoonen K, Buntrock C, Ebert DD, Smit F, Reynolds III CF, Beekman ATF, Cuijpers P. Preventing the onset of major depressive disorder: a meta-analytic review of psychological interventions. Int J Epidemiol. 2014;43(2). https://doi.org/10.1093/ije/dyt175.

154. Moreno-Peral P, Conejo-Cerón S, Rubio-Valera M, Fernández A, Navas-Campaña D, Rodríguez-Morejón A, Motrico E, Rigabert A, Luna J de D, Martín-Pérez C, Rodríguez-Bayón A, Ballesta-Rodríguez MI, Luciano JV, Bellón JÁ. Effectiveness of psychological and/or educational interventions in the prevention of anxiety. JAMA Psychiatry. 2017;56(9):1026–33. https://doi.org/10.1001/jamapsychiatry.2017.2509 Wiley, New York.
155. Üstün TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJL. Global burden of depressive disorders in the year 2000. Br J psychiatry RCP. 2004;184(5):386–92.
156. Olesen J, Gustavsson A, Svensson M, Wittchen H, Jönsson B. The economic cost of brain disorders in Europe. Eur J Neurol. 2012;19(1):155–62 Wiley Online Library.
157. Sobocki P, Jönsson B, Angst J, Rehnberg C. Cost of depression in Europe. J Ment Health Policy Econ. 2006;9(2):87–98 PMID:17007486.
158. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2005.
159. Donker T, Blankers M, Hedman E, Ljotsson B, Petrie K, Christensen H. Economic evaluations of Internet interventions for mental health: a systematic review. Psychol Med. 2015;45(16):3357–76 Cambridge University Press.
160. Paganini S, Teigelkötter W, Buntrock C, Baumeister H. Economic evaluations of internet- and mobile-based interventions for the treatment and prevention of depression: a systematic review. J Affect Disord. 2017;225:733–55. https://doi.org/10.1016/j.jad.2017.07.018 Elsevier.
161. Andrews G, Williams AD. Internet psychotherapy and the future of personalized treatment. Depress Anxiety. 2014;31(11):912–5 PMID:25407580.
162. Williams AD, O'Moore K, Mason E, Andrews G. The effectiveness of internet cognitive behaviour therapy (iCBT) for social anxiety disorder across two routine practice pathways. Internet Interv. 2014;1(4):225–9. https://doi.org/10.1016/j.invent.2014.11.001.
163. Hedman E, Ljótsson B, Kaldo V, Hesser H, El Alaoui S, Kraepelien M, Andersson E, Rück C, Svanborg C, Andersson G, Lindefors N. Effectiveness of Internet-based cognitive behaviour therapy for depression in routine psychiatric care. J Affect Disord. 2014;155(1):49–58 PMID:24238951.
164. El Alaoui S, Hedman E, Ljótsson B, Lindefors N. Long-term effectiveness and outcome predictors of therapist-guided internet-based cognitive-behavioural therapy for social anxiety disorder in routine psychiatric care. BMJ Open. 2015;5(6):e007902 PMID:26105031.
165. El Alaoui S, Hedman E, Kaldo V, Hesser H, Kraepelien M, Andersson E, Rück C, Andersson G, Ljótsson B, Lindefors N. Effectiveness of Internet-based cognitive-behavior therapy for social anxiety disorder in clinical psychiatry. J Consult Clin Psychol. 2015;83(5):902–14 PMID:26009780.
166. Nordgreen T, Gjestad R, Andersson G, Carlbring P, Havik OE. The implementation of guided Internet-based cognitive behaviour therapy for panic disorder in a routine-care setting: effectiveness and implementation efforts. Cogn Behav Ther. 2017;1–14 PMID:28714775.
167. Titov N, Dear BF, Staples LG, Bennett-Levy J, Klein B, Rapee RM, Andersson G, Purtell C, Bezuidenhout G, Nielssen OB. The first 30 months of the MindSpot Clinic: evaluation of a national e-mental health service against project objectives. Aust New Zeal J Psychiatry. 2016;000486741667159 PMID:27733709.
168. Titov N, Dear BF, Staples LG, Bennett-Levy J, Klein B, Rapee RM, Shann C, Richards D, Andersson G, Ritterband L, Purtell C, Bezuidenhout G, Johnston L, Nielssen OB. MindSpot Clinic: an accessible, efficient, and effective online treatment service for anxiety and depression. Psychiatr Serv. 2015;66(10):1043–50 PMID:26130001.
169. Titov N, Dear B, Nielssen O, Staples L, Hadjistavropoulos H, Nugent M, Adlam K, Nordgreen T, Bruvik KH, Hovland A. ICBT in routine care: a descriptive analysis of successful clinics in five countries. Internet Interv. 2018 Elsevier.
170. Karyotaki E, Riper H, Twisk J, Hoogendoorn A, Kleiboer A, Mira A, Mackinnon A, Meyer B, Botella C, Littlewood E, Andersson G, Christensen H, Klein JP, Schröder J,

Bretón-López J, Scheider J, Griffiths K, Farrer L, Huibers MJH, Phillips R, Gilbody S, Moritz S, Berger T, Pop V, Spek V, Cuijpers P. Efficacy of Self-guided Internet-Based Cognitive Behavioral Therapy in the Treatment of Depressive Symptoms. JAMA Psychiatry. 2017. https://doi.org/10.1001/jamapsychiatry.2017.0044.

171. Ebert DD, Baumeister H. Internet-based self-help interventions for depression in routine care. JAMA Psychiatry. 2017;1(4):205–15. https://doi.org/10.1001/jamapsychiatry.2017.1394.
172. Lin J, Faust B, Ebert DD, Krämer L, Baumeister H. A web-based acceptance-facilitating intervention for identifying patients' acceptance, uptake, and adherence of internet- and mobile-based pain interventions: randomized controlled trial. J Med Internet Res. 2018;20(8):e244 Toronto, Canada: JMIR Publications Inc.
173. Littlewood E, Duarte A, Hewitt C, Knowles S, Palmer S, Walker S, Andersen P, Araya R, Barkham M, Bower P, Brabyn S, Brierley G, Cooper C, Gask L, Kessler D, Lester H, Lovell K, Muhammad U, Parry G, Richards DA, Richardson R, Tallon D, Tharmanathan P, White D, Gilbody S. A randomised controlled trial of computerised cognitive behaviour therapy for the treatment of depression in primary care: the Randomised Evaluation of the Effectiveness and Acceptability of Computerised Therapy (REEACT) trial. Health Technol Assess. 2015;19(101):1–174 PMID:26685904.
174. Brabyn S, Araya R, Barkham M, Bower P, Cooper C, Duarte A, Kessler D, Knowles S, Lovell K, Littlewood E, Mattock R, Palmer S, Pervin J, Richards D, Tallon D, White D, Walker S, Worthy G, Gilbody S. The second Randomised Evaluation of the Effectiveness, cost-effectiveness and Acceptability of Computerised Therapy (REEACT-2) trial: does the provision of telephone support enhance the effectiveness of computer-delivered cognitive behaviour therapy? A ra. Health Technol Assess (Rockv). 2016;20(89):1–64 PMID:27922448.
175. Muñoz RF. The efficiency model of support and the creation of digital apothecaries. Clin Psychol Sci Pract. 2017;24(1):46–9. https://doi.org/10.1111/cpsp.12174.
176. Mohr DC, Weingardt KR, Reddy M, Schueller SM. Three problems with current digital mental health research and three things we can do about them. Psychiatr Serv. 2017;68(5):427–29. https://doi.org/10.1176/appi.ps.201600541 American Psychiatric Association Arlington, VA.
177. Kaltenthaler E, Parry G, Beverley C, Ferriter M. Computerised cognitive-behavioural therapy for depression: systematic review. Br J Psychiatry. 2008;193(3):181–84 Cambridge University Press.
178. Lillevoll K, Vangberg H, Griffiths K, Waterloo K, Eisemann M. Uptake and adherence of a self-directed internet-based mental health intervention with tailored e-mail reminders in senior high schools in Norway. BMC Psychiatry. 2014. https://doi.org/10.1186/1471-244x-14-14.
179. Whiteside U, Lungu A, Richards J, Simon GE, Clingan S, Siler J, Snyder L, Ludman E. Designing messaging to engage patients in an online suicide prevention intervention: survey results from patients with current suicidal ideation. J Med Internet Res. 2014;16(2) JMIR Publications Inc.
180. Woodford J, Farrand P, Bessant M, Williams C. Recruitment into a guided internet based CBT (iCBT) intervention for depression: lesson learnt from the failure of a prevalence recruitment strategy. Contemp Clin Trials. 2011;32(5):641–8. https://doi.org/10.1016/j.cct.2011.04.013.
181. Paul CL, Piterman L, Shaw JE, Kirby C, Forshaw KL, Robinson J, Thepwongsa I, Sanson-Fisher RW. Poor uptake of an online intervention in a cluster randomised controlled trial of online diabetes education for rural general practitioners. Trials Engl. 2017;18(1):137 PMID:28335809.
182. Meisel SF, Drury H, Perera-Delcourt RP. Therapists' attitudes to offering eCBT in an inner-city IAPT service: a survey study. Cogn Behav Ther. 2018;11 Cambridge University Press.

183. Hennemann S, Beutel ME, Zwerenz R. Ready for eHealth? Health professionals' acceptance and adoption of ehealth interventions in inpatient routine care. J Health Commun. 2017;22(3):274–84 Taylor & Francis.
184. Mitchell N, Gordon PK. Attitudes towards computerised CBT for depression amongst a student population. Behav Cogn Psychother. 2007 [cited 2017 Mar 22];35(04):421–30. https://doi.org/10.1017/s1352465807003700.
185. Cranen K, Veld RH in't, Ijzerman M, Vollenbroek-Hutten M. Change of patients' perceptions of telemedicine after brief use. Telemed J e-Health. 2011;17(7):530–35. https://doi.org/10.1089/tmj.2010.0208.
186. Baumeister H, Seifferth H, Lin J, Nowoczin L, L?king M, Ebert D. Impact of an acceptance facilitating intervention on patients' acceptance of internet-based pain interventions: a randomized controlled trial. Clin J Pain. 2015;31(6). https://doi.org/10.1097/ajp.0000000000000118.
187. Ebert DD, Berking M, Cuijpers P, Lehr D, Pörtner M, Baumeister H. Increasing the acceptance of internet-based mental health interventions in primary care patients with depressive symptoms. A randomized controlled trial. J Affect Disord. 2015; https://doi.org/10.1016/j.jad.2015.01.056.
188. Ebert DD, Donkin L, Andersson G, Andrews G, Berger T, Carlbring P, Rozenthal A, Choi I, Laferton JAC, Johansson R, Kleiboer A, Lange A, Lehr D, Reins JA, Funk B, Newby J, Perini S, Riper H, Ruwaard J, Sheeber L, Snoek FJ, Titov N, Ünlü Ince B, Van Bastelaar K, Vernmark K, Van Straten A, Warmerdam L, Salsman N, Cuijpers P. Does Internet-based guided-self-help for depression cause harm? An individual participant data meta-analysis on deterioration rates and its moderators in randomized controlled trials. Psychol Med. 2016;46(13). https://doi.org/10.1017/s0033291716001562.
189. Christensen H, Farrer L, Batterham PJ, Mackinnon A, Griffiths KM, Donker T. The effect of a web-based depression intervention on suicide ideation: secondary outcome from a randomised controlled trial in a helpline. BMJ Open. 2013;3(6):1–10 PMID:23811172.
190. Mewton L, Andrews G. Cognitive behaviour therapy via the internet for depression: a useful strategy to reduce suicidal ideation. J Affect Disord. 2014;170C:78–84 PMID:25233243.
191. Rozental A, Boettcher J, Andersson G, Schmidt B, Carlbring P. Negative effects of internet interventions: a qualitative content analysis of patients' experiences with treatments delivered online. Cogn Behav Ther. 2015;44(3):223–36 PMID:25705924.
192. Boettcher J, Rozental A, Andersson G, Carlbring P. Side effects in Internet-based interventions for Social Anxiety Disorder. Internet Interv. 2014;1(1):3–11. https://doi.org/10.1016/j.invent.2014.02.002.
193. Rozental A, Magnusson K, Boettcher J, Andersson G, Carlbring P. For better or worse: an individual patient data meta-analysis of deterioration among participants receiving Internet-based cognitive behavior therapy. J Consult Clin Psychol. 2017;85(2):160–77 PMID:27775414.
194. Wampold BE, Imel ZE. The Great psychotherapy debate. the evidence for what makes psychotherapy work. 2nd ed. New York: Routledge; 2015.
195. Domhardt M, Geßlein H, von Rezori RE, Baumeister H. Internet-and mobile-based interventions for anxiety disorders: a meta-analytic review of intervention components. Depress Anxiety. 2018 Wiley Online Library.
196. Ebert DD, Berking M, Thiart H, Riper H, Laferton JAC, Cuijpers P, Sieland B, Lehr D. Restoring depleted resources: efficacy and mechanisms of change of an internet-based unguided recovery training for better sleep and psychological detachment from work. Heal Psychol. 2015;34(Suppl):1240–51 PMID:26651465.
197. Warmerdam L, van Straten A, Jongsma J, Twisk J, Cuijpers P. Online cognitive behavioral therapy and problem-solving therapy for depressive symptoms: exploring mechanisms of change. J Behav Ther Exp Psychiatry. 2010;41(1):64–70 PMID:19913781.
198. Ebert DD, Lehr D, Heber E, Riper H, Cuijpers P, Berking M. Internet-and mobile-based stress management for employees with adherence-focused guidance: efficacy and mechanism of change. Scand J Environ Heal. 2016;42(5):382–94.

199. Boettcher J, Renneberg B, Berger T. Patient expectations in internet-based self-help for social anxiety. Cogn Behav Ther. 2013;42(3):203–14 PMID:23697570.
200. Lévesque A, Campbell ANC, Pavlicova M, Hu M-C, Walker R, McClure EA, Ghitza UE, Bailey G, Stitzer M, Nunes EV. Coping strategies as a mediator of internet-delivered psychosocial treatment: secondary analysis from a NIDA CTN multisite effectiveness trial. Addict Behav. 2017;65:74–80 PMID:27776269.
201. Mogoaşe C, Cobeanu O, David O, Giosan C, Szentagotai A. Internet-based psychotherapy for adult depression: what about the mechanisms of change? J Clin Psychol. 2017;73(1):5–64 PMID:27684405.
202. Hedman E, Andersson E, Andersson G, Lindefors N, Lekander M, Rück C, Ljótsson B. Mediators in internet-based cognitive behavior therapy for severe health anxiety. PLoS One. 2013;8(10):e77752. https://doi.org/10.1371/journal.pone.0077752 Thombs B, editor. Guilford Press.
203. Graham AL, Papandonatos GD, Cobb CO, Cobb NK, Niaura RS, Abrams DB, Tinkelman DG. Internet and telephone treatment for smoking cessation: mediators and moderators of short-term abstinence. Nicotine Tob Res. 2015;17(3):299–308 PMID:25156528, Oxford University Press.
204. Ljótsson B, Hesser H, Andersson E, Lindfors P, Hursti T, Rück C, Lindefors N, Andersson G, Hedman E. Mechanisms of change in an exposure-based treatment for irritable bowel syndrome. J Consult Clin Psychol. 2013;81(6):1113–26 PMID:23750460.
205. Morgan AJ, Mackinnon AJ, Jorm AF. Behavior change through automated e-mails: mediation analysis of self-help strategy use for depressive symptoms. Behav Res Ther. 2013;51(2):57–62 PMID:23262114.
206. Alpay L, van der Boog P, Dumaij A. An empowerment-based approach to developing innovative e-health tools for self-management. Health Inf J. 2011;17(4):247–55 Sage Publications Sage UK: London, England.
207. Crisp D, Griffiths K, Mackinnon A, Bennett K, Christensen H. An online intervention for reducing depressive symptoms: secondary benefits for self-esteem, empowerment and quality of life. Psychiatry Res. 2014;216(1):60–66 Elsevier.
208. Samoocha D, Bruinvels DJ, Elbers NA, Anema JR, van der Beek AJ. Effectiveness of web-based interventions on patient empowerment: a systematic review and meta-analysis. J Med Internet Res. 2010;12. https://doi.org/10.2196/jmir.1286.
209. Kuijpers W, Groen WG, Aaronson NK, van Harten WH. A systematic review of web-based interventions for patient empowerment and physical activity in chronic diseases: relevance for cancer survivors. J Med Internet Res. 2013;15(2) JMIR Publications Inc.
210. Cowpertwait L, Clarke D. Effectiveness of web-based psychological interventions for depression: a meta-analysis. Int J Ment Health Addict. 2013;11(2):247–68. https://doi.org/10.1007/s11469-012-9416-z Springer.
211. Baumeister H, Reichler L, Munzinger M, Lin J. The impact of guidance on Internet-based mental health interventions-a systematic review. Internet Interv. 2014:205–15. https://doi.org/10.1016/j.invent.2014.08.003.
212. Johansson R, Andersson G. Internet-based psychological treatments for depression. Expert Rev Neurother. 2012;12(7):861–9; quiz 870 PMID:22853793.
213. Andersson G, Carlbring P, Berger T, Almlöv J, Cuijpers P. What makes internet therapy work? Cogn Behav Ther. 2009;38(sup1):55–60 PMID:19675956.
214. Andersson G, Paxling B, Wiwe M, Vernmark K, Felix CB, Lundborg L, Furmark T, Cuijpers P, Carlbring P. Therapeutic alliance in guided internet-delivered cognitive behavioural treatment of depression, generalized anxiety disorder and social anxiety disorder. Behav Res Ther. 2012;50(9):544–50 PMID:22728647.
215. Ebert DD, Hannig W, Tarnowski T, Sieland B, Götzky B, Berking M. Web-based rehabilitation aftercare following inpatient psychosomatic treatment. Rehabilitation (Stuttg). 2013;52(3):164–72 PMID:23761205.

216. Preschl B, Maercker A, Wagner B. The working alliance in a randomized controlled trial comparing online with face-to-face cognitive-behavioral therapy for depression. BMC Psychiatry. 2011;11(1):189 PMID:22145768.
217. Cook JE, Doyle C. Working alliance in online therapy as compared to face-to-face therapy: preliminary results. Cyberpsychol Behav. 2002;5(2):95–105 PMID:12025884.
218. Bengtsson J, Nordin S, Carlbring P. Therapists' Experiences of conducting cognitive behavioural therapy online vis-à-vis face-to-face. Cogn Behav Ther. 2015;1–10 PMID:26090947, Routledge.
219. Knaevelsrud C, Maercker A. Does the quality of the working alliance predict treatment outcome in online psychotherapy for traumatized patients? J Med Internet Res. 2006;8(4):e31 PMID:17213049.
220. Mohr DC, Cuijpers P, Lehman K. Supportive accountability: a model for providing human support to enhance adherence to eHealth interventions. J Med Internet Res. 2011 Mar 10 [cited 2017 May 15];13(1):e30 PMID:21393123.
221. Terhorst Y, Rathner EM, Baumeister H, Sander L. Help from the App-Store? a systematic review of apps for depression (in press). Verhaltenstherapie 2017.
222. Sucala M, Cuijpers P, Muench F, Cardoș R, Soflau R, Dobrean A, Achimas-Cadariu P, David D. Anxiety: there is an app for that. A systematic review of anxiety apps. Depress Anxiety. 2017;34(6):518–25 Wiley Online Library.
223. Neary M, Schueller SM. State of the field of mental health apps. Cogn Behav Pract. 2018 Elsevier.
224. Klein JP, Knaevelsrud C, Bohus M, Ebert DD, Gerlinger G, Günther K, Jacobi C, Löbner M, Riedel-Heller SG, Sander J. Internetbasierte Selbstmanagementinterventionen. Nervenarzt Springer; 2018;1–9.
225. Alpaydin E. Introduction to machine learning. MIT press; 2009. ISBN:0262303264.
226. Yarkoni T, Westfall J. Choosing prediction over explanation in psychology: lessons from machine learning. Perspect Psychol Sci. 2017;12(6):1100–22 SAGE Publications Sage CA: Los Angeles, CA.
227. Breiman L. Statistical modeling: the two cultures (with comments and a rejoinder by the author). Stat Sci. 2001;16(3):199–231 Institute of Mathematical Statistics.
228. Ward JS, Barker A. Undefined by data: a survey of big data definitions; 2013. arXiv:13095821.
229. Becker D, van Breda W, Funk B, Hoogendoorn M, Ruwaard J, Riper H. Predictive modeling in e-mental health: a common language framework. Internet Interv Neth. 2018;12:57–67 PMID:30135769.
230. Wongkoblap A, Vadillo MA, Curcin V. Researching mental health disorders in the era of social media: systematic review. J Med Internet Res. 2017;19(6):e228 PMID:28663166 Canada.
231. Kang K, Yoon C, Kim EY. Identifying depressive users in Twitter using multimodal analysis. In: 2016 International conference on big data smart comput (BigComp), IEEE;2016. p. 231–38.
232. Park S, Kim I, Lee SW, Yoo J, Jeong B, Cha M. Manifestation of depression and loneliness on social networks: a case study of young adults on Facebook. In: Proceedings of the 18th ACM conference on comput support cooperative work social computing, ACM; 2015. p. 557–70.
233. Hu Q, Li A, Heng F, Li J, Zhu T. Predicting depression of social media user on different observation windows. In: 2015 IEEE/WIC/ACM International conference on web intelligence agent technology (WI-IAT), IEEE; 2015. p. 361–64.
234. Tsugawa S, Kikuchi Y, Kishino F, Nakajima K, Itoh Y, Ohsaki H. Recognizing depression from twitter activity. In: Proceedings of the 33rd annual ACM conference on human factors in computing systems, ACM; 2015. p. 3187–96.
235. Park S, Lee SW, Kwak J, Cha M, Jeong B. Activities on Facebook reveal the depressive state of users. J Med Internet Res. 2013;15(10) JMIR Publications Inc.

236. Wang X, Zhang C, Sun L. An improved model for depression detection in micro-blog social network. In: 2013 IEEE 13th international conference on data mining workshops, IEEE; 2013. p. 80–87.
237. De Choudhury M, Counts S, Horvitz E. Social media as a measurement tool of depression in populations. In: Proceedings of the 5th annual ACM web science conference, ACM; 2013. p. 47–56.
238. Mowery D, Smith H, Cheney T, Stoddard G, Coppersmith G, Bryan C, Conway M. Understanding depressive symptoms and psychosocial stressors on Twitter: a corpus-based study. J Med Internet Res. 2017;19(2):e48 PMID:28246066 Canada.
239. Reece A. Chronology and patterns of psychiatric morbidity in substance-dependent and medical patients. Australas Psychiatry. 2009;17(2):170–71. https://doi.org/10.1177/103985620901700203 US: Informa Healthcare.
240. Reece AG, Danforth CM. Instagram photos reveal predictive markers of depression. EPJ Data Sci. 2017;6(1):15 SpringerOpen.
241. Lin H, Jia J, Guo Q, Xue Y, Li Q, Huang J, Cai L, Feng L. User-level psychological stress detection from social media using deep neural network. In: Proceedings of the 22nd ACM international conference on multimedia, ACM; 2014. p. 507–16.
242. Schwartz HA, Sap M, Kern ML, Eichstaedt JC, Kapelner A, Agrawal M, Blanco E, Dziurzynski L, Park G, Stillwell D. Predicting individual well-being through the language of social media. In: Biocomput 2016 proceedings of the pacific symposium world scientific; 2016. p. 516–27.
243. Liu P, Tov W, Kosinski M, Stillwell DJ, Qiu L. Do Facebook status updates reflect subjective well-being? Cyberpsychology, Behav Soc Netw. 2015;18(7):373–79 Mary Ann Liebert, Inc., 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA.
244. Settanni M, Azucar D, Marengo D. Predicting individual characteristics from digital traces on social media: a meta-analysis. Cyberpsychology Behav Soc Netw. 2018;21(4):217–28 Mary Ann Liebert, Inc. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA.
245. Coppersmith G, Dredze M, Harman C. Quantifying mental health signals in Twitter. In: Proceedings of the workshop on computational linguistics and clinical psychology: from linguistic signal to clinical reality; 2014. p. 51–60.
246. Harman G, Dredze MH. Measuring post traumatic stress disorder in Twitter. In: ICWSM 2014.
247. Chancellor S, Lin Z, Goodman EL, Zerwas S, De Choudhury M. Quantifying and predicting mental illness severity in online pro-eating disorder communities. In: Proceedings of the 19th ACM conference on computer-supported cooperative work & social computing, ACM; 2016. p. 1171–84.
248. Moessner M, Feldhege J, Wolf M, Bauer S. Analyzing big data in social media: text and network analyses of an eating disorder forum. Int J Eat Disord. 2018 PMID:29746710 United States.
249. Song J, Song TM, Seo D-C, Jin JH. Data mining of web-based documents on social networking sites that included suicide-related words among korean adolescents. J Adolesc Health. 2016;59(6):668–73 PMID:27693129 United States.
250. Braithwaite SR, Giraud-Carrier C, West J, Barnes MD, Hanson CL. Validating machine learning algorithms for Twitter data against established measures of suicidality. JMIR Ment Heal. 2016;3(2) JMIR Publications Inc.
251. O'Dea B, Wan S, Batterham PJ, Calear AL, Paris C, Christensen H. Detecting suicidality on Twitter. Internet Interv. 2015;2(2):183–88 Elsevier.
252. Zhang L, Huang X, Liu T, Li A, Chen Z, Zhu T. Using linguistic features to estimate suicide probability of Chinese microblog users. In: International conference on human centered computing, Springer; 2014. p. 549–59.
253. Burnap P, Colombo G, Amery R, Hodorog A, Scourfield J. Multi-class machine classification of suicide-related communication on Twitter. Online Soc networks media. 2017;2:32–44 Elsevier.

254. Torous J, Larsen ME, Depp C, Cosco TD, Barnett I, Nock MK, Firth J. Smartphones, sensors, and machine learning to advance real-time prediction and interventions for suicide prevention: a review of current progress and next steps. Curr Psychiatry Rep. 2018;20(7):51 PMID:29956120 United States.
255. Kornfield R, Sarma PK, Shah DV, McTavish F, Landucci G, Pe-Romashko K, Gustafson DH. Detecting recovery problems just in time: application of automated linguistic analysis and supervised machine learning to an online substance abuse forum. J Med Internet Res. 2018;20(6):e10136 PMID:29895517 Canada.
256. Cepeda MS, Reps J, Fife D, Blacketer C, Stang P, Ryan P. Finding treatment-resistant depression in real-world data: how a data-driven approach compares with expert-based heuristics. Depress Anxiety. 2017. https://doi.org/10.1002/da.22705 US: Wiley.
257. Morales S, Barros J, Echavarri O, Garcia F, Osses A, Moya C, Maino MP, Fischman R, Nunez C, Szmulewicz T, Tomicic A. Acute mental discomfort associated with suicide behavior in a clinical sample of patients with affective disorders: ascertaining critical variables using artificial intelligence tools. Front Psychiatry. 2017;8:7 PMID:28210230 Switzerland.
258. Whelan R, Watts R, Orr CA, Althoff RR, Artiges E, Banaschewski T, Barker GJ, Bokde ALW, Buchel C, Carvalho FM, Conrod PJ, Flor H, Fauth-Buhler M, Frouin V, Gallinat J, Gan G, Gowland P, Heinz A, Ittermann B, Lawrence C, Mann K, Martinot J-L, Nees F, Ortiz N, Paillere-Martinot M-L, Paus T, Pausova Z, Rietschel M, Robbins TW, Smolka MN, Strohle A, Schumann G, Garavan H. Neuropsychosocial profiles of current and future adolescent alcohol misusers. Nature 2014;512(7513):185–89 PMID:25043041 England.
259. Chekroud AM, Foster D, Zheutlin AB, Gerhard DM, Roy B, Koutsouleris N, Chandra A, Esposti MD, Subramanyan G, Gueorguieva R, Paulus M, Krystal JH. Predicting barriers to treatment for depression in a U.S. National sample: a cross-sectional, proof-of-concept study. Psychiatr Serv. 2018;69(8):927–34 PMID:29962307 United States.
260. Jordan P, Shedden-Mora MC, Lowe B. Predicting suicidal ideation in primary care: an approach to identify easily assessable key variables. Gen Hosp Psychiatry. 2018;51:106–11 PMID:29428582 United States.
261. Tran T, Luo W, Phung D, Harvey R, Berk M, Kennedy RL, Venkatesh S. Risk stratification using data from electronic medical records better predicts suicide risks than clinician assessments. BMC Psychiatry. 2014;14(1):76 BioMed Central.
262. Hoexter MQ, Dougherty DD, Shavitt RG, D'Alcante CC, Duran FLS, Lopes AC, Diniz JB, Batistuzzo MC, Evans KC, Bressan RA, Busatto GF, Miguel EC. Differential prefrontal gray matter correlates of treatment response to fluoxetine or cognitive-behavioral therapy in obsessive–compulsive disorder. Eur Neuropsychopharmacol. 2013;23(7):569–80. https://doi.org/10.1016/j.euroneuro.2012.06.014 Hoexter, Marcelo Q., Department of Psychiatry, University of Sao Paulo Medical School, Rua Ovidio Pires de Campos 785–31 andar Ala Norte-sala 9 (PROTOC), CEP 05403-010, Sao Paulo, Brazil: Elsevier Science.
263. Lueken U, Straube B, Yang Y, Hahn T, Beesdo-Baum K, Wittchen H-U, Konrad C, Strohle A, Wittmann A, Gerlach AL, Pfleiderer B, Arolt V, Kircher T. Separating depressive comorbidity from panic disorder: a combined functional magnetic resonance imaging and machine learning approach. J Affect Disord Neth. 2015;184:182–92 PMID:26093832.
264. Jimenez-Serrano S, Tortajada S, Garcia-Gomez JM. A mobile health application to predict postpartum depression based on machine learning. Telemed J E Health. 2015;21(7):567–74 PMID:25734829 United States.
265. Marzano L, Bardill A, Fields B, Herd K, Veale D, Grey N, Moran P. The application of mHealth to mental health: opportunities and challenges. Lancet Psychiatry. 2015;2(10):942–48 Elsevier.
266. Pantelopoulos A, Bourbakis NG. A survey on wearable sensor-based systems for health monitoring and prognosis. IEEE Trans Syst Man, Cybern Part C (Appl Rev IEEE). 2010;40(1):1–12.

267. Schueller SM, Begale M, Penedo FJ, Mohr DC. Purple: a modular system for developing and deploying behavioral intervention technologies. J Med Internet Res. 2014;16(7) JMIR Publications Inc.
268. Torous J, Kiang M V, Lorme J, Onnela J-P. New tools for new research in psychiatry: a scalable and customizable platform to empower data driven smartphone research. JMIR Ment Health. 2016;3(2) JMIR Publications Inc.
269. Mohr DC, Zhang M, Schueller SM. Personal sensing: understanding mental health using ubiquitous sensors and machine learning. Annu Rev Clin Psychol. 2017;13:23–47 PMID:28375728 United States.
270. Bourla A, Mouchabac S, El Hage W, Ferreri F. e-PTSD: an overview on how new technologies can improve prediction and assessment of Posttraumatic Stress Disorder (PTSD). Eur J Psychotraumatol. 2018;9(sup1):1424448 PMID:29441154 United States.
271. Trull TJ, Solhan MB, Tragesser SL, Jahng S, Wood PK, Piasecki TM, Watson D. Affective instability: measuring a core feature of borderline personality disorder with ecological momentary assessment. J Abnorm Psychol. 2008;117(3):647 American Psychological Association.
272. Dennis ML, Scott CK, Funk RR. Ecological momentary assessment to predict the risk of relapse. Drug Alcohol Depend. 2015;146:e262. https://doi.org/10.1016/j.drugalcdep.2014.09.179.
273. Chih M-Y, Patton T, McTavish FM, Isham AJ, Judkins-Fisher CL, Atwood AK, Gustafson DH. Predictive modeling of addiction lapses in a mobile health application. J Subst Abuse Treat. 2014;46(1):29–35 PMID:24035143 United States.
274. Saeb S, Kording K, Mohr DC. Making activity recognition robust against deceptive behavior. PLoS One. 2015;10(12):e0144795 PMID:26659118 United States.
275. Pratap A, Atkins DC, Renn BN, Tanana MJ, Mooney SD, Anguera JA, Arean PA. The accuracy of passive phone sensors in predicting daily mood. Depress Anxiety. 2018 PMID:30129691 United States.
276. Hung GC-L, Yang P-C, Chang C-C, Chiang J-H, Chen Y-Y. Predicting negative emotions based on mobile phone usage patterns: an exploratory study. JMIR Res Protoc. 2016;5(3):e160 PMID:27511748 Canada.
277. Jaques N, Taylor S, Azaria A, Ghandeharioun A, Sano A, Picard R. Predicting students' happiness from physiology, phone, mobility, and behavioral data. In: International conference on affective computing and intelligent interaction and workshops [proceedings]. ACII United States; 2015:222–28 PMID:28515966.
278. Sano A. Measuring college students' sleep, stress, mental health and wellbeing with wearable sensors and mobile phones. Massachusetts Institute of Technology; 2016 [cited 2017 May 10]. https://dspace.mit.edu/handle/1721.1/106066.
279. Sano A, Taylor S, McHill AW, Phillips AJ, Barger LK, Klerman E, Picard R. Identifying objective physiological markers and modifiable behaviors for self-reported stress and mental health status using wearable sensors and mobile phones: observational study. J Med Internet Res. 2018;20(6):e210 PMID:29884610 Canada.
280. Lu H, Frauendorfer D, Rabbi M, Mast MS, Chittaranjan GT, Campbell AT, Gatica-Perez D, Choudhury T. Stresssense: detecting stress in unconstrained acoustic environments using smartphones. In: Proceedings of the 2012 ACM conference on ubiquitous computing, ACM; 2012. p. 351–60.
281. Abbas H, Garberson F, Glover E, Wall DP. Machine learning approach for early detection of autism by combining questionnaire and home video screening. J Am Med Inform Assoc. 2018;25(8):1000–07 PMID:29741630, England.
282. Sathyanarayana A, Joty S, Fernandez-Luque L, Ofli F, Srivastava J, Elmagarmid A, Arora T, Taheri S. Sleep quality prediction from wearable data using deep learning. JMIR mHealth uHealth. 2016;4(4):e125 PMID:27815231 Canada.

283. Barnett I, Torous J, Staples P, Sandoval L, Keshavan M, Onnela J-P. Relapse prediction in schizophrenia through digital phenotyping: a pilot study. Neuropsychopharmacology. 2018;1 Nature Publishing Group.
284. Depp CA, Thompson WK, Frank E, Swartz HA. Prediction of near-term increases in suicidal ideation in recently depressed patients with bipolar II disorder using intensive longitudinal data. J Affect Disord. 2017;208:363–8 Elsevier.
285. Hofmann SG, Curtiss J, McNally RJ. A complex network perspective on clinical science. Perspect Psychol Sci. 2016;11(5):597–605 PMID:27694457.
286. van de Leemput IA, Wichers M, Cramer AOJ, Borsboom D, Tuerlinckx F, Kuppens P, van Nes EH, Viechtbauer W, Giltay EJ, Aggen SH. Critical slowing down as early warning for the onset and termination of depression. Proc Natl Acad Sci. 2014;111(1):87–92.
287. Fried EI, van Borkulo CD, Cramer AOJ, Boschloo L, Schoevers RA, Borsboom D. Mental disorders as networks of problems: a review of recent insights. Soc Psychiatry Psychiatr Epidemiol. 2017;52(1):1–10. https://doi.org/10.1007/s00127-016-1319-z.
288. Wampold BE, Imel ZE. The great psychotherapy debate: the evidence for what makes psychotherapy work. Routledge; 2015. ISBN:1136672605.
289. Loerinc AG, Meuret AE, Twohig MP, Rosenfield D, Bluett EJ, Craske MG. Response rates for CBT for anxiety disorders: need for standardized criteria. Clin Psychol Rev. 2015;42:72–82 Elsevier.
290. Hofmann SG, Asnaani A, Vonk IJJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy: a review of meta-analyses. Cognit Ther Res. 2012;36(5):427–40. https://doi.org/10.1007/s10608-012-9476-1.
291. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. Am J Psychiatry Am Psychiatric Assoc. 2006;163(11):1905–17.
292. Kessler RC. The potential of predictive analytics to provide clinical decision support in depression treatment planning. Curr Opin Psychiatry. 2018;31(1):32–39 Wolters Kluwer.
293. Riley RD, Ensor J, Snell KIE, Debray TPA, Altman DG, Moons KGM, Collins GS. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. BMJ. 2016;353:i3140 PMID:27334381 England.
294. Gori A, Lauro-Grotto R, Giannini M, Schuldberg D. Predicting treatment outcome by combining different assessment tools: toward an integrative model of decision support in psychotherapy. J Psychother Integr. 2010;20(2):251–69. https://doi.org/10.1037/a0019768 Gori, Alessio, Department of Psychology, University of Florence, via di San Salvi, 12, 50135, Florence, Italy: Educational Publishing Foundation.
295. Hoogendoorn M, Berger T, Schulz A, Stolz T, Szolovits P. Predicting social anxiety treatment outcome based on therapeutic email conversations. IEEE J Biomed Health Inf. 2017;21(5):1449–59 IEEE.
296. Lenhard F, Sauer S, Andersson E, Mansson KN, Mataix-Cols D, Ruck C, Serlachius E. Prediction of outcome in internet-delivered cognitive behaviour therapy for paediatric obsessive-compulsive disorder: a machine learning approach. Int J Methods Psychiatr Res. 2018;27(1) PMID:28752937 United States.
297. Mansson KNT, Frick A, Boraxbekk C-J, Marquand AF, Williams SCR, Carlbring P, Andersson G, Furmark T. Predicting long-term outcome of Internet-delivered cognitive behavior therapy for social anxiety disorder using fMRI and support vector machine learning. Transl Psychiatry 2015;5:e530 PMID:25781229 United States.
298. Askland KD, Garnaat S, Sibrava NJ, Boisseau CL, Strong D, Mancebo M, Greenberg B, Rasmussen S, Eisen J. Prediction of remission in obsessive compulsive disorder using a novel machine learning strategy. Int J Methods Psychiatr Res. 2015;24(2):156–69 Wiley Online Library.

299. Sundermann B, Bode J, Lueken U, Westphal D, Gerlach AL, Straube B, Wittchen H-U, Strohle A, Wittmann A, Konrad C, Kircher T, Arolt V, Pfleiderer B. Support vector machine analysis of functional magnetic resonance imaging of interoception does not reliably predict individual outcomes of cognitive behavioral therapy in panic disorder with agoraphobia. Front Psychiatry. 2017;8:99 PMID:28649205, Switzerland.
300. Kessler RC, van Loo HM, Wardenaar KJ, Bossarte RM, Brenner LA, Cai T, Ebert DD, Hwang I, Li J, de Jonge P, Nierenberg AA, Petukhova MV, Rosellini AJ, Sampson NA, Schoevers RA, Wilcox MA, Zaslavsky AM. Testing a machine-learning algorithm to predict the persistence and severity of major depressive disorder from baseline self-reports. Mol Psychiatry. 2016;21(10):1366–71. https://doi.org/10.1038/mp.2015.198.
301. Kessler RC, Hwang I, Hoffmire CA, McCarthy JF, Petukhova M V, Rosellini AJ, Sampson NA, Schneider AL, Bradley PA, Katz IR. Developing a practical suicide risk prediction model for targeting high-risk patients in the Veterans health Administration. Int J Methods Psychiatr Res. 2017;26(3):e1575 Wiley Online Library.
302. Perlis RH. A clinical risk stratification tool for predicting treatment resistance in major depressive disorder. Biol Psychiatry. 2013;74(1):7–14 Elsevier.
303. Mikus A, Hoogendoorn M, Rocha A, Gama J, Ruwaard J, Riper H. Predicting short term mood developments among depressed patients using adherence and ecological momentary assessment data. Internet Interv Neth. 2018;12:105–10 PMID:30135774.
304. Chekroud AM, Zotti RJ, Shehzad Z, Gueorguieva R, Johnson MK, Trivedi MH, Cannon TD, Krystal JH, Corlett PR. Cross-trial prediction of treatment outcome in depression: a machine learning approach. Lancet Psychiatry. 2016;3(3):243–250 Elsevier.
305. Chekroud AM, Gueorguieva R, Krumholz HM, Trivedi MH, Krystal JH, McCarthy G. Reevaluating the efficacy and predictability of antidepressant treatments: a symptom clustering approach. JAMA Psychiatry. 2017;74(4):370–378 American Medical Association.
306. Spring Health. https://www.springhealth.com/about/.
307. Bremer V, Becker D, Kolovos S, Funk B, van Breda W, Hoogendoorn M, Riper H. Predicting therapy success and costs for personalized treatment recommendations using baseline characteristics: data-driven analysis. J Med Internet Res. 2018;20(8):e10275 PMID:30131318 Canada.
308. Ebert DD, Cuijpers P. It time to invest in the prevention of depression. JAMA Netw. 2018;1(2):e180335. https://doi.org/10.1001/jamanetworkopen.2018.0335 Open American Medical Association.
309. Walton A, Nahum-Shani I, Crosby L, Klasnja P, Murphy S. Optimizing digital integrated care via micro-randomized trials. Clin Pharmacol Ther. 2018 Wiley Online Library.
310. Collins LM. Optimization of behavioral, biobehavioral, and biomedical interventions: the multiphase optimization strategy (MOST). Springer; 2018. ISBN:3319722069.
311. Nahum-Shani I, Hekler EB, Spruijt-Metz D. Building health behavior models to guide the development of just-in-time adaptive interventions: a pragmatic framework. Heal Psychol. 2015;34(S):1209 American Psychological Association.
312. Nahum-Shani I, Smith SN, Spring BJ, Collins LM, Witkiewitz K, Tewari A, Murphy SA. Just-in-time adaptive interventions (JITAIs) in mobile health: key components and design principles for ongoing health behavior support. Ann Behav Med. 1–17. https://doi.org/10.1007/s12160-016-9830-8 Springer US.
313. Goldstein SP, Evans BC, Flack D, Juarascio A, Manasse S, Zhang F, Forman EM. Return of the JITAI: applying a just-in-time adaptive intervention framework to the development of m-health solutions for addictive behaviors. Int J Behav Med. 2017;24(5):673–82 PMID:28083725 England.
314. Jaimes LG, Llofriu M, Raij A. A stress-free life: just-in-time interventions for stress via real-time forecasting and intervention adaptation. In: BODYNETS 2014-9th international conference on body area networks 2014;1:197–203. https://doi.org/10.4108/icst.bodynets.2014.258237.

315. Thomas JG, Bond DS. Behavioral response to a just-in-time adaptive intervention (JITAI) to reduce sedentary behavior in obese adults: implications for JITAI optimization. Health Psychol. 2015;34(Suppl):1261–7 PMID:26651467.
316. Spruijt-Metz D, Nilsen W. Dynamic models of behavior for just-in-time adaptive interventions. IEEE Pervasive Comput. 2014;13(3):13–7. https://doi.org/10.1109/MPRV.2014.46.
317. Juarascio AS, Parker MN, Lagacey MA, Godfrey KM. Just-in-time adaptive interventions: a novel approach for enhancing skill utilization and acquisition in cognitive behavioral therapy for eating disorders. Int J Eat Disord. 2018 PMID:30051495 United States.
318. Wahle F, Kowatsch T, Fleisch E, Rufer M, Weidt S. Mobile sensing and support for people with depression: a pilot trial in the wild. JMIR mHealth uHealth. 2016;4(3):e111 PMID:27655245 Canada.
319. Burns MN, Begale M, Duffecy J, Gergle D, Karr CJ, Giangrande E, Mohr DC. Harnessing context sensing to develop a mobile intervention for depression. J Med Internet Res. 2011;13(3):e55 PMID:21840837 Canada.
320. Ben-Zeev D, Kaiser SM, Brenner CJ, Begale M, Duffecy J, Mohr DC. Development and usability testing of FOCUS: a smartphone system for self-management of schizophrenia. Psychiatr Rehbil J. 2013;36(4):289–96 PMID:24015913.
321. Gustafson DH, McTavish FM, Chih M-Y, Atwood AK, Johnson RA, Boyle MG, Levy MS, Driscoll H, Chisholm SM, Dillenburg L, Isham A, Shah D. A smartphone application to support recovery from alcoholism: a randomized clinical trial. JAMA Psychiatry. 2014;71(5):566–72 PMID:24671165.
322. Pina L, Rowan K, Roseway a, Johns P, Hayes GR, Czerwinski M. In situ cues for ADHD parenting strategies using mobile technology. In: Proceedings of the-PERVASIVEHEALTH 2014 8th international conference on pervasive computing technologies for healthcare 2014. p. 17–24. https://doi.org/10.4108/icst.pervasivehealth.2014.254958.
323. Forman EM, Goldstein SP, Zhang F, Evans BC, Manasse SM, Butryn ML, Juarascio AS, Abichandani P, Martin GJ, Foster GD. OnTrack: development and feasibility of a smartphone app designed to predict and prevent dietary lapses. Transl Behav Med. 2018 PMID:29617911 England.
324. Luxton DD. Artificial intelligence in behavioral and mental health care. Academic Press; 2015. ISBN:0128007923.
325. DeVault D, Artstein R, Benn G, Dey T, Fast E, Gainer A, Georgila K, Gratch J, Hartholt A, Lhommet M. SimSensei Kiosk: a virtual human interviewer for healthcare decision support. In: Proceedings of the 2014 international conference on Autonomous agents and multi-agent systems. International Foundation for Autonomous Agents and Multiagent Systems; 2014. p. 1061–68.
326. Bird T, Mansell W, Wright J, Gaffney H, Tai S. Manage your life online: a web-based randomized controlled trial evaluating the effectiveness of a problem-solving intervention in a student sample. Behav Cogn Psychother. 2018;1–13 PMID:29366432 United States.
327. Burton C, Tatar AS, McKinstry B, Matheson C, Matu S, Moldovan R, Macnab M, Farrow E, David D, Pagliari C, Blanco AS, Wolters M. Pilot randomised controlled trial of Help4Mood, an embodied virtual agent-based system to support treatment of depression. J Telemed Telecare. 2016;22(6):348–355. https://doi.org/10.1177/1357633x15609793 Burton, Christopher, University of Aberdeen Aberdeen, Aberdeen, United Kingdom: Sage Publications.
328. Crutzen R, Peters G-JY, Portugal SD, Fisser EM, Grolleman JJ. An artificially intelligent chat agent that answers adolescents' questions related to sex, drugs, and alcohol: an exploratory study. J Adolesc Health. 2011;48(5):514–19 PMID:21501812 United States.
329. Provoost S, Lau HM, Ruwaard J, Riper H. Embodied conversational agents in clinical psychology: a scoping review. J Med Internet Res. 2017;19(5) JMIR Publications Inc.
330. Khoury MJ, Ioannidis JPA. Big data meets public health. Science. 2014;346(6213):1054–55 (80-) American Association for the Advancement of Science.
331. Pearl J. Myth, confusion, and science in causal analysis. 2009.

332. Goldstein BA, Navar AM, Pencina MJ, Ioannidis J. Opportunities and challenges in developing risk prediction models with electronic health records data: a systematic review. J Am Med Inf Assoc. 2017;24(1):198–208 Oxford University Press.
333. Moons KGM, Altman DG, Reitsma JB, Ioannidis JPA, Macaskill P, Steyerberg EW, Vickers AJ, Ransohoff DF, Collins GS. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. 2015;162(1):W1–W73 American College of Physicians.
334. DeMasi O, Kording K, Recht B. Meaningless comparisons lead to false optimism in medical machine learning. PLoS One. 2017;12(9):e0184604 PMID:28949964 United States.
335. Pearl J, MacKenzie D. The book of why: the new science of cause and effect. 1st ed. New York: Basic Books; 2018.
336. Chen JH, Asch SM. Machine learning and prediction in medicine—beyond the peak of inflated expectations. N Engl J Med. 2017;376(26):2507 NIH Public Access.
337. Cadwalladr C, Graham-Harrison E. Revealed: 50 million Facebook profiles harvested for Cambridge Analytica in major data breach. Guard 2018;17.
338. Gianfrancesco MA, Tamang S, Yazdany J, Schmajuk G. Potential biases in machine learning algorithms using electronic health record data. JAMA Intern Med. 2018.
339. Nahum-Shani I, Smith SN, Spring BJ, Collins LM, Witkiewitz K, Tewari A, Murphy SA. Just-in-time adaptive interventions (JITAIs) in mobile health: key components and design principles for ongoing health behavior support. Ann Behav Med. 2017;52(6):446–62 Oxford University Press US.