Computerized Cognitive Behavioral Therapy for Treatment of Depression in Multiple Sclerosis

A Narrative Review of Current Findings and Future Directions

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Depression is common in multiple sclerosis (MS), affecting up to 50% of patients at some point in their lifetime. Although the rate of depression in MS is higher than that in the general population and that in patients with other chronic medical conditions, depression in MS is underdiagnosed and undertreated. Antidepressant agents are used empirically in the management of MS-related depression, but evidence specifically demonstrating the efficacy of these medications in patients with MS is sparse. Considerable work suggests that psychological interventions such as cognitive behavioral therapy (CBT) may be effective in the management of depression in MS. Recently there has been an expansion of computerized adaptations of CBT, allowing patients to complete therapy sessions remotely via online programs. This article reviews our current understanding of depression in MS and the role of CBT in its management, focusing on recent developments in computerized formats for CBT. Four computerized CBT programs that have been previously tested in patients with MS are described: Deprexis, MoodGYM, Beating the Blues, and MS Invigor8. We conclude that despite challenges inherent to computerized CBT interventions, such platforms have the potential to positively affect mental health care delivery to the MS patient population. *Int J MS Care*. 2019;21:113-123.

Multiple sclerosis (MS) is the most common autoimmune demyelinating disease of the central nervous system (CNS). The disease classically presents in young adulthood with acute or subacute onset of neurologic symptoms due to a CNS inflammatory event. The presenting symptoms of an MS exacerbation can be wide-ranging, reflecting the variability of CNS inflammatory insults. Common neurologic manifestations include visual impairment (optic neuritis), brainstem dysfunction (nystagmus, intranuclear ophthalmoplegia), weakness, sensory abnormalities, and poor balance. Importantly, MS can also present with an array of cognitive and psychological symptoms (including fatigue, cognitive dysfunction, and depression) that are not always evident on routine examination.[1]

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Depression in MS

Overview

Neuropsychiatric dysfunction, and particularly depression, is common in MS, with as many as 40% to 50% of patients with MS reporting depression at some point in their lifetime.[2] The prevalence of depression in patients with MS is three to four times higher than that in the general population and is also higher than that in patients with other chronic medical conditions.[3-6] Studies of the rates of depression in first-degree relatives of patients with MS have shown familial incidence that is identical to that in the general population, suggest-

ing that MS-related depression may be a manifestation of neurologic disorder itself and intrinsically different from a primary psychiatric diagnosis of depression.[7] Numerous studies have shown that depression confers significant morbidity in MS—it has been associated with poorer quality of life,[8] impairment in work productivity,[9] and lower adherence to disease-modifying therapy[10] and may exacerbate symptoms of cognitive dysfunction.[11] Depression is also a predictor of suicidality in people with MS.[12,13]

Pathologic-Radiographic Correlates

The pathophysiological correlate of depression in MS is believed to be multifactorial and remains an area of ongoing investigation. Neuroinflammatory, neuroendocrine, and neurotrophic dysregulation have all been hypothesized, but there is no single unifying pathobiological correlate of MS-related depression.[14] Magnetic resonance imaging (MRI) white matter lesion volume and regional atrophy of the left frontotemporal cortex, particularly the arcuate fasciculus[15,16] and hippocampal dentate gyrus,[17] have correlated with depression. In other work, depression and the severity of depression symptoms have been linked to MRI measures of "destructive" pathology in MS (particularly frontoparietal atrophy and extent of T1 "black holes") in the absence of a relationship to T2 lesion volume.[18] Although MS is classically described as an inflammatory disease of the white matter, recent histopathologic advances have illustrated that gray matter pathology (cortical atrophy and demyelination) is ubiquitous and correlates with a variety of MS-related neuropsychiatric symptoms, including depression.[19] Ongoing work with high-resolution imaging continues to explore the relationship between this pathology and depression.

Pharmacologic Treatment

Despite the well-documented clinical burden of neuropsychiatric symptoms in patients with MS, depression is strikingly undertreated.[12,20,21] In a study of 260 patients with MS under the care of a neurologist, two-thirds of the patients who met the criteria for major depressive disorder were not receiving any antidepressant medication.[20] A larger community sample study of 542 patients with MS found that of those who had clinically significant depressive symptoms, 59% were not using any antidepressant agents.[21] One proposed explanation for this effect is that patients with MS are less willing to seek treatment for depression when symptoms arise, as evidenced by one study that demonstrated that when patients with MS reporting symptoms of depression were sent a letter prompting them to seek treatment, more than 70% did not do so.[22]

Research regarding the efficacy of pharmacologic treatments for depression in MS is limited. Two randomized controlled trials (RCTs) have been conducted assessing the effects of antidepressant agents in MS, one for paroxetine and another for desipramine.[23,24] A Cochrane review of these two trials concluded that antidepressant drug treatment showed only a trend toward effectiveness, with the only statistically significant effect on depression being a modest reduction in depression score (≤7, as rated by the Hamilton Depression Rating Scale) after 12 weeks of treatment with paroxetine (started at 10 mg/d and increased to 40 mg/d if tolerated).[25] Several additional open-label trials that tested the effectiveness of antidepressant drugs such as duloxetine, sertraline, and fluvoxamine found the drugs to be well-tolerated and generally effective in treating depression in patients with MS,[26-28] although there are insufficient data to conclude that any particular drug is more effective than another.[6]

Psychotherapeutic Treatment

Considerable work has demonstrated that psychotherapy is as important as pharmacotherapy in the management of depression. Psychotherapeutic interventions, particularly cognitive behavioral approaches, have been shown to be beneficial in treating depression in MS.[29,30] Cognitive behavioral therapy (CBT) is a widely used and evidence-based treatment for depression in the general population, and it may even be superior to antidepressant drugs.[31] The underlying principle of CBT is that an individual's thoughts and behaviors are largely determined by the way in which they perceive the world.[32] Therapists using a CBT framework help people identify and reappraise negative thoughts and develop coping strategies, which, in turn, may allow people to better manage their problems. Cognitive behavioral therapy is a present-oriented therapy, meaning that it is focused on solving current problems people are facing rather than past issues.

Cognitive behavioral therapy may be especially useful for patients with MS and depression because the technique develops a problem-focused coping framework, which patients with MS and depression may underuse.[33] Several studies have found that CBT (administered with a therapist in person or over the telephone) can

be highly effective in reducing depressive symptoms in patients with MS,[34-36] with one study suggesting that CBT may be as effective as pharmacotherapy.[37] In this study, patients with MS and depression were treated with weekly therapist-administered CBT, supportive-expressive group psychotherapy, or sertraline (doses varying from 50-200 mg). Sertraline and CBT were equally effective and significantly better than supportive-expressive group psychotherapy at lowering scores on the Beck Depression Inventory (BDI) and at lowering the incidence of major depressive disorder diagnosis per the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)*. Six months after treatment, the effect of CBT and sertraline persisted, suggesting stability of the interventions.[37]

Meta-analysis data seem to support the finding that CBT is effective in treating MS-related depression. One early meta-analysis of depression treatment in MS (published when only one pharmacotherapy RCT was available) showed no significant difference between psychotherapy and pharmacotherapy.[38] Interestingly, the authors found that psychotherapy that focused on developing coping skills (strategies inherent to CBT) seemed to outperform traditional insight-oriented psychotherapy. More recent meta-analyses reviewing the use of CBT for treatment of MS-related depression have found that CBT is effective, with a medium treatment effect for depression compared with standard of care.[30] Similarly, a 2006 Cochrane Review[29] that assessed the effectiveness of various psychological interventions for patients with MS indicated that CBT is "beneficial in the treatment of depression, and in helping people adjust to, and cope with, having MS."(p2) One intuitive hypothesis for the effectiveness of CBT in MS-related depression is that CBT's emphasis on coping skills empowers patients to address unpredictable challenges intrinsic to the disease and, thereby, minimizes the likelihood of depression related to the inability to cope.[38]

Computerized CBT for Treatment of Depression

In-person psychotherapy sessions may be impractical for many patients with MS-related disability. In recent years, there has been an expansion of online computerized interventions for self-help treatment of mental disorders. These programs can improve knowledge about and symptoms of mental disorders such as depression, helping to address the unmet need for treatment.[39] Among these programs are computerized adaptations of CBT, which provide individuals with the opportunity to complete CBT sessions at home. The programs are developed to teach patients the principles of CBT through interactive internet and computer platforms. Computerized CBT offers a convenient and cost-effective alternative to traditional psychotherapies,[40] often less than 10% the cost of traditional face-to-face CBT.[41] These interventions could provide patients with MS who have mobility limitations, or simply those who have other obligations and are unable to make trips to a clinic, a means of addressing depression symptoms.

Several reviews have shown that computer-based therapy for depression is effective and comparable with face-to-face treatment.[42-46] Richards and Richardson[42] conducted a systematic review and meta-analysis of 19 RCTs of computer-based therapy for depression. Although the review was inclusive of a variety of computer-based programs, most used a CBT framework, with a pooled effect size of $d = -0.56$ (95% CI, −0.71 to −0.41) for self-reported symptoms of depression after treatment with computer-based interventions.

Although there is substantial evidence that computerized CBT can be an effective form of treatment for people who have depression, not all research has shown benefit (Table 1). Gilbody et al[47] investigated the efficacy of computerized CBT compared with treatment as usual (TAU) in a large RCT that evaluated 691 patients reporting elevated symptoms of depression. Patients were randomized into one of three groups: TAU from general practitioners, the computerized CBT program Beating the Blues in addition to TAU, or the computerized CBT program MoodGYM in addition to TAU. There were no constraints on TAU in the trial, and participants were free to receive any treatment they sought as part of their usual care, including antidepressant agents and counseling. Neither of the CBT programs offered an advantage over TAU in improving depressive symptoms (assessed by the Patient Health Questionnaire-9 [PHQ-9]) at any of the measurement time points (4, 12, and 24 months after randomization). It is unclear, however, whether the lack of effect is due to lack of uptake in the intervention because computerized sessions were incomplete for many patients (a median of one of the six sessions in MoodGYM completed and a median of two of the eight sessions in Beating the Blues completed).

Table 1. Summary of computerized CBT studies for depression

Study	Patient population	Intervention	Comparison	Main results
Meyer et al,[53] 2009	396 adults recruited via internet depression forums	9 wk of Deprexis	Waitlist control	Intervention group patients had significant reduction in depression symptoms (BDI) compared with control group.
Berger et al,[58] 2011	76 adults with major depression or dysthymia	10 wk of Deprexis with weekly therapist support via e-mail	1) Deprexis without therapist support; 2) Waitlist control	Relative to waitlist control group, there were significant improvements in depression symptoms in both Deprexis-only and Deprexis-with-therapist-support conditions, as measured by BDI. No significant differences between the 2 Deprexis groups were found.
Moritz et al,[57] 2012	210 adults with depressive symptoms	8 wk of Deprexis	Waitlist control	Compared with control group, group with immediate access to Deprexis had significant reduction in depression symptoms (BDI).
Schroder et al,[59] 2014	78 adults with epilepsy and depressive symptoms	9 wk of Deprexis	Waitlist control	Patients in Deprexis intervention group had significant decrease in depressive symptoms (BDI) compared with waitlist control.
Meyer et al,[56] 2015	163 adults with severe depressive symptoms	3 mo of Deprexis	Waitlist control	Intervention group had a significant reduction in depression symptoms (PHQ-9), with a greater reduction than control group.
Proudfoot et al,[60] 2004	274 adults with anxiety or depression	9 wk of Beating the Blues	TAU	Intervention group had significantly lower scores on BDI-II after intervention.
Cavanagh et al,[61] 2006	219 adults with anxiety and/or depression	8 sessions of Beating the Blues	No comparison	Pre-post analysis demonstrated statistically significant improvement on CORE-OM, WSA, and single-item measures of anxiety and depression.
Cavanagh et al,[62] 2011	295 individuals self- or clinician-referred for Beating the Blues	8 sessions of Beating the Blues	No comparison	Participants had significant decrease in symptoms of depression (PHQ-9), and half of sample who initially met criteria for anxiety and/or depression no longer did after treatment.
Gilbody et al,[47] 2015	691 adults with depressive symptoms	8 sessions of Beating the Blues	1) 5 sessions of MoodGYM; 2) TAU	Neither computerized CBT program was more effective than usual GP care in improving depressive symptoms (PHQ-9).
Christensen et al,[54] 2002	2909 individuals registered on MoodGYM site	5 sessions of MoodGYM	No comparison	Depression and anxiety scores (GDAS) decreased significantly over time as users completed additional MoodGYM sessions.
Christensen et al,[65] 2004	525 adults with depressive symptoms	5 sessions of MoodGYM	1) Internet psychoeducation (BluePages); 2) Control intervention with attention placebo	Both MoodGYM and BluePages were more effective than control intervention at reducing depressive symptoms (CESD), with no differences between the two.
Calear et al,[66] 2009	1477 adolescents	5 sessions of MoodGYM	Waitlist control	Intervention group had a significant drop in anxiety levels (RCMAS) relative to waitlist control. Only male participants in intervention group had significant decrease in depressive symptoms (CESD).
Farrer et al,[63] 2011	155 adults with moderate-to-high scores on a measure of psychological distress	5 wk of MoodGYM and 1 wk of internet psychoeducation (BluePages)	1) MoodGYM, internet psychoeducation (BluePages), and weekly support from telephone counselor; 2) Weekly support from telephone counselor; 3) TAU	Participants who used MoodGYM, with and without telephone tracking, had significant reduction in depression (CESD) compared with TAU condition. Telephone tracking did not result in any additional advantage in reducing depression.
Twomey et al,[64] 2014	149 adults with anxiety, depression, and/or stress	5 sessions of MoodGYM	Waitlist control	After intervention, the MoodGYM group had significantly greater reduction in general psychological distress and stress than control group, but not in depression and anxiety as measured by DASS-21.

Abbreviations: BDI, Beck Depression Inventory; CBT, cognitive behavioral therapy; CESD, Center for Epidemiologic Studies Depression Scale; CORE-OM, Clinical Outcomes in Routine Evaluation–Outcome Measure; DASS-21, Depression, Anxiety, and Stress Scale-21; GDAS, Goldberg Depression and Anxiety Scales; GP, general practitioner; PHQ-9, Patient Health Questionnaire-9; RCMAS, Revised Children's Manifest Anxiety Scale; TAU, treatment as usual; WSA, Work and Social Adjustment Scale.

Although recruitment of patients with MS for computerized CBT trials can be challenging,[48] several trials of computerized CBT programs have been completed in MS (Table 2).[48-52] Some of these trials have shown promising results, such as reductions in depressive symptoms,[50,51] but these programs need to be optimized to meet the needs of patients with MS. In various trials, some of the main patient-reported drawbacks were that 1) the tool was not personalized enough to meet individualized needs of patients with MS and 2) the programs offered limited explanation of the relationship between chronic disease/MS and depression.[49,51] There are a variety of programs available to patients with MS for computerized CBT, and to date, none has proved more effective than another. In the following section we review the treatment effects of four computerized CBT programs that have been previously tested in patients with MS: Deprexis,[53] MoodGYM,[54] Beating the Blues,[55] and MS Invigor8.[50]

Examples of Computerized CBT Programs

Deprexis

Deprexis (https://us.deprexis.com) is an interactive Web-based intervention that features several cognitive behavioral approaches to treating depression. The program consists of ten modules, plus an introductory and summary module, that focus on 1) behavioral activation; 2) cognitive modification; 3) mindfulness and acceptance; 4) interpersonal skills, 5) relaxation, physical exercise, and lifestyle modification; 6) problem solving; 7) childhood experiences and early schemas; 8) positive psychology interventions; 9) dreamwork and emotion-focused interventions; and 10) psychoeducation.[53] Each of the modules can be completed within 10 to 60 minutes, depending on an individual's speed and engagement with the program. Users interact with the program by simulated dialogues in which they are presented with various concepts, exercises, and questions and are then asked to respond by selecting one of several response options. Subsequent content is based on their response, resulting in a simulated conversation between the user and the program.[53] A newer version of the Deprexis program provides users with the option of receiving daily text messages designed to reinforce key ideas presented in the program (eg, "Which thoughts are going through your mind right now? Are they helpful? If so, let them be! If not, let them go calmly.")[56] The program also presents various illustrations, audio recordings, and questionnaires for symptom tracking, such as the PHQ-9.

Several studies have been conducted assessing the efficacy of Deprexis. An initial study by Meyer and colleagues[53] found that Deprexis can be effective in improv-

***Table 2.* Summary of computerized CBT studies in MS**

Study	Patient population	Intervention	Comparison	Main results
Fischer et al,[51] 2015	90 adults with MS and depressive symptoms	9 wk of Deprexis	Waitlist control	Scores on BDI decreased significantly in Deprexis intervention group and increased in control group.
Cooper et al,[48] 2011	24 adults with MS and clinically significant levels of depression	8 sessions of Beating the Blues	TAU	In this feasibility study, there was a low recruitment rate, and only half of participants completed all 8 CBT sessions. There was a modest but larger decrease on BDI-II scores in Beating the Blues group compared with TAU group.
Hind et al,[49] 2010	17 adults with MS and mild-to-moderate depressive symptoms	5 sessions of MoodGYM	8 sessions of Beating the Blues	Participants in this qualitative study reported that fatigue and poor concentration, as well as lack of human input, made it difficult to complete computerized CBT sessions. MoodGYM was reported as having inappropriate and culturally specific material.
Moss-Morris et al,[50] 2012	40 individuals with MS and symptoms of fatigue	8 sessions of MS Invigor8	TAU	Fatigue, measured by the Chalder Fatigue Scale and MFIS, was significantly reduced in MS Invigor8 group compared with control group. MS Invigor8 group also showed significantly greater reductions in depression and anxiety (HADS).
van Kessel et al,[52] 2016	39 adults with MS and symptoms of fatigue	8 sessions of MS Invigor8 with weekly therapist support via e-mail	MS Invigor8 without therapist support	Patients in group with therapist support had greater reductions in fatigue severity and impact (CFS and MFIS) compared with MS Invigor8 only group. There were no effects on anxiety or depression (HADS) in either group.

Abbreviations: BDI, Beck Depression Inventory; CBT, cognitive behavioral therapy; CFS, Chalder Fatigue Scale; HADS, Hospital Anxiety and Depression Scale; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; TAU, treatment as usual.

ing symptoms of depression. Participants in the study were assigned to either 9 weeks of the Deprexis intervention in addition to TAU or 9 weeks of a delayed-access condition in which participants were offered the intervention at the end of the wait period. Of the 396 participants initially randomized, 86 were considered dropouts (never logged on to the program or never completed a session of at least 10 minutes). Of the remaining 310 participants, fewer than 50% completed more than three of 12 sessions. Nonetheless, there was a significant reduction in depression symptoms among participants in the immediate-access CBT group who completed both the baseline and posttreatment BDI, indicated by an average drop of 6.26 points on the BDI score. Those in the delayed-treatment group did not improve during the wait period but dropped 5.94 points on average after receiving treatment. Effects were maintained 6 months after baseline in both groups, with approximately 80% of participants reporting being generally satisfied with the treatment. Since this initial study, several follow-up studies have been conducted, including an independent RCT,[57] a study with therapist guidance throughout the program,[58] a study of patients with epilepsy,[59] and a study of patients with severe depressive symptoms.[56] These studies supported the efficacy of Deprexis for symptoms of depression, and the study by Berger et al[58] demonstrated that it is effective with or without therapist support.

There is a single study examining the efficacy of Deprexis in patients with MS.[51] In this study, patients with MS and self-reported depression symptoms were randomized into either a 9-week Deprexis intervention group or a waitlist control group. Of the 90 patients initially randomized, 71 completed the trial. Scores on the BDI decreased significantly in the Deprexis group and increased in the control group. In addition, there were improvements on the psychological well-being subscale of the World Health Organization Quality of Life Scale and on the motor fatigue subscale of the Fatigue Scale for Motor and Cognitive Function among patients in the intervention group. Moreover, at the 6-month follow-up, BDI scores remained significantly lower than at baseline in participants in the Deprexis group. Most patients in the study reported that the program met or exceeded their expectations. However, more than half also suggested that the program may need to be altered to meet the specific needs of patients with MS. Currently, there is an ongoing multicenter RCT of the Deprexis program with patients with MS (ClinicalTrials.gov identifier: NCT02740361) that will have important implications for this program.

Beating the Blues

Beating the Blues (www.beatingtheblues.co.uk) is a computerized intervention based on CBT that was developed by Judith Proudfoot and her team at King's College London. Beating the Blues is designed to be interactive and engaging for the patient, using video vignettes of patient case studies that act as models for the real patient.[55] The program begins with a 15-minute video introducing the patient to the therapy, followed by eight treatment sessions that are typically completed once weekly and last approximately 50 minutes each. The sessions combine both cognitive and behavioral components, which are individualized to the patient and build on previous sessions. The program modules address topics such as unhelpful thinking, core beliefs, attribution style, problem solving, and task breakdown.[60] There are also homework projects to be completed between sessions, including thought records, behavioral experiments, and problem diaries.[61] In some studies of the Beating the Blues program, participants completed the computerized sessions in the clinic under supervision from a health professional.[60-62] Progress reports generated from the program, such as anxiety, depression, and suicidality reports, could then be provided to the health professional. However, there is also a self-guided program that patients can complete on their own (www.beatingtheblues.co.uk/patients/).

Several studies have supported the efficacy of the Beating the Blues program.[60-62] One of the first studies of the program, conducted by Proudfoot et al,[60] examined its efficacy in patients with depression and/or anxiety. Two hundred seventy-four participants were recruited over two phases of recruitment and randomized to receive either the 9-week CBT intervention or TAU. Those in the intervention group completed sessions in the clinic, with a nurse providing support if there were any difficulties with the program. In phase 1 of the study, 65% of those receiving CBT completed the program, and, in phase 2, the CBT group completion rate increased to 78%. Participants in the computerized CBT group had significantly lower scores on the BDI-II after the intervention. Moreover, those in the CBT group continued to have lower scores at follow-up 1, 3, and 6 months after the intervention. Subsequent work by Cavanagh et al[61] examined Beating the Blues in

a naturalistic and nonrandomized routine care setting. Participants completed the Beating the Blues treatment sessions and were administered the Clinical Outcomes in Routine Evaluation-Outcome Measure and the Work and Social Adjustment Scale before treatment, after treatment, and at 6-month follow-up. Single-item measures of anxiety and depression were collected weekly as well through the Beating the Blues program. The trial showed significant improvement on all outcome measures, and, moreover, among those who completed the 6-month follow-up, improvements on the Clinical Outcomes in Routine Evaluation-Outcome Measure and Work and Social Adjustment Scale were maintained.

Cooper et al[48] tested the feasibility of Beating the Blues in patients with MS, randomizing 24 patients to the Beating the Blues program or TAU. Participants completed the program at home without support, other than technical support when needed. The recruitment rate, calculated as the fraction of invited participants who were interested and eligible who consented to enroll, was low at 4.1%. There was a modest but larger decrease in BDI-II scores in the Beating the Blues group compared with the TAU group. Of the 12 patients in the CBT arm, three-fourths completed at least four sessions and half completed all eight sessions. The time to complete the sessions was also longer than expected, ranging from 13 to 20 weeks, due to poor adherence to the weekly schedule. Thus, although feasible, the authors suggest that future research should explore options such as therapist support alongside the computerized Beating the Blues CBT to optimize the intervention.

MoodGYM

MoodGYM (www.moodgym.com.au) is a computerized CBT intervention originally developed by researchers at the Centre for Mental Health Research at the Australian National University to prevent and treat depression in young people.[54] The program consists of five modules, each 20 to 40 minutes long, designed to be completed in a sequential manner. Each of the modules focuses on various elements of CBT, including the relationship between thoughts and feelings, behavioral activation, cognitive restructuring, relaxation, and problem solving.[63,64] The modules are interactive and contain various quizzes, animations, and exercises to be completed by the user. The goals of the program are to teach CBT techniques in a way that is accessible to the community and to help prevent and treat depression. MoodGYM is one of the most widely used online CBT programs, with more than 1,000,000 users worldwide according to their website.

Previous research has shown that the MoodGYM program can effectively treat depression.[63,65,66] One of the initial studies of MoodGYM compared its effectiveness in reducing depressive symptoms to an internet psychoeducation website focusing on depression literacy (BluePages).[65] Five hundred twenty-five participants were randomly divided into a CBT (MoodGYM) group, a psychoeducation depression literacy (BluePages) group, or a control group in which participants were called weekly to discuss lifestyle and environmental factors influencing depression. Results showed that both MoodGYM and BluePages were more effective than the control intervention at reducing depressive symptoms (based on Center for Epidemiologic Studies Depression Scale scores), with no difference between the two interventions. MoodGYM participants completed half of the 29 exercises assigned, and there was a 25% dropout rate in this group, whereas there was a 15% dropout rate in the BluePages group. Follow-up 6 months after treatment indicated that the reduction in depressive symptoms remained significant in the CBT group only, whereas at 12 months both the CBT and depression literacy groups had significantly reduced depression symptoms compared with the control group.[67] Later work by Farrer et al[63] assessed whether adding weekly telephone tracking to the intervention could improve effectiveness and found that telephone tracking did not result in any additional advantage in reducing depressive symptoms or increasing adherence.

A meta-analysis by Twomey and O'Reilly[68] of 11 studies using MoodGYM for treatment of depression revealed a small effect size after treatment with MoodGYM (g = 0.36; 95% CI, 0.17-0.56) that was reduced to a nonsignificant level after correcting for publication bias. Larger effect sizes were seen in studies that had high adherence, face-to-face guidance, and no treatment controls. The authors did find some benefits in studies assessing MoodGYM's utility to treat symptoms of anxiety, and they affirm with caution that the program may provide some benefit for a sizable minority of its users, especially people with anxiety.

A qualitative study by Hind et al[49] examined the utility of both MoodGYM and Beating the Blues in people with MS. Seventeen participants with MS were assigned to either Beating the Blues (eight weekly sessions) or MoodGYM (five weekly sessions). Participants

completed weekly written evaluations and underwent interviews. On completion of the study, participants reported several difficulties with the computerized CBT programs. Fatigue and poor concentration made it difficult to focus and complete the hour-long sessions. Participants felt the lack of human input made it difficult for them to properly apply the CBT techniques. Moreover, participants stated that the programs failed to address how having a chronic medical condition affected their depression. MoodGYM particularly was cited as having inappropriate and culturally specific material by participants in the study. Of the 17 participants, six did not complete the intervention (four MoodGYM participants and two Beating the Blues participants). This research suggests that there may be challenges associated with using computerized CBT programs in populations with chronic medical conditions such as MS.

MS Invigor8

MS Invigor8 is an interactive computerized CBT program targeted to patients with MS. Unlike Deprexis, MoodGYM, and Beating the Blues, MS Invigor8 was developed to treat fatigue rather than depression. However, people with depression may still get some benefit from this program. Researchers at the University of Southampton in the United Kingdom and colleagues designed this internet program based on their therapist-delivered CBT.[50] Patients with MS helped test and develop the modules of the program and provided feedback about the usefulness and acceptability of the information. MS Invigor8 consists of eight weekly sessions that take approximately 25 to 50 minutes to complete. The program gives overviews of MS fatigue and CBT and covers topics such as altering thinking patterns and behaviors, activity scheduling, managing stress, and coping with emotions.[52] There are also homework tasks that the patient can complete between sessions and save in an online workbook as well as optional video and audio clips demonstrating skills such as relaxation techniques.[50] The program features self-assessments, which allows the program to be customized to individual patients' difficulties and progress.

A pilot study of MS Invigor8 by Moss-Morris et al[50] demonstrated that the intervention is feasible for patients with MS and may reduce fatigue along with anxiety and depression. Forty patients were recruited and randomized to complete the CBT program or continue standard care. The CBT group received up to three sessions of telephone support from an assistant psychologist, in which the psychologist helped explain and reinforce the concepts of CBT. Of the 23 CBT participants, 15 completed more than half the sessions (although only one finished all eight). Fatigue, measured by the Chalder Fatigue Scale and the Modified Fatigue Impact Scale, was significantly reduced in the CBT group compared with the control group at follow-up 10 weeks after baseline. The CBT group also showed significantly greater reductions in depression and anxiety, as measured by the Hospital Anxiety and Depression Scale.

van Kessel et al[52] conducted a follow-up study of MS Invigor8 to assess the usefulness of the program with an added component of e-mail support. A total of 39 patients with MS were recruited and randomized to complete either the MS Invigor8 program as usual or MS Invigor8 with e-mail support from an experienced psychologist who maintained contact with participants for 10 minutes weekly via e-mail and provided guidance throughout the program. The study showed that patients with e-mail support had greater reductions in fatigue severity and impact (as measured by the Chalder Fatigue Scale and the Modified Fatigue Impact Scale) at 10 weeks compared with the MS Invigor8–only group. They also had improved adherence, with 12 patients (63%) completing more than half of the CBT sessions in this group compared with 7 (35%) in the MS Invigor8–only group. MSInvigor8, however, did not seem to have any effect on anxiety or depression (as measured by the Hospital Anxiety and Depression Scale), although both groups did have relatively low scores at baseline. More research is needed to determine the efficacy of the MS Invigor8 program, particularly in larger-scale RCTs.

Discussion

This review explores the potential utility of computerized CBT in the treatment of MS-related depression. Although an imperfect tool, preliminary evidence suggests that computer-based CBT may be effective in reducing depression symptoms in patients with MS whose functional impairment may prevent face-to-face therapy or who may not be able to make the time commitment for face-to-face therapy.[50,51] The option for remote computerized CBT would allow for many more patients to receive treatment for depression, addressing a presently unmet need for delivering psychiatric care. In a practical sense, computer-based programs have many systems-level advantages that could facilitate more widespread use (cost-effectiveness, reduced demand

on psychiatric professionals/institutions, adaptability to advances in technology). For example, text-message reminders, smartphone applications, biosensors, and video interface could all be incorporated into future iterations of therapy programs, offering new methods of engaging patients and managing symptoms. Challenges inherent to the usefulness of any remote computerized intervention will undoubtedly include patient adherence to the intervention and significant participant dropout—issues that hamper several of the reviewed studies in the previous section.

In the meta-analysis by Richards and Richardson,[42] an overall mean dropout rate of 57% was reported for all computer-based psychological treatments. Dropout rates were higher in studies that did not include any form of human support as part of the intervention, with a mean dropout rate of 74% for such unsupported interventions. The lack of human interaction in computerized CBT programs is a significant limitation of the programs. When patients come into a clinic for treatment, they often develop a personal relationship with the therapist, which fosters greater motivation and adherence. Computerized CBT programs rely more on a patient's own motivation, which may be difficult for some patients, particularly those with depression. In the Gilbody et al[47] trial, participants with clinical depression were found to have great difficulty engaging with the computer programs repeatedly in the absence of support and did not adhere to the programs. With incomplete uptake of an intervention, it will be impossible to fully assess clinical benefit.

Another concern in the absence of a therapist is patient safety. Often, computerized CBT studies screen for and exclude participants expressing suicidal ideation[51,58,63] and sometimes monitor suicidality throughout the study.[48,57] In studies that used Beating the Blues, for example, progress reports that included depression ratings and reported suicidality were sent to the patient's general practitioner or other health professional weekly.[60-62] However, outside of participation in research studies, it is not clear how suicidality would be handled to ensure that at-risk individuals receive appropriate care. This may be particularly important in MS given the high rates of depression and suicide.[12,13]

In addition, an important consideration for the implementation of computerized CBT strategies in an MS population is that the clinical problems that necessitate computerized intervention (weakness, coordination impairment, debilitating fatigue, poor concentration) also interfere with the patient's ability to complete an online intervention. Hind et al[49] found that issues such as fatigue and poor concentration make it difficult for patients with MS to focus on and complete the treatment sessions, and in some instances people felt that existing social isolation was exacerbated by using the intervention. A common frustration noted by patients in the studies by Hind et al[49] and Fischer et al[51] was that computerized modules have limited ability to adapt to issues particular to their MS. This is perhaps one facet of face-to-face communication that will never be easily replicated by computerized programs, and it remains to be seen whether software can be developed to address this criticism.

Programs developed specifically for use in patients with MS (such as MS Invigor8) could ideally address such patient concerns in future iterations of the software, but, for many programs, cost limitations and reduced generalizability limit the development of disease-specific designs. Another potential option, as highlighted by many of the trials herein, would be the inclusion of therapist guidance alongside the CBT program. Clinicians can then supplement computerized therapy to address individualized patient concerns and act as a resource for answering broader questions about the pathophysiology of depression in chronic disease. Research cited in this review is mixed as to whether the programs may be enhanced with clinical support,[52,58,63,68] although

PRACTICE POINTS

- Depression is a common and clinically significant comorbidity in MS that is often undertreated.
- Cognitive behavioral therapy (CBT), a psychotherapy approach that focuses on restructuring negative thought patterns and behaviors and developing coping strategies, is effective in treating MS-related depression.
- Recent developments in technology have led to alternative options for treatment of depression, including computerized CBT. Computerized CBT allows individuals to complete CBT sessions remotely through online programs.
- Computerized CBT may be a convenient and effective option for the treatment of depression in people with MS, although certain challenges may make the intervention difficult to implement.

a promising finding from Andersson and Cuijpers[69] was the improved effect of computerized psychological treatment on depression with support (effect size, d = 0.61; 95% CI, 0.45-0.77) versus no support (d = 0.25; 95% CI, 0.14-0.35). Positive effects on compliance and retention are also likely advantages of such a strategy.[42] More research is needed to find the optimal strategy for professional guidance of computerized CBT (ie, type of therapist used, frequency of contact, modality of communication). Randomized controlled trials, particularly ones with control groups receiving standard treatments such as pharmacotherapy or traditional face-to-face CBT, should be conducted to determine whether this form of therapy is indeed effective. Additional studies should be performed to compare alternative computerized CBT packages.

Although computerized therapy platforms may be a convenient way of providing mental health interventions, whether they will be able to make a lasting positive impact on the psychiatric care of patients with MS and others with chronic illness remains to be seen. There are a variety of practical obstacles to its widespread implementation, but the hope is that by working to optimize such technology, and not merely pointing to its flaws, we will be able to provide psychiatric care to patients with MS who would otherwise have none. □

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