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## Internet-based Cognitive Behavioral Therapy for Depression: Current Progress & Future Directions

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### Abstract

The World Health Organization (WHO) estimates that during a given 12-month period approximately 34 million people suffering from major depressive disorder go untreated in Europe and the Americas alone.<sup>1</sup> Barriers to treatment include geographic distance, lack of mental health insurance, prohibitive cost of treatment, long wait-lists, and perceived stigma. Over the past two decades internet-based cognitive behavioral therapy (iCBT) programs have proliferated. A growing body of research supports the efficacy of iCBT for depression and other psychiatric conditions, and these programs may help address barriers that hinder access to effective treatment. The present review describes common iCBT programs along with the evidence base supporting their efficacy in reducing symptoms of depression, reviews research on moderators of treatment response, and provides suggestions for future directions in research and care.

### Keywords

Internet; Cognitive Behavioral Therapy; Treatment; Depression; Moderators

### Introduction

Since its initial development in the 1960s,<sup>2,3</sup> cognitive behavioral therapy (CBT) has flourished and emerged as one of the most commonly practiced and the most extensively researched form of psychotherapy.<sup>4</sup> A large body of research supports the efficacy of CBT in alleviating depressive symptoms and lowering the risk of relapse.<sup>4,5</sup> Over the past few decades, CBT protocols have been tailored to target a range of psychiatric disorders beyond depression, including anxiety disorders,<sup>6,7</sup> bipolar disorder,<sup>8</sup> substance use disorders,<sup>9,10</sup> personality disorders<sup>11</sup> and psychotic disorders.<sup>12,13</sup> In recent years, CBT has also been adapted to incorporate newly developed interventions and techniques (e.g., mindfulness- and acceptance-based strategies). Despite this progress, the dominant delivery format of CBT has persisted: face-to-face individual or group therapy. The development of internet-based adaptations of CBT (iCBT), coupled with the exponential growth of internet access

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throughout the world, has the potential to reshape the landscape of behavioral and mental healthcare. The World Health Organization (WHO) estimates that during a given 12-month period approximately 34 million individuals suffering from major depressive disorder (MDD) go untreated in Europe and the Americas alone.<sup>1</sup> Barriers to receiving treatment include costs, long wait-lists, limited access to psychiatric treatment where one lives, and perceived stigma of seeking treatment for a psychiatric disorder. Internet-based interventions have been proposed as one solution to help bridge this treatment gap. In this review, we discuss common iCBT programs for depression, the evidence base supporting these interventions, and the benefits as well as limitations of these programs. We also discuss moderators of treatment response and suggest directions for future research and care.

## iCBT Programs for Depression

The majority of internet-based interventions for depression are cognitive behavioral in nature. Although there are differences in format and content, these programs all provide web-based access to materials that teach participants the core cognitive skills (e.g., the ability to identify and modify negative cognitions and depressogenic biases in information processing) and behavioral skills (e.g., behavioral activation, problem solving strategies) encouraged in traditional face-to-face CBT. Early versions of these programs were offline (e.g., delivered via CD-ROM). For example, the cognitive behavioral *Beating the Blues* (*BTB*) program was initially offered via CD-ROM, but was subsequently adapted for web-based delivery (available at <http://www.beatingtheblues.co.uk>).<sup>14,15</sup> *BTB* was developed in the UK and consists of 8 web-based modules. Each module takes approximately 50-minutes to complete, and gradually guides participants through information on the cognitive behavioral model of depression, and teaches a range of common cognitive and behavioral skills. Similar to individual CBT, “homework” is assigned at the end of each module to provide patients the opportunity to practice the skills learned in a given module.

Another early web-based platform is *MoodGYM*<sup>16</sup> (<https://moodgym.anu.edu.au>), which was developed by researchers in Australia. This program consists of 5 cognitive behavioral modules (lasting approximately 30–45 minutes each), focusing on the relationship between thoughts and emotions, identifying cognitive distortions and negative thoughts, strategies to modify negative thoughts, assertiveness and self-esteem training, behavioral activation, and problem solving. Module content is presented through web pages, interactive features, and supplementary pop-up windows. A personal workbook is also provided, containing assessments (e.g., of depressive/anxiety symptoms, negative cognitions) and 29 CBT-based exercises. Additional early, seminal work on iCBT was conducted in Sweden,<sup>17</sup> and also in the Netherlands (e.g., *Interapy*: <http://www.interapy.nl/home>).<sup>18</sup> Since then, the iCBT literature has expanded rapidly, with numerous additional web-based programs developed and tested.

iCBT programs differ in the extent to which they provide guidance or support. As reviewed in more detail below, unguided or “stand-alone” programs have been associated with relatively poorer outcomes and higher dropout rates than programs incorporating guidance or support. Guidance is provided in a variety of different forms, including informational and supportive automated emails sent to participants,<sup>19</sup> brief (e.g., approximately 3–5 minute)

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weekly phone calls from therapists or research assistants providing encouragement, support and clarification of iCBT lesson content and homework,<sup>19</sup> text-based communication between clients and clinicians,<sup>18</sup> and, on the more time-intensive end of the support spectrum, providing online CBT via scheduled hour-long sessions.<sup>20</sup>

As noted above, although there are some differences in format and in the information presented, iCBT programs present similar cognitive behavioral content to participants via websites. Creative variants on these common iCBT formats also have been developed. For example, a CBT-based program named *Panoply* leverages a peer-to-peer crowdsourcing platform to facilitate the core cognitive skill of identifying and challenging negative thoughts.<sup>21</sup> Specifically, through the *Panoply* platform, users submit brief descriptions of recent stressors and accompanying negative thoughts. These descriptions are then reviewed by other users who receive online training to provide one of three responses: (1) “support” (i.e., providing emotional support and active listening); (2) “debug” (i.e., aiding in identifying and correcting cognitive distortions); (3) “reframe” (i.e., offering alternative, more realistic ways of viewing the stressor). Importantly, all responses are reviewed by other *Panoply* users prior to being returned to the individual who submitted the original post. Responses deemed inappropriate are discarded. In sum, *Panoply* is different from other iCBT programs in that the work of identifying and modifying negative cognitions is outsourced to other users. An additional unique aspect of this platform is that users not only receive helpful feedback from others, but also have the opportunity to practice cognitive skills by delivering feedback to fellow *Panoply* users. A parallel iPhone app (*Koko*; <http://itskoko.com>) derived from the web-based *Panoply* platform has been developed. However, several of the *Panoply* features are not currently present in this app (e.g., training of other users to provide support, debug and reframe responses).

Researchers have also begun to capitalize on rapid advancements in technology to facilitate the diagnosis and treatment of depression. Examples of these innovations include using “passive” (i.e., no user input required) data collected from built-in smartphone sensors to predict elevated depressive symptoms and to suggest interventions;<sup>22,23</sup> differentiating depressive versus manic mood states from speech patterns detected from phone conversations;<sup>24</sup> predicting depressive symptoms from Facebook activity;<sup>25</sup> delivering CBT interventions via videogame format;<sup>26</sup> and using smartphone-based mental health apps to treat depression and anxiety.<sup>27–29</sup>

## The Benefits of iCBT

Internet-based treatments offer a range of benefits over traditional face-to-face therapy. First, and as noted above, many individuals suffering from depression do not receive treatment because they cannot access care.<sup>1</sup> Internet-based interventions can substantially enhance access in a variety of ways: A) iCBT can be readily accessed from the comfort and convenience of home (or anywhere with an internet connection); B) the scalability of iCBT can drastically increase functional capacity of the care system, thereby overcoming current challenges of inadequate availability of care; and C) the temporal aspects of access can be substantially improved because time elapsed from screening/referral to the iCBT first session can be within the same day, whereas wait-times for initiation of face-to-face therapy

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are commonly on the order of weeks. Moreover, it is critical to appreciate that while face-to-face sessions need to be scheduled days or weeks in advance due to therapist availability, iCBT sessions can be completed whenever the patient feels best motivated to engage with the therapeutic content as judged by him/her in real time.

Second, some individuals may not seek treatment because they do not have insurance or cannot afford the out-of-pocket fees for treatment. Internet-based interventions are – at least currently – offered for a relatively small fee or free of charge. Data on the cost effectiveness of iCBT for depression is somewhat limited. A recent review indicated that, overall, the literature supports the cost-effectiveness of guided iCBT, and to a lesser extent unguided interventions not involving human support.<sup>30</sup> (See also Warmerdam et al.<sup>31</sup> and Hollinghurst et al.<sup>32</sup>). However, the available evidence remains somewhat mixed and more studies are needed to address this important question, including the relative cost-efficiency of internet-based versus face-to-face psychotherapeutic or pharmacologic treatment.

Third, the perceived stigma of seeing a mental health professional for a psychiatric disorder may keep individuals from seeking help. The ability to access internet-delivered treatment from the privacy of one's home may increase access to care and help bridge the treatment gap.

In addition to these potential benefits, internet-based therapy – at least as currently provided – poses some risks. In particular, current iCBT programs are relatively ill-equipped to handle clinical crises such as active suicidality. In traditional face-to-face outpatient treatment, clinicians can assess for suicide risk in person, and determine whether a higher level of care is needed (e.g., hospitalization). Studies of internet-based interventions often incorporate self-report instruments to assess depressive symptoms, many of which include items assessing suicidal thoughts (e.g., Patient Health Questionnaire-9; PHQ-9).<sup>33</sup> If a patient endorses elevated suicidality on a self-report measure, it is recommended that a clinician contact the participant to ascertain the nature and severity of the participant's suicidality and to determine their risk status (e.g., by administering the Columbia-Suicide Severity Rating Scale;<sup>34</sup> <http://www.cssrs.columbia.edu/>). Following such an evaluation, a clinician can decide whether continued iCBT treatment is appropriate or whether a patient requires a higher level of care. Some iCBT platforms, such as the *Sadness Program* (<https://thiswayup.org.au>), include automated emails that are triggered when participants endorse severe depressive symptoms or suicidality on self-report measures administered at the start of each lesson. These emails are sent to assigned clinician(s), who may be psychologists, psychiatrists, other mental health specialists, or general practitioners (GP) depending on the study.<sup>19,35</sup> It is the responsibility of the assigned clinician to then contact participants to follow-up with a more detailed suicide assessment by phone.<sup>36</sup> Many iCBT studies have excluded participants with higher levels of baseline suicidality, in order to minimize the risk of clinical crises occurring.<sup>19,36</sup> Although more research is needed, there is some evidence that iCBT may be therapeutically beneficial even among depressed individuals who endorse suicidal ideation. One study found that 31% of participants who were prescribed the *Sadness Program* within a primary care setting reported having at least some suicidal ideation during the 2-week time period before starting the program.<sup>35</sup> Subgroup analyses focused on patients endorsing suicidal thoughts at the beginning of treatment indicated significant

improvement over the course of the program in depressive symptoms (Cohen's  $d = 1.08$ ), suicidal ideation ( $d = 1.10$ ) and overall psychological distress ( $d = 1.07$ ). Ultimately, it is up to the clinician(s) administering the iCBT intervention to manage risk according to the clinical and risk management guidelines of their institution.

Moreover, face-to-face CBT allows clinicians to develop an individual case conceptualization and tailor treatment to the unique needs of each patient. The majority of existing iCBT programs provide the same "one-size-fits-all" CBT content to every user. These iCBT programs place the task of individualizing the content on participants, who will need to apply them to their unique life circumstances and symptoms (e.g., using the homework assignments). As iCBT programs evolve they will likely become more interactive and better able to adapt to the idiosyncratic needs of each patient (e.g., tailoring content to symptom severity and symptom profiles). For example, the *Panoply* program provides personalized feedback based on the particular stressors and negative thoughts reported by users. Similarly, and as described below, "tailored" iCBT platforms have been developed that attempt to adapt program content based on the presenting symptoms of each patient.<sup>37</sup>

## How Effective are iCBT Programs for Depression?

As discussed above, there are a number of possible benefits of internet-delivered treatment for depression. However, the proliferation of internet-based adaptations of CBT raises the important question: *How effective are these iCBT programs for the treatment of depression?* An early meta-analysis of 12 computer-based (10 iCBT and 2 offline, computerized programs) interventions for depression found a moderate post-treatment effect size ( $d = .56$ ) reflecting greater symptom improvement relative to participants assigned to control groups. Intriguingly, this effect size was moderated by whether these programs were guided ( $d = .61$ ) versus unguided ( $d = .25$ ).<sup>38</sup> Subsequent reviews identified a similar pattern of findings, with guided programs yielding larger effects than unguided interventions.<sup>39–42</sup> For example, a meta-analysis of 19 randomized clinical trials of iCBT for depression found a moderate effect size ( $d = .56$ ) favoring iCBT over control groups in improving depressive symptoms.<sup>40</sup> However, unguided interventions yielded smaller effect sizes ( $d = .38$ ) than guided programs ( $d = .78$  for therapist support;  $d = .58$  for administrative support).

It is important to emphasize that the majority of iCBT studies to date have relied on wait-list control groups, with the next most common control condition being treatment as usual. Patients assigned to a wait-list condition do not receive the intervention during the trial, but they do complete the same symptom assessments as the treatment group. (Wait-list participants are typically given access to the iCBT content following their final assessment). The greater improvement among participants assigned to iCBT over wait-list control groups could be due to the cognitive and/or behavioral skills taught in treatment. However, greater symptom improvement among iCBT participants could also reflect the influence of "common" therapeutic factors, including greater expectations of improvement. In order to control for these factors, future studies will need to test iCBT versus more stringent or credible control conditions, such as a psychosocial placebo control condition that elicits similar expectations of symptom improvement relative to the treatment condition. Of course, one particularly relevant comparison condition for iCBT is traditional, face-to-face CBT. To

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date, there have only been a few trials with relatively small sample sizes comparing iCBT to face-to-face individual<sup>43</sup> or group<sup>44,45</sup> CBT. Interestingly, these studies each found similar depressive symptom improvement across groups. Although preliminary, these data suggest that iCBT may be as effective as face-to-face CBT in reducing depressive symptoms.

Given that anxiety is a common comorbidity of depression, it is important to note that transdiagnostic iCBT programs have been developed and found to significantly reduce both depression and anxiety symptoms.<sup>46</sup> In addition, “tailored” iCBT programs have been developed to target the idiosyncratic symptoms or problems of each patient. One study of MDD patients with a range of different comorbidities tested a standard “one-size-fits-all” iCBT protocol versus a “tailored” iCBT intervention that adapted the program content based on the presenting symptoms of each patient. For example, in the tailored iCBT condition, a patient reporting substantial worry in addition to depression would receive a CBT-based module targeting worry in addition to cognitive behavioral content addressing depressive symptoms.<sup>37</sup> Although both the standard and tailored iCBT groups evidenced significant depressive and anxiety symptom improvement, subgroup analyses indicated that those with higher pre-treatment depression scores (as well as more comorbidity) derived relatively greater therapeutic benefit from the tailored program. Finally, iCBT programs have been adapted for children and adolescents and shown to significantly reduce depressive symptoms in youth.<sup>47</sup>

In addition to well-controlled randomized clinical trials, it is especially important to assess the “real world” utility of iCBT to enhance access to low-cost, effective treatment. Indeed, several effectiveness studies indicate that iCBT can be effectively delivered in routine clinical care with similar therapeutic benefits as those observed in randomized clinical trials.<sup>48–50</sup> However, one large and recent effectiveness trial in the UK questioned the therapeutic benefits of iCBT in a primary care setting.<sup>51</sup> Specifically, there was no significant difference in symptom improvement between depressed patients randomly assigned to usual GP care, or to either the *Beating the Blues* or *MoodGYM* iCBT combined with usual GP care. However, these findings are difficult to interpret for two reasons. First, approximately 19% of participants in the usual GP care arm *also* reportedly accessed iCBT content, either on their own or on the recommendation of their GP or mental health professional. In addition, the percentage of patients who completed all of the iCBT lessons in the *Beating the Blues* (18%) and *MoodGYM* (16%) groups was low. These findings highlight the challenge of maintaining iCBT treatment adherence in real-world settings.

## Does iCBT Reduce the Risk of Relapse?

MDD is a highly recurrent disorder. Approximately 80% of those who have experienced a major depressive episode experience a recurrence.<sup>52</sup> In addition, the risk of depression recurrence increases by approximately 16% with each successive episode.<sup>53</sup> These data underscore the importance of treatments that not only reduce current depressive symptoms but also lower the risk of depression relapse. One of the benefits of traditional, face-to-face CBT is its ability to lower the risk of relapse following treatment termination. In fact, a meta-analysis found that face-to-face CBT was associated with a lower risk of depression relapse than antidepressant medication treatment.<sup>5</sup> In order to support the dissemination of

iCBT, similar relapse prevention findings would be helpful. In their meta-analytic review, Richards and Richardson found 14 studies that included follow-up data examining whether patients who received a course of iCBT for depression maintained their gains relative to control conditions.<sup>40</sup> On average, iCBT patients reported lower levels of depressive symptoms than control participants, but the between-group effect size at follow-up ( $d=.20$ ) was smaller than at post-treatment ( $d=.56$ ). One recent study found no significant differences between iCBT and face-to-face CBT in depressive symptoms at a 3-month post-treatment follow-up assessment,<sup>43</sup> although there was a nonsignificant trend in the direction of greater symptom improvement in the iCBT group. It is important to note that only about two thirds of participants completed the follow-up assessment in the latter study, limiting the authors' ability to draw firm conclusions from these data.

## Dropout Rates in iCBT

One of the attractive features of internet-based interventions is their scalability and potential to reach large numbers of depressed individuals who are not currently receiving treatment. Several early studies of iCBT platforms were unguided, “stand-alone” interventions. A concern that was raised early on in the development and testing of internet-based interventions for depression was the relatively high attrition rate in these stand-alone programs.<sup>54</sup> Indeed, a meta-analysis of 40 iCBT studies found that over half (57%) of patients assigned to treatment drop out.<sup>40</sup> In an effort to reduce dropout rates and increase treatment adherence, iCBT programs have incorporated therapist or administrative support. For instance, a study by Christensen and colleagues used brief weekly phone calls or emails from research assistants to check in with participants and clarify questions about program content.<sup>54</sup> In their meta-analysis, Richards and Richardson found that dropout rates were significantly higher in stand-alone iCBT programs (74%) relative to either therapist support (28%) or administrative support (38%).<sup>40</sup> For comparison, dropout rates in traditional, face-to-face CBT are approximately 17% in randomized clinical trials<sup>55</sup> and 25% in non-randomized effectiveness studies.<sup>56</sup> Thus, some form of staff support seems important to increase patient engagement and to reduce attrition rates in iCBT interventions. With regard to predictors of dropout, a recent individual patient data (IPD) meta-analysis of 2,705 participants across ten randomized clinical trials of internet-based interventions for depression identified younger age, male gender, lower educational level, and presence of comorbid anxiety symptoms as being significantly associated with greater likelihood of dropout.<sup>57</sup>

Clearly, additional work is needed to identify ways to lower attrition rates in existing iCBT programs. However, some have argued that attrition from internet-based interventions, which have the potential to reach vast numbers of individuals who may otherwise not seek treatment, may be less of a concern than attrition from face-to-face treatment.<sup>58</sup> By analogy, “massive open online courses” (MOOCs) provide (generally free) educational courses across a wide array of topics to any interested individual with internet access. Although the percentage of individuals who complete a given online course is typically low, a single MOOC may enroll upwards of several hundred thousand students.<sup>59</sup> Inspired by the rapid growth of MOOCs, Muñoz and colleagues coined the phrase “massive open online interventions” (MOOIs) to refer to internet-based treatments that could reach a similarly vast

number of individuals, and perhaps help offset relatively high dropout rates.<sup>58</sup> For example, at the time of this writing, the *MoodGYM* program has reportedly been used by over 850,000 individuals, even if one study indicates that fewer than 7% of *MoodGYM* users progress beyond the first two modules (out of a total of 5 modules).<sup>60</sup>

## For Whom is iCBT Most Effective?

A critical goal for the field is to identify those individuals who may derive the most therapeutic benefit from internet-based interventions, as well as those who would be better suited to receive a traditional form of treatment, such as pharmacotherapy and/or face-to-face psychotherapy (or combined treatment). In other words, depressed individuals may vary in their likelihood of responding to iCBT by virtue of their unique psychosocial, demographic, neurobiological, or clinical profile. In recent years there have been studies aimed at identifying predictors of treatment response to face-to-face CBT and pharmacotherapy. For example, one study found that CBT was more effective than selective serotonin reuptake inhibitor (SSRI) pharmacotherapy in reducing depressive symptoms for individuals who were experiencing a relatively large number of life stressors, were unemployed or were married (or cohabitating).<sup>61</sup> In terms of neural markers of differential treatment response, glucose hypometabolism in the insula has been linked to better treatment response to CBT than to a SSRI for depression, whereas insula *hypermetabolism* has been associated with the reverse pattern (i.e., better outcomes for SSRI than CBT).<sup>62</sup>

Comparatively little research has examined predictors of treatment response to iCBT. Within the few existing studies, the following variables have been found to predict greater depressive symptom improvement in iCBT: relatively higher depression severity,<sup>63–65</sup> being separated, widowed or divorced,<sup>63</sup> having a higher level of education,<sup>63</sup> female gender,<sup>64,66</sup> as well as lower levels of dysfunctional attitudes and lower perceived mastery (i.e., decreased sense of control over situations).<sup>66</sup> More recently, and within the context of a study examining iCBT combined with face-to-face therapist guidance, researchers found that being married (or cohabitating), having higher life satisfaction, and having had more depressive episodes predicted better treatment outcomes; in contrast, higher levels of dysfunctional thinking predicted poorer outcomes.<sup>67</sup> In summary, there is substantial variability across studies in the moderator variables examined, as well as in findings. Notably, several studies have found that *higher* depression severity,<sup>63–65</sup> as well as *more frequent* depressive episodes,<sup>67</sup> predicts *better* treatment outcomes to iCBT. Given the lack of clinician contact, and relatively brief nature of the interventions, many iCBT studies purposefully excluded more severely depressed patients who may reasonably require more intensive face-to-face treatment.<sup>19,36</sup> Still, the abovementioned findings suggest that, on average, individuals with relatively more severe depression at the beginning of treatment may derive greater therapeutic benefit from iCBT treatment than those with lower depression severity. Nevertheless, these studies were not designed to address whether or not individuals with higher levels of depressive symptoms exhibit relatively greater symptom improvement in an alternative treatment, such as face-to-face CBT. Additional research is required comparing depressive symptom improvement for relatively lower vs. higher severity depressed patients randomly assigned to iCBT vs. face-to-face CBT (or pharmacotherapy).

## Prognostic vs. Prescriptive Predictors of Treatment Response

The above findings indicate that there may be certain pre-treatment patient characteristics that can help predict who is more or less likely to improve in iCBT. Although such general “prognostic predictors” are clinically informative, research testing “prescriptive predictors” (i.e., testing for statistical interactions between pre-treatment predictor variables and treatment condition)<sup>61</sup> is needed to examine whether certain variables (e.g., clinical, demographic, psychosocial, neurobiological) predict differential response to iCBT relative to *other* treatment options.<sup>1</sup> In other words, whereas prognostic variables predict outcome *across* treatments, prescriptive variables (also referred to as moderators) predict a different pattern of outcomes for two or more treatments.<sup>61</sup> Such research could ultimately inform treatment selection. That is, consistent with the pursuit of personalized medicine in psychiatry, these types of studies can lead to the identification of pre-treatment characteristics that provide clinicians with clinically useful information regarding which intervention has the highest likelihood of improving an individual’s depression. To date, the few iCBT studies that have tested pre-treatment predictor by treatment group interactions have mostly yielded null findings. For example, one study examined predictors of symptom improvement within a clinical trial comparing iCBT versus internet-delivered problem-solving therapy.<sup>65</sup> The authors did not find any moderators that differentially predicted outcome between these two treatments. Similarly, Donker and colleagues compared iCBT to internet-delivered interpersonal therapy, and found that no pre-treatment variables interacted with intervention group in differentially predicting outcome.<sup>66</sup> In another study, the personality characteristic of altruism moderated treatment outcome such that those with higher levels of altruism evidenced greater symptom improvement in face-to-face group CBT than in iCBT.<sup>64</sup> However, the nine other moderator variables they tested were not significant.

Although there are more studies testing prescriptive predictors of treatment response in face-to-face treatment of depression<sup>69</sup> and anxiety<sup>70</sup>, findings in the iCBT literature have similarly been disappointing with few consistent moderators identified. Given the large sample sizes required to provide adequately powered tests of predictors of differential response to two or more treatments,<sup>70</sup> most existing studies may be underpowered to detect statistically significant treatment moderators. In addition, the above studies tested the role of *individual* moderating variables in predicting response to iCBT. More recent statistical methods allow for the combining of multiple moderators rather than relying on single variables, each of which may have small effects when considered individually.<sup>68,71,72</sup> For example, among depressed patients randomly assigned to interpersonal therapy versus SSRI pharmacotherapy, one study used principal-components analysis to derive a composite moderator from a set of 32 pre-treatment variables.<sup>72</sup> Their final composite moderator was comprised of a weighted combination of eight variables and, notably, was a stronger predictor (effect size = .31) of differential treatment response than any individual pre-treatment variable (largest single moderator effect size = .12).

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<sup>1</sup>Terminology for these two different classes of predictors differ. Some reserve the term “predictor” for prognostic predictors and use the term “moderator” for prescriptive predictors.<sup>68</sup>

Multivariate machine learning (ML) methods offer another empirical approach to combining individual predictors in an effort to identify more robust, and ultimately clinically informative, moderators of treatment response.<sup>73</sup> ML refers to a family of different statistical methods involving the use of algorithms to identify meaningful patterns within data. For example, one study applied ML analysis to pretreatment resting electroencephalography (EEG) data and found that the resulting ML-derived combination of EEG markers yielded better prediction of SSRI response (81% specificity, 95% sensitivity) than any individual predictor (60% specificity, 86% sensitivity).<sup>71</sup> For recent similar findings, see Checkroud et al.<sup>73</sup> and Etkin et al.<sup>74</sup> To our knowledge, no study has examined whether brain-based variables may predict treatment response in iCBT. Earlier we noted that glucose metabolism in the insula has been found to differentiate treatment response to face-to-face CBT versus SSRIs.<sup>62</sup> It remains to be seen whether or not neural variables are more sensitive than clinical/demographic variables in predicting treatment response to iCBT. Given their costs, and in order to be clinically useful, neural variables must provide *incremental predictive validity* above and beyond other much more inexpensive and easily administered measures (e.g., clinical, demographic, or psychosocial variables).

## Future Directions

Future research in iCBT should aim to extend work to date in several respects. First, more rigorous control groups (e.g., active placebo controls, face-to-face CBT) will enable testing for differential efficacy. In this context, relatively large samples will be needed to confer sufficient power to test for clinical group differences, as well as to support predictor and moderator analyses. In addition, with rapid advances in mobile technology there is opportunity for commensurate swift evolution in the manner in which iCBT programs are delivered. Most fundamentally, with the rapid proliferation of smartphone apps, it is likely that these will quickly become the dominant mode of accessing such programs, in comparison with computer- and web-based methods. This will yield several notable advantages, including the convenience and ease with which patients can carry the program with them and complete homework activities in their day-to-day lives. Given that many patients fail to adhere to iCBT treatment,<sup>51,60</sup> the extent to which individuals are more likely to access and ideally complete iCBT courses on their smartphones versus on their computers is an important question for future research.

With a progression to iCBT via smartphones, there will also be the potential to integrate ecological momentary assessment (EMA), as well as passive data acquired from built-in smartphone sensors (e.g., GPS, accelerometer, meta-data from calls and text messages) to measure other indices of patient behavior and clinical status, into the therapeutic process. The Mobylyze App is one example, seeking to detect depressive mood states based on passive data and to intervene with suggestions of behavioral strategies to boost mood.<sup>22</sup>

Finally, advances in iCBT will also need to be incorporated into the larger ongoing transformational effort to redesign healthcare. In this context, behavioral and mental health services are being better integrated with primary care, and delivery as well as payment models are evolving to support improved public health via population health management.<sup>75,76</sup> Indeed, approaches such as iCBT are emblematic of this movement,

representing a scalable approach that can be offered proximate to screening in the primary care office, to improve access, enhance outcomes and reduce cost. It remains to be determined which sub-populations of patients will be best suited for these versus alternative interventions, and which methods and amount of patient contact (e.g., brief weekly phone calls from iCBT staff providing encouragement, support and clarification of iCBT lesson content and homework) will best facilitate treatment adherence and completion. In addition, given that the bulk of iCBT studies have been conducted outside of the United States, research is needed to determine how internet-based treatment should be modified to be best integrated into the American healthcare system. Finally, it will be critical to ensure privacy and the security of patient data given the advancements in technology and the rapid proliferation of internet- and smartphone-delivered interventions.

## Conclusion

The field of iCBT has advanced considerably in the past two decades, yielding several popular tools that appear to be efficacious and effective for the treatment of depression. This approach holds promise for improved access, enhanced outcomes, and reduced cost. Still, further research is needed to determine the best approaches to patient selection and for optimizing engagement, as well as the best overall manner for integrating these tools into the larger healthcare delivery system. Likewise, further research is needed to advance our understanding of predictors of treatment response and underlying mechanisms of change in order to further refine and improve existing internet-based treatments. In this context, it is likely that smartphones will soon become the dominant mode of delivery for iCBT applications. It is exciting to consider how this field will rapidly change and advance in the service of helping patients who suffer from depressive symptoms.

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